Physicochemical characterization, drug release and mechanical analysis of ibuprofen-loaded ultra-high molecular weight polyethylene for orthopedic applications

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Abstract

In this study, the preparation of a novel functional material for orthopedic implants using compression molding was investigated. The new functional material is envisioned to avoid inflammatory reactions in vivo after prosthesis implantation. Ibuprofen-loaded UHMWPE samples were prepared in two concentrations (3% and 5%) and samples were characterized in terms of physicochemical and mechanical properties. In addition, the drug-release profile was investigated. The manufacturing process resulted in a homogeneous polymer matrix with homogeneous drug dispersion. The addition of ibuprofen had a minor effect on physicochemical properties but a more significant influence on the mechanical behavior of the specimens was observed. Drug release was demonstrated and overall the results obtained showed a positive outcome with regard to the intended use. The properties analyzed remained within an acceptable range for medical application and the drug-release profile obtained for the material developed shows promise for its use as an anti-inflammatory system.

Keywords: UHMWPE, ibuprofen, biomaterial, drug delivery, orthopedic implants, material characterization.

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1. Introduction

Total knee arthroplasty (TKA) is a standard technique used to improve mobility and reduce pain in patients with osteoarthritis, and it has been in use for the past 50 years1,2. TKA is a procedure that replaces the knee joint with a set of tibial and femoral components composed of metal alloys with a polymer spacer as the articular surface3. Ultra-high molecular weight polyethylene (UHMWPE) has been used as the standard material to produce the insert implanted between the femoral and tibial components in TKA procedures, due to its excellent mechanical properties and biocompatibility4.

Despite the attractive mechanical properties of UHMWPE, which account for its use to manufacture spacers, the constant movement and contact against the tribological pair lead to wear of the polyethylene component5. In addition to geometrical changes associated with the wear, which may affect the performance of the implant, wear particles are generated. This wear debris is known to trigger foreign body reactions that may lead to chronic inflammation and ultimately to osteolysis, future aseptic loosening and the need for revision surgery6,7, which represents a negative aspect of UHMWPE and limits the life span of the implant7.

When these particles are detected by the immunological system, they are phagocytosed by macrophages and multinucleated cells are formed, which lead to the activation of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6. This process results in the proliferation and maturation of osteoclasts, multinucleated cells responsible for bone resorption. On the other hand, the proliferation of osteoblasts, bone forming cells, is reduced, generating an imbalance between osteogenesis and bone resorption8. One approach to inhibit the development of this inflammatory reaction is the use of anti-inflammatory or bone resorption suppressors as a post-operative treatment9.

Recent studies have demonstrated the 10-year implant survival rate for TKR was 96.1%, and the 20-year implant survival rate was 89-7%. However, for younger and more active patients the lifetime risk of revision increased up to 35% with great differences between female and male patients (15% lower for women in same age group)10. Although TKA has high success rates, with more than a million procedures...
conducted every year\cite{10}, problems related to inflammatory reactions, such as osteolysis, are one of the main factors linked to the high number of revision surgeries\cite{11}. According to AJRR (American Joint Replacement Registry)\cite{12}, in 2016, 3.4% of all knee replacement procedures performed in the United States were revision surgeries, and 13% of these were related to inflammatory reactions surrounding the implant area.

Various alternatives related to the manufacturing process and material composition have been tested over the past few years to maintain the positive aspects of this material and, at the same time, improve its relationship with the human body and the wear properties. Crosslinked-UHMWPE has emerged as a promising material for total hip arthroplasty with some improved properties when compared with conventional UHMWPE. However, in TKA, this material has not demonstrated the same benefits. This is due to the multidirectional cyclic movements of the knee combined with a reduction in the mechanical properties and fatigue resistance observed for crosslinked-UHMWPE\cite{13}. Thus, conventional UHMWPE has shown better performance in TKA procedures and remains, along with Vitamin E-loaded UHMWPE, the preferred choice of material.

UHMWPE with the antioxidant Vitamin E incorporated was developed as an alternative to reduce the oxidative reaction that occurs during in vivo use. In the material matrix this antioxidant reacts with free radicals and retards the oxidative process\cite{14}. UHMWPE with Vitamin E has been used in arthroplasty procedures and has shown positive results in terms of wear resistance and particle interaction with the immunological system\cite{15}.

In order to reduce the number of revision procedures by reducing inflammatory reactions and infections, researchers all around the world have been testing the incorporation of different drugs, such as vancomycin\cite{16}, gentamicin\cite{17}, bupivacaine\cite{18} and bisphosphonates\cite{19}, to avoid infection and inhibit bone resorption. Although there have been some good outcomes, this kind of technology is still in the pre-clinical testing phase as it deals with humans, and therefore has not yet been used in arthroplasty procedures.

In this paper, researchers propose the incorporation of clove oil, a traditional ayurvedic medicine with antioxidant and anti-inflammatory properties, to the UHMWPE polymeric matrix. The aim is to reduce inflammatory reactions and infections around the implant area.

2. Experimental

2.1 Materials

UHMWPE resin (GUR 1020, Ticona) was the main material used to prepare the specimens, along with IBU (Viafarma, Joinville, Brazil). As a way to compare the material properties and behavior, specimens with drug concentrations of 3wt% and 5wt% were prepared as well as specimens without the addition of the anti-inflammatory drug. The specimens were named UHMWPE, UHMWPE 3% IBU and UHMWPE 5% IBU.

2.2 Preparation of specimens

Specimens were prepared according to the methodology proposed by Suhardi et al.\cite{15} with some modifications. The compression molding process was carried out in a hydraulic press with a load capacity of 15 tons (Bonevau, Rio do Sul, Brazil). Samples of UHMWPE 3% IBU (0.3 g IBU: 9.7 g of UHMWOE) and UHMWPE 5% IBU (0.5 g IBU: 9.5 g of UHMWPE) were previously prepared by mixing the polymer and the drug for 10 min. Each formulation was placed in the mold and kept at 150 °C and 5 Mpa for 15 min to reach total material consolidation. After this period, the specimens were cooled to room temperature. All test specimens were prepared according to standard specifications as will be detailed in the following sections.

2.3 Specimen characterization

2.3.1 Physicochemical analysis

Differential scanning calorimetry (DSC) was conducted on all specimens to determine the thermal parameters, such as melting point temperature ($T_m$), melting enthalpy and the degree of crystallinity according to ASTM F2625-10. Three samples, with masses of between 0.003 g and 0.008 g, were extracted from each formulation proposed and sealed in an appropriate aluminum pan for posterior analysis in DSC equipment (PerkinElmer 600, São Paulo, Brazil). Tests were run with a heating/cooling rate of 10 °C/min and the crystallinity degree was obtained by integration of the endotherm peak between 50 °C and 160 °C. Thin films were prepared for Fourier-transform infrared spectroscopy and microscopy experiments. The films were obtained from different regions of specimens to address the material uniformity. Specimens of 1 cm x 1 cm x 1 cm were removed from each specimen and embedded in paraffin. Slices of 200 µm and 90 µm were obtained from paraffin-embedded specimens with the aid of a microtome for Fourier infrared (FTIR) spectroscopy and microscopy analysis, respectively. The FTIR spectroscopy was performed in the transmission mode and according to ASTM 2102-13. Optical microscopy (Nikon E-200) was performed to evaluate the quality of the consolidation process. The films were evaluated under 100 X magnification. Lastly, density measurements of three specimens of each formulation were taken following Archimedes’ principle. The specimens were prepared with at least 1 mm of thickness for each 1 g of material with a maximum of 5 g, as recommended by the technical standard ASTM D792-13.
2.3.2 Drug release test

Spectrophotometric analysis was conducted using a UV-Vis spectrophotometer (Model UV-5200, Global Trade Technology, Monte Alto, Brazil) to obtain the release profile and investigate the way in which the drug would be eluted from the UHMWPE when implanted in the human body. IBU, in concentrations of (mg/ml) 0.0652, 0.125, 0.25, 0.5, 1.0, 2.0, 2.5, 3.0 and 4.0, was dissolved in phosphate buffer solution (PBS, pH = 7.4) and then analyzed in the spectrophotometer at a wavelength ($\lambda_{\text{max}}$) of 264 nm to prepare the IBU calibration curve (Figure S1, Supporting Information, Supplementary Material). The UHMWPE specimens with IBU were then immersed in 3 mL of PBS and placed in a Dubnoff bath at a temperature of 37.0 ± 0.5 °C. The entire PBS volume was collected from each specimen after 6 h and 24 h, then every 24 h for one week and subsequently twice a week until the 30th day of the drug release test (Figure S2). After each PBS collection, the amount taken for the test was replaced with fresh PBS. Due to the nature of the system developed, the models chosen to analyze the data were the zero-order model, Higuchi model and Korsmeyer-Peppas model (also known as the power law model)\(^{[20]}\). The curves resulting from this analysis are provided in Figures S3 – S5.

2.3.3 Mechanical testing

Mechanical testing was performed according to technical standard ASTM D638 with some modifications. These experiments were carried out on a universal testing machine (DL 3000, EMIC, São José dos Pinhais, Brazil) operating with a load cell of 500 N and at a test speed of 1 mm/min, with the use of an Instron extensometer (Cat. No. 2630-107, Instron, Norwood, USA) with a gauge length of 25 mm and travel length of +25/-2.5 mm. The length between grips in the Instron, Norwood, USA) with a gauge length of 25 mm and travel length of +25/-2.5 mm. The length between grips was 33.9 mm. Three specimens of each drug concentration were machined into a dumbbell-shaped format, 2 mm thick and with a cross-section area of 6 mm², to obtain the elastic modulus and tensile yield strength of the specimens for posterior analysis of the effect of the IBU on the mechanical properties. The elastic modulus specimens were obtained in the linear strain region of 0.0005 to 0.0025 mm/mm.

### Table 1. Physicochemical properties.

| Composition        | $T_m$ [°C]  | $T_{\text{onset}}$ [°C] | $X$ [%]   | Density [kg/m³]  |
|--------------------|-------------|-------------------------|-----------|------------------|
| UHMWPE             | 131.94 ± 0.98 | 122.47 ± 0.94          | 53.12 ± 1.70 | 927.30 ± 3.70    |
| UHMWPE 3% IBU      | 131.02 ± 0.55 | 122.34 ± 0.32          | 53.69 ± 3.97 | 930.43 ± 7.22    |
| UHMWPE 5% IBU      | 131.06 ± 0.50 | 121.72 ± 0.27          | 52.58 ± 0.37 | 928.28 ± 3.48    |

Figure 1. Microscopic images taken with a magnification of 200X: (a) UHMWPE, (b) UHMWPE 3% IBU and (c) UHMWPE 5% IBU.
associated with the CH$_2$ bending movement and at 720 cm$^{-1}$ with the CH$_2$ rocking vibration. For the IBU, bands between 3300 cm$^{-1}$ and 2500 cm$^{-1}$ correspond to the stretching of OH in the carboxylic acid groups and the vibration of C-H in CH$_3$ and in the phenyl functional groups. As previously mentioned, a characteristic band of IBU, with a high intensity, is located at 1720 cm$^{-1}$ representing the stretching of the carbonyl bond C=O$^{[23]}$.

### 3.2 Drug release test

The two UHMWPE formulations with IBU are classified as a possible drug-release system by diffusion, where the drug is eluted from the polymeric matrix over a prolonged time frame. The data obtained from the drug release tests were analyzed by mathematical methods developed from the First Law of Fick$^{[24,25]}$. The IBU calibration curve used to analyze

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**Figure 2.** FTIR spectra for (a) IBU, (b) UHMWPE, (c) UHMWPE 3% IBU and (d) UHMWPE 5% IBU.
the data obtained by spectrophotometry analysis is shown in
Figure S1 in the Supporting Information. The coefficients
used to calculate the amount of IBU released at each interval
of analysis were extracted from this curve, leading to the
total amount released by the system at the end of the test.
The results obtained over the 30-day period of IBU release
are shown in Figure 3 (%) and Figure S2 (mg/ml).

The results for the percentage of drug released show
that of the total drug theoretically incorporated in the
specimens, UHMWPE 3% IBU eluted approximately
7.8% and UHMWPE 5% IBU released 9.7% within the
first 7 days of the tests. The UHMWPE 3% IBU specimen
released 1.59 mg in the first week while UHMWPE 5% IBU
released 2.90 mg/ml. In the second week, around 12.00% of
the total was eluted from UHMWPE 3% IBU and 14.79%
from UHMWPE 5% IBU, representing 2.26 mg and 4.42 mg,
respectively. After 30 days, UHMWPE 3% IBU had released
3.81 mg and UHMWPE 5% IBU 7.05 mg, representing
19.62% and 23.91%, respectively. These data demonstrate
that the IBU release is more accentuated at the beginning of
the eluting period, followed by a more controlled and smooth
release over time. The total amounts theoretically incorporated
in each specimen were 20.39 mg for UHMWPE 3% IBU
and 29.95 mg for UHMWPE 5% IBU.

The kinetic release profiles (Figure S3-S5) for the materials
developed showed that the data for the UHMWPE 5% IBU
specimen best fitted the Higuchi’s Model (with a correlation
coefficient of 0.9942), while for the UHMWPE 3% IBU
specimen the best fit was obtained with the Korsmeyer-Peppas
model (with a correlation factor of 0.9949). Although the
UHMWPE 3% IBU release coefficient indicated a non-Fickian diffusion release\(^{24,25}\), with a release exponent
of 0.6091, the correlation coefficient obtained with Higuchi’s
Model was also higher than 0.99, which suggests that the
UHMWPE 3% IBU release may also be governed by Fickian
diffusion. An overview of the results obtained from the
kinetic analysis is given in Table 2.

The kinetic release coefficients obtained for the Higuchi
model confirm that the IBU release is governed by diffusion,
with values of less than 0.5, indicating transport governed by
Fick’s Law\(^{20,24}\). In addition, considering Higuchi’s Model,
the kinetic release coefficient of UHMWPE 3% IBU was
0.013, which is smaller than the value for UHMWPE 5% IBU
of 0.015. Therefore, the higher concentration of IBU in the
polymer seems to facilitate the diffusion of the drug, as a
greater portion of it may be in contact with the polymer matrix.

The application of mathematical models indicated that
the UHMWPE/IBU formulation as a system is governed
by Higuchi’s Model, especially the formulation with the
higher IBU concentration. This suggests that at the higher
concentration a greater portion of the anti-inflammatory is in
contact with the matrix, which would facilitate its diffusion
process. The results demonstrate a gradual drug release over
time, which is of interest for polymeric systems intended for
anti-inflammatory applications\(^{23}\), such as the prevention
of osteolysis. Furthermore, the drug release occurred
over a longer period compared with other systems, such as
bupivacaine\(^{16}\), vancomycin\(^{15}\) and gentamicin-loaded
UHMWPE\(^{5}\), in which antibiotic elution occurred over 5,
12 and 25 days, respectively. While antibiotic systems are
designed to achieve release in short periods after implantation
to avoid infections, an anti-inflammatory is expected to act
for a longer period, to mitigate capsular formation after
implantation as well as osteolysis due to particle generation.

3.3 Mechanical testing

The tensile curves obtained from the tests are shown in
Figures 4a, 4b and 4c for UHMWPE, UHMWPE 3% IBU
and UHMWPE 5% IBU, respectively. The three formulations
tested showed similar mechanical behavior and the error
between specimens within the same group was small.
The differences between the material compositions demonstrate a
decrease in their elastic modulus \(p<0.05\), as expected

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**Figure 3.** Drug release in percentage (%) over a 30-day period.

**Table 2.** Kinetic analysis results.

| SPECIMEN                  | UHMWPE 3% IBU | UHMWPE 5% IBU |
|---------------------------|---------------|---------------|
| KINETIC MODEL             |               |               |
| ZERO-ORDER MODEL          | 0.002         | 0.003         |
| HIGUCHI MODEL             | 0.013         | 0.015         |
| KORSMEYER-PEPPAS MODEL    | 0.008         | 0.013         |

K = release kinetic coefficient; r = correlation coefficient; n = release exponent
Results are summarized in Table 3. The results in Table 3 and Figure 5 indicate that the addition of 3% of IBU to the polymeric matrix decreased the elastic modulus by 16%. However, despite this decrease, the value remained within the range recommended for the use of UHMWPE as a biomaterial\(^{[22]}\). The 5% formulation provided a similar result, with a decrease of up to 20% in relation to the UHMWPE without the drug. These results suggest that the addition of IBU facilitates the molecular chain mobility and increases the ductility of the material.

No significant difference was noted for the tensile yield strength when comparing UHMWPE, UHMWPE 3% IBU and UHMWPE 5% IBU (p>0.05), which means that the addition of the drug did not have a notable impact on this parameter. The same behavior has been observed for alendronate and vancomycin-loaded UHMWPE, with drug contents of less than or equal to 5%.

### 4. Conclusions

The results reported herein demonstrate the incorporation of IBU, an anti-inflammatory drug, into UHMWPE for the first time. The consolidation process selected produced specimens with a homogeneous matrix, total polymer fusion and a good IBU dispersion, as demonstrated by the microscopy analysis. The addition of IBU resulted in minor effects on the crystallinity, melting point temperature, onset temperature and density. The drug release experiments demonstrated controlled and sustained drug release. Specimens with higher drug content resulted in greater percentages of release. The mechanical tests showed the influence of IBU on the mechanical properties of UHMWPE. The modulus of elasticity values for the two IBU formulations (0.0005 and 0.0025 mm/mm) were up to 20% lower when compared with the UHMWPE without the drug. Despite the impact on the mechanical properties, the results obtained were satisfactory, demonstrating that the addition of IBU had only a slight impact on the quasi-static mechanical properties of the UHMWPE. The wear behavior and cyclic load effects need to be evaluated in future work. Overall, the specimens of UHMWPE with IBU incorporated showed positive results with regard to their use in arthroplasty procedures. Further tests and improvements must be carried out to achieve a better combination of parameters and obtain a raw material suitable for knee implants, aimed at reducing the number of inflammatory reactions and, consequently, the number of revision surgeries.

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Supplementary Material

Supplementary material accompanies this paper.
Figure S1. IBU calibration curve.
Figure S2. Drug release in mg/day in 30 days.
Figure S3. Zero order model fit.
Figure S4. Higushi model fit.
Figure S5. Korsmeyer-peppas model fit.
This material is available as part of the online article from http://www.scielo.br/polimeros