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PCL/Ibuprofen Implants Fabricated by Selective Laser Sintering for Orbital Repair

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Abstract

This paper describes the properties of porous polycaprolactone/ibuprofen implants fabricated by SLS for orbital floor repair. The specimens prepared showed homogeneous morphology and pore interconnectivity. PCL/ibuprofen specimens presented a higher degree of sintering than pure PCL specimens. The PCL/ibuprofen specimen sintered under the highest laser power showed the lowest crystallinity value due to a fast cooling rate resulting from the strong laser absorption presented by the PCL/ibuprofen mixture. The specimens showed a significant increase in the flexural modulus when the laser energy density used in the manufacturing was increased. The DMA tests indicated that solubilization and the formation of secondary chemical interactions between the drug and the PCL did not occur. The PCL/ibuprofen specimens showed the occurrence of non-linear drug release with respect to time, suggesting Fickian release kinetics via a diffusion mechanism. The release profile for porous plates of PCL/ibuprofen prepared by selective laser sintering indicated that these devices could be applied for bone regeneration and the control of the inflammatory process soon after implantation.

1. Introduction

Polymers have been gaining popularity for the reconstruction of the ocular internal orbit because of their ease of use and the associated reduction in surgical morbidity [1-4]. Moreover, they are characterized by a reduced operation time, a multitude of available sizes and shapes and a potentially endless supply. In this context, polymers are classified as non-resorbable and resorbable materials. Porous high density polyethylene (HDPE) is a non-resorbable and inert polymer which has been widely used in a porous form for orbital floor reconstruction since 1985. It is available in sheets of different sizes and thicknesses, typically 0.85 mm, 1.5 mm and 3.0 mm, and the pore size ranges from 100 to 200 μm [2,4]. The porous structure permits tissue ingrowth and fibrovascularization of the implant and reduces foreign body reaction and capsule formation. Fibrovascular ingrowth also provides positional stability to the implant, thus preventing migration and extrusion [4]. In clinical practice, HDPE implants are used both for the reconstruction of mid-large fractures and for smaller defects, due to the different sizes available. When there are complications with the use of HDPE implants due to infection, anti-inflammatories and antibiotic prophylaxis should be administered [1,4]. The disadvantages of non-resorbable porous polyethylene implants include the adhesion of extraocular muscle or orbital fibroadipose tissue to the implant. Complications such as lower lid retraction and external scarring are common. Biodegradable polymers have gained popularity for the reconstruction of orbital floor fracture due to their ease of use, the elimination of donor-site morbidity and because they offer more controllable and predictable absorption kinetics than biological grafts [1, 5, 6].
The main advantage of a resorbable implant for orbital floor repair is the maintenance of the orbital contents in the presence of herniation forces during the initial healing phase, transferring the load after the healing has taken place and the implant is no longer needed, particularly for small fractures [1, 5, 6].

Selective laser sintering is a fabrication technique that permits the development of porous polymeric devices, such as scaffolds and drug delivery systems, with controlled composition and structure [7-12]. In this study, the properties of resorbable porous polycaprolactone/ibuprofen implants fabricated by SLS for orbital floor repair were investigated, since these implants have the potential to promote orbital floor defect healing and bone growth, minimizing inflammation and other complications due to implant insertion.

2. Experimental

2.1 Materials

The polymeric powder used in this study was commercial polycaprolactone (Sigma-Aldrich), with an average molecular weight of 70,000 to 90,000 g/mol, melt flow index of 1.0 g/10min, and density of 1.145 g/cm³ at 25°C. The PCL was ground cryogenically in a mechanical grinder and sieved. Particle size ranges of 125–212 μm were obtained (Figure 1). The ibuprofen (IBP), a nonsteroidal anti-inflammatory, was obtained from Pharmanostra (São Paulo, Brazil). The material has the appearance of a white crystalline powder with a density of 1.175 g/cm³. The IBP melting temperature determined by DSC was 77.4 ºC.

2.2 Selective laser sintering of porous plate specimens

The specimens (dimensions of 35 × 5.0 × 1.4 mm) were sintered in SLS equipment using a CO2 laser (9 Watts) with a 250 μm diameter laser beam. For the manufacture of the specimens, the laser scanning speed was maintained at 50 mm/s, the hatch spacing was 100 μm, and the laser energy densities were 0.04, 0.14 and 0.27 J/mm². The powder bed temperature was 45°C. Table 1 shows the IBP content in the polycaprolactone specimens and the processing conditions. For each condition were fabricated ten (10) specimens for analyses.

2.3 X-Ray diffraction and scanning electron microscopy

The X-ray diffraction measurements were performed using a Philips PW1150 vertical diffractometer. The Cu–Kα nickel filtered radiation was detected in the range of 6–50°. The results of this analysis were used to determine the structure and crystallinity of the specimens. The specimens were observed with a Philips XL30 scanning electron microscope in order to investigate the fracture surface, ibuprofen dispersion and specimen structure. The specimens were coated with gold in a Bal-Tec Sputter Coater (SCD005).

2.4 Flexural test and dynamic mechanic analysis

Mechanical analysis was performed on a TA Instruments analyzer, model Q800, with single cantilever mode. Stress–strain curves were obtained at a strain rate of 2 mm/min and 30 °C. The storage modulus (E’) and the loss factor (tan δ = E”/E’) were determined at a fixed frequency of 1 Hz, at temperatures of -80 to 100 oC and with a heating rate of 3 oC/min.

2.5 Drug release test

The dry specimens with known drug content and thickness were immersed in a 50 mL phosphate buffer solution (pH = 7.4) (to maintain sink conditions), shaken horizontally in a Dubnoff bath (Quimis S.A, Brazil) at a rate of 60 rev/min to minimize the boundary effect, and maintained at a temperature of 37.0 ± 0.5 °C. The total receptor solution volume was removed periodically at 48 h intervals and replaced with a fresh solution. After appropriate dilution with the buffer solution, the total drug release was obtained against a predetermined calibration curve using UV-Vis spectrophotometry at λmax 246 nm, on a Hitachi 2010 double-beam UV-visible spectrophotometer.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Ibuprofen content (%)</th>
<th>Energy density (J/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0</td>
<td>0.04</td>
</tr>
<tr>
<td>P2</td>
<td>0</td>
<td>0.14</td>
</tr>
<tr>
<td>P3</td>
<td>0</td>
<td>0.27</td>
</tr>
<tr>
<td>P11</td>
<td>15</td>
<td>0.04</td>
</tr>
<tr>
<td>P12</td>
<td>15</td>
<td>0.14</td>
</tr>
<tr>
<td>P13</td>
<td>15</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Fig. 1. Micrographs of (A) PCL and (B) IBP particles.
3. Results and discussion

The surface micrographs of specimens sintered using a laser energy density of 0.04, 0.14 or 0.27 J/mm² with an ibuprofen content of 0 or 15 % are shown in Figures 2 and 3, respectively. The specimens showed homogeneous morphology, PCL particle coalescence and pore interconnectivity, resulting in properties appropriate for application in the biomedical field as devices for tissue regeneration and growth.

Specimens of pure PCL sintered at lower laser energy density (0.04 and 0.14 J/mm²) showed elevated porosity with the frequent formation of necks between the PCL particles. Specimens manufactured with a laser energy density of 0.14 J/mm² showed higher densification with the formation of a co-continuous phase and extensive neck grown between the PCL particles, as shown in Figure 2.

Specimens of PCL/IBP (Figure 3) showed a higher degree of sintering than the pure PCL specimens. This finding can be attributed to the molecular structure of ibuprofen, which contains a C-O bond with high infrared laser absorption at a wavelength of 10 μm, corresponding to the stretching of the C-O group. The laser energy absorption of IBP can accelerate the PCL matrix sintering through a thermal conduction effect.

In order to identify and quantify the crystalline phase in the PCL and PCL/IBP specimens obtained, X-ray diffraction (XRD) analysis was performed. Figure 6 shows the XRD results for the pure PCL and PCL/IBP specimens. The diffractogram of the pure PCL specimens shows two peaks at 2θ 21.6 and 23.8. These peaks are indexed to the (110) and (200) planes of an orthorhombic crystalline structure [13, 14]. The diffractograms of the PCL/IBP specimens showed the same peaks at 2θ 21.6 and 23.8.

Table 2 shows the values for the crystallinity of the pure PCL and PCL/IBP specimens sintered using 0.04, 0.14 and 0.27 J/mm² of laser energy density. The pure PCL specimens sintered presented crystallinity from 55 to 65%. Specimens of PCL/IBP presented crystallinity values ranging from 33 to 63%. Specimens prepared using higher laser power densities had lower crystallinity values, probably due to the faster
cooling rate after laser sintering. The PCL/IBP specimen sintered under higher laser power (PI3) had the lowest crystallinity value due to the fast cooling rate resulting from the strong laser absorption presented by the PCL/IBP mixture.

Dynamic mechanical analysis was performed to investigate the viscoelastic characteristics of the pure PCL and PCL/IBP specimens. The plots of the storage modulus ($E'$) as a function of temperature are shown in Figure 7. All specimens manufactured showed a significant decrease in the values of $E'$ from 40 °C, close to the glass transition temperature of PCL. The pure PCL and PCL/IBP specimens sintered using higher laser energy density (P3 and PI3) showed higher values for the storage modulus $E'$ and similar stiffness in the quasi-static flexural test.

Table 3 shows the values for the flexural modulus and strength at 10% strain for the pure PCL and PCL/IBP specimens sintered using 0.04, 0.14 and 0.27 J/mm² of laser energy density. Pure PCL specimens showed a significant increase in the flexural modulus and strength at 10% strain with an increase in the laser energy density applied in the manufacturing process. This effect is due to the greater degree of sintering which results in increased stiffness.

The PCL/IBP specimens had higher values for the flexural modulus than the pure PCL specimens due to the higher degree of sintering (higher densification observed in the micrographs) caused by the strong laser absorption by IBP.

The values for the glass transition temperature ($T_g$) obtained from the dissipative tangent (Tan δ) in the dynamic mechanical analysis (Table 4) ranged from 32 to 36 oC for the pure PCL and PCL/IBP specimens. The presence of 15% (by mass) of IBP in the PCL specimens did not result in a significant change in the $T_g$ value, suggesting that solubilization and important secondary chemical interactions (Van der Waals, dipole-dipole or hydrogen bonds) between the drug and the PCL matrix did not occur in this manufacturing process.

Figure 8 shows the profiles for the release of ibuprofen from the PCL/IBP specimens sintered using different laser energy densities. The total drug released from the specimens tested during the analysis was around 75% after 1600 minutes, indicating a fast release. The drug release from the PCL/IBP specimens was non-linear with respect to time, suggesting the action of different mechanisms. The analysis applying the Higuchi model indicated Fickian kinetics for the ibuprofen release from PCL/IBP specimens, the main mechanism being diffusion. However, there may be a combination of diffusion and erosion mechanisms acting, with drug reservoirs in the closed pores of the matrix also affecting this behavior.
The DMA tests indicated that the higher degree of sintering caused by the strong laser absorption by ibuprofen. The PCL/ibuprofen specimens showed a higher degree of sintering than the pure PCL specimens due to the interactions between the drug and the PCL matrix did not cause a significant change in the Tg values, suggesting that solubilization and the formation of secondary chemical interac-
tions between the drug and the PCL matrix did not occur in the manufacturing process.

The total drug released from the tested specimens during the analysis was around 75% and the release was fast. The drug release from the PCL/ibuprofen specimens was non-linear with respect to time, suggesting Fickian release kinetics via a diffusion mechanism. The release profile for the porous plates of PCL/ibuprofen prepared by selective laser sintering indicated that these devices may be applied as implants for bone regeneration and the control of inflammatory process soon after implantation.

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