Impregnation of Ibuprofen into Polycaprolactone Using Supercritical Carbon Dioxide

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Abstract. Polycaprolactone (PCL) is a Food and Drug Administration (FDA) approved biodegradable polyester used in tissue engineering applications. Ibuprofen is an anti-inflammatory drug which has good solubility in supercritical CO\textsubscript{2} (SCCO\textsubscript{2}). The solubility of CO\textsubscript{2} in PCL allows for the impregnation of CO\textsubscript{2}-soluble therapeutic agents into the polymer via a supercritical fluid (SCF) process. Polymers impregnated with bio-active compounds are highly desired for medical implants and controlled drug delivery. In this study, the use of CO\textsubscript{2} to impregnate PCL with ibuprofen was investigated. The effect of operating conditions on the impregnation of ibuprofen into PCL was investigated over two pressure and two temperature levels, 150 bar and 200 bar, 35 \degree C and 40 \degree C, respectively. Polycaprolactone with drug-loadings as high as 27\% w/w were obtained. Impregnated samples exhibited controlled drug release profiles over several days.

1. Background
Supercritical CO\textsubscript{2} processing of PCL has been well documented [1-8]. Supercritical CO\textsubscript{2} can penetrate and plasticize PCL, thereby creating a pathway for the impregnation of CO\textsubscript{2}-soluble therapeutic agents such as ibuprofen, an anti-inflammatory drug [9]. In this work, the use of SCCO\textsubscript{2} for impregnation of PCL with ibuprofen was investigated. The effect of operating pressure and temperature was tested for the SCCO\textsubscript{2} impregnation of PCL. The dissolution of ibuprofen from the SCCO\textsubscript{2}-processed PCL matrix was also studied.

2. Experimental Set-up
Polycaprolactone (\(M_w=1.2\times10^4\)Da, 99\% purity) was purchased from Sigma Aldrich. Ibuprofen (99\% purity) was supplied by Nanomaterials Technology. The impregnation experiments were conducted by placing a 10ml glass beaker containing PCL in a 100ml stainless steel reactor. Along with the PCL, a 5ml glass beaker with an excess of ibuprofen was loaded in the reactor. Once the operating temperature was achieved, the system was pressurized with carbon dioxide up to the set pressure. The system was isolated for 4 hours prior to depressurization. Samples were collected and analyzed by differential; scanning calorimetry (DSC), thermogravimetric analysis (TGA), scanning electron microscopy (SEM), and reverse-phase high pressure liquid chromatography (RP-HPLC).
2.1. Analytical techniques
A TA Instruments Hi-Res Modulated TGA 2950 (air flow, gradient 20°C/min) and a TA Instruments DSC 2010 (nitrogen flow, gradient 20°C/min) were used for thermal analysis. A Hitachi S3400i was used to take SEM images; samples were deposited on double sided carbon tape and coated with a Emitech K550x Gold Sputter Coater.

Drug-loading was quantified by a RP-HPLC method developed on a Waters system which included a 717 plus autosampler, 515 HPLC pump, and a Waters 996 photodiode array detector at an absorbance wavelength of $\lambda = 220$ nm. A Lichrosorb RP18 analytical column was housed in an Activon column oven at 60°C. A mobile phase of 1:1 acetonitrile to deionized water at a flow-rate of 1.5 ml min$^{-1}$ was used. Samples were dissolved in acetonitrile.

The drug-loaded samples underwent a dissolution study under sink conditions for the drug. The dissolution study was conducted using the paddle method in 100ml of deionized water at 37°C, and 50rpm. The concentration of dissolved ibuprofen was quantified using a UV spectrophotometer.

3. Results and Discussion
3.1. PCL impregnation with ibuprofen
The drug-loadings of ibuprofen in PCL are listed in Table 1, along with the experimental conditions, solubility of ibuprofen in SCCO$_2$ and $T_m$ values of the impregnated samples. The drug-loading was quantified using a RP-HPLC method and the $T_m$ values were obtained using DSC analysis (Figure 1). Experiments IMPG1 and IMPG3 had the lowest and highest drug-loading, respectively. The impregnation of IMPG1 was conducted at the lowest temperature and lowest pressure and corresponded to the lowest solubility of ibuprofen in SCCO$_2$ [9]. The solubility of ibuprofen in SCCO$_2$, however, does not fully account for the differences in drug-loadings. In fact, ibuprofen solubility is highest at experimental conditions used to produce IMPG4, but the highest loading was obtained for IMPG3.

In Figure 1 the DSC and TGA profiles of the drug-loaded samples are displayed. There are three noticeable TGA thermal transitions at 200°C, 400°C and 500°C. Ibuprofen undergoes degradation above 200°C, as a consequence the extent of weight loss observed around 200°C is an indication of the amount of ibuprofen in the samples. Sample IMPG3 presented the higher weight variation at 200°C, followed in order by IMPG4, IMPG2 and IMPG1. The TGA results confirmed the drug-loadings as determined by RP-HPLC. The TGA analysis also indicated that

| Sample  | T(°C) | P(bar) | Drug-loading† (wt%) | $T_m$§ (°C) | Solubility of ibuprofen in CO$_2$ (mole fraction x 10$^3$) [9] |
|---------|-------|--------|---------------------|-------------|-----------------------------------------------------|
| Neat PCL| -     | -      | -                   | 66          | -                                                   |
| Ibuprofen | -     | -      | -                   | 78          | -                                                   |
| IMPG1   | 35    | 150    | 1.83                | 68          | 2.7                                                |
| IMPG2   | 35    | 200    | 3.18                | 66          | 4.2                                                |
| IMPG3   | 40    | 150    | 27.16               | 58          | 3.7                                                |
| IMPG4   | 40    | 200    | 9.67                | 59          | 6.8                                                |

† determined by RP-HPLC
§ determined by DSC
Figure 1. Thermal analysis of samples: DSC profiles (left), TGA profiles (right)

dense gas treatment does not affect the onset of degradation of PCL. The $T_m$ of the samples are listed in Table 1. All samples exhibited a $T_m$ between $55^\circ C$ and $70^\circ C$ with drug-loadings above 3% corresponding to a reduction in $T_m$ values.

Drug-loading efficiency depends on the solubility of the drug into CO$_2$, the ability of CO$_2$ to penetrate the polymer and the partition coefficient of the drug between the dense gas and the polymer phase. The drug-loadings obtained in this study are not directly related to the solubility of ibuprofen in CO$_2$ (Table 1). The ability of CO$_2$ to penetrate the polymer appears to play a more important role, in fact the higher drug-loading were achieved for samples IMPG3 and IMPG4. Both samples were produced under conditions in which CO$_2$ penetrates deeply into the polymer. A consequence of CO$_2$ penetration within the PCL molecules is the melting point depression of the polymer. At ordinary conditions, PCL melts at $66^\circ C$; the $T_m$ of PCL in the presence of SCCO$_2$ at 147bar is $36.6^\circ C$, at 163bar is $36.2^\circ C$, and at 276bar is $34.2^\circ C$ [9]. By interpolation, the $T_m$ at 150bar is approximately $36.6^\circ C$, and at 200bar is $35^\circ C$. Samples IMPG3 and IMPG4 were produced at 40°C and 150bar and 200bar, respectively. In both cases the PCL was melted and CO$_2$ was penetrating deeply within the polymer chains acting as a carrier for solubilized ibuprofen.

The partition of the drug between the SCCO$_2$ and the polymer was more favourable at 150 bar than at the higher pressure; as the solubility of the drug in SCCO$_2$ increased with pressure, the partition with the PCL became less favourable. It has to be noted that the solubility of ibuprofen in SCCO$_2$ at 150bar is lower than at 200 bar. However, this does not limit the overall amount of drug available for the impregnation since an excess of drug is present in the system. As ibuprofen migrates from the SCCO$_2$ phase into the polymer more drug can dissolve, maintaining a constant concentration of drug in the SCCO$_2$ phase. The presence of wide pores is evident for samples IMPG3 and IMPG4 (Figure 2). Upon depressurization, CO$_2$ escaped the melt polymer phase creating such large pores.

The SEM images of the IMPG samples exhibit macro- and nanopores on the surface of IMPG1, IMPG2, IMPG3 and IMPG4 (Figure 2). Samples IMPG3 and IMPG4 (Figure 2) had peculiar morphologies as it showed the more spherical indentations and/or cavities. Sample IMPG3 had a higher occurrence of these cavities. The drug-loading was the highest at 40°C and 150bar, whereas the PCL morphology was most altered at both of the 40°C impregnation experiments.
Figure 2. SEM images of IMPG1 (top left), IMPG2 (top right), IMPG3 (bottom left) and IMPG4 (bottom right)

3.2. Drug Dissolution

Figure 3. Dissolution profiles of drug-loaded PCL samples

Free ibuprofen dissolved in approximately 1.5hrs, whereas all the PCL samples impregnated with ibuprofen exhibited sustained release over 72hrs (Figure 3). Samples IMPG1 (94wt%) and
Table 2. Release exponent calculation

| Sample | n     | Fit ($R^2$) |
|--------|-------|-------------|
| IMPG1  | 0.5211| 0.9971      |
| IMPG2  | 0.4912| 0.9923      |
| IMPG3  | 0.5588| 0.9621      |
| IMPG4  | 0.3977| 0.9534      |

IMPG3 (30wt%) had the highest and lowest wt% of ibuprofen dissolved in 72hrs, respectively.

The dissolution profiles were analyzed using the Korsmeyer-Peppas model [10-12]. The simplified equation (Equation 1) was used to relate the amount of drug released over time to the total time elapsed, where $a$ = constant incorporating structural and geometrical characteristics of drug dosage form and $n$ = the release exponent. A release exponent of 0.5 signifies Fickian release [10-12].

$$f_1 = at^n$$ (1)

The calculations for the release exponent for the impregnated samples are listed in Table 2. All samples exhibited near-Fickian dissolution profiles. The error in the fit was minimal for the samples produced at 35°C. All the PCL samples impregnated with ibuprofen using SCCO$_2$ exhibited sustained release over a period of 72hrs.

4. Conclusion

The various samples exhibited macro- and nano-porous structures dependent on the experimental conditions. The SCCO$_2$ processing of PCL was extended to create devices for controlled drug delivery. Ibuprofen was solubilized in SCCO$_2$ and impregnated in PCL. Drug-loadings ranged from 2wt% to 27wt%. Unique surface structures were also attained during the impregnation process under various experimental conditions. The thermal properties of PCL were not significantly altered after the impregnation process. A sustained Fickian-type release profile was achieved for all the impregnation conditions over a span of 72hrs. Carbon dioxide was used to alter the morphology of PCL and impregnate PCL with ibuprofen, thus extending the use of SCCO$_2$ for tissue engineering applications. Applications such as scaffolds and controlled drug delivery devices can be addressed using supercritical fluid technology.

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