Preparation of ibuprofen-loaded HDPE tubular devices for application as urinary catheters

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ABSTRACT: In this study, high-density polyethylene tubes with the incorporation of ibuprofen (IBP) were investigated with a view to their application as urinary catheters. The melt extrusion process was used to prepare the urinary catheters, and the influence of the manufacturing parameters on the material properties was evaluated. Samples prepared at lower temperature resulted in a more homogeneous material with a smoother surface, lower crystallinity, and better mechanical properties. The drug release was faster in the first 4 days, due to the accumulation of the drug on the outer surface of tubes. The concentration of IBP released was similar to the drug content in commercially available topical formulations (5%). Furthermore, after 2 days of immersion, the release achieved the concentration known to inhibit bacterial growth (6 mg/mL). These characteristics indicate that this material has good potential for application in urinary catheters. © 2017 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 2017, 134, 45661.

KEYWORDS: applications; biomaterials; biomedical applications; drug delivery systems; extrusion

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INTRODUCTION

Urinary catheterization is a common procedure in hospitals and is recommended for urine retention and urinary incontinence, for the administration of drugs and measurement of urine output and in cases of urological surgery.1,2 It is estimated that 25% of hospital patients will need a catheter at some point during their stay.3 Problems associated with urinary catheter insertion and long-term use include urothelial damage and exfoliation, bladder wall edema, inflammation, and biofilm-related infections.1,3–5 Inflammation may occur because of mechanical trauma during device insertion or as a consequence of infection, while bacterial contamination and infection can occur either right after placement or during long-term use. Recent studies have indicated that there is a relationship between inflammation and bacterial colonization. Guiton et al.6 investigated how the inflammatory response elicited by urinary catheter insertion impacts on Enterococcus faecalis biofilm formation. Inflammation triggered by urinary catheterization was observed to be essential for E. faecalis colonization, and minimal inflammation was observed when infection was simulated without the silicone tube.6 These results supported the hypothesis that inflammation created favorable conditions for bacterial growth.

Urinary catheters consist of flexible and soft materials such as latex, silicone, and polyethylene.7,8 Novel technologies have been developed to improve the performance of these devices; however, most of the modifications are focused on antimicrobial activity and lubrication.1,7,9,10 Fisher et al.9 proposed the impregnation of a urinary catheter with a mixture of sparfloxacin, rifampicin, and triclosan to functionalize the material with antimicrobial activity.9 In vitro tests demonstrated promising results against the colonization of clinically relevant strains like Staphylococcus aureus, Proteus mirabilis, and Escherichia coli.9 In addition to antimicrobial properties, new coating materials have been explored to reduce the friction between the catheter and the urethra mucosa in order to prevent tissue damage during the device insertion and minimize inflammation. Hydrogels were proposed as catheter coatings to provide lubrication and reduce mechanical trauma during catheter placement.10 However, the use of hydrogels has been associated with increased deposition of salt crystals on the material surface.11 The aggregation of crystals can block the catheter lumen, which usually requires the replacement of the device. A new urinary
catheterization generates more pain and increases the chances of inflammation and infection in the patient.\textsuperscript{10,12}

Although current technologies have led to improvements in the urinary catheter properties, new materials are still needed to improve the \textit{in vivo} performance of these types of biomedical devices. Combining a polymeric catheter with anti-inflammatory and antimicrobial drugs may help reduce pain and inflammation as well as avoid bacterial colonization. Ibuprofen (IBP) is a traditional nonsteroidal anti-inflammatory agent.\textsuperscript{13} Recent studies have shown that this compound and its co-formulations have an antimicrobial effect against bacteria and fungi relevant to the urinary tract, such as \textit{S. aureus} and \textit{Candida albicans}.\textsuperscript{13,14} Furthermore, IBP has high thermal stability, facilitating the catheter manufacture through the melt extrusion process, which has been widely employed in the production of polymeric drug delivery systems.\textsuperscript{15–17} Due to its attractive properties, IBP is a good candidate for incorporation into urinary catheters. The synergic anti-inflammatory and antimicrobial activities may help these devices achieve long-term functionality minimizing inflammation and bacterial infection.

This article proposes, for the first time, the use of IBP to manufacture polyethylene-based catheters loaded with a drug delivery system. The influence of the melt extrusion parameters on the material properties was investigated. The surface morphology, polymeric matrix structure, and mechanical properties, as well as the drug distribution and release characteristics, were studied. Promising results demonstrated the potential use of this drug in the manufacture of bioactive urinary catheters.

**EXPERIMENTAL**

**Materials**

High-density polyethylene (HDPE) was acquired from Braskem, with a melt index of 6.4 g/10 min (190°C/2.16 kg), density of 0.957 g/cm\textsuperscript{3}, and melt temperature of 132.53°C. IBP was acquired from Valdequimica Chemicals Ltd (Lot VCD56774) with a purity of 99.5% and a density of 0.59 g/cm\textsuperscript{3}.

**Melt Extrusion Process**

An Axplastic mono-screw extruder (model LAB AX-14) with an \textit{L/D} ratio of 20, equipped with an extrusion die for small diameter tubes with an outer diameter of 9 mm and inner diameter of 6 mm, was used to prepare the samples. The vertical extrusion process was carried out with an airflow passing through the extrusion die. The downstream cooling system was composed of cold air (10°C) and a chill ceramic plate (15°C). Table 1 shows the processing conditions employed in the fabrication of the tubes.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Screw speed (rpm)</th>
<th>Drug concentration (wt %)</th>
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<tbody>
<tr>
<td>150</td>
<td>160</td>
<td>25</td>
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</table>

**Table 1. Processing Parameters Applied to Prepare HDPE and HDPE/IBP Tubes**

Scanning Electron Microscopy

Philips (XL 30) and JEOL (JSM-6390LV) scanning electronic microscopes (SEM) were used to elucidate the macrostructure and microstructure of the HDPE and HDPE/IBP tubes. The samples were mechanically fractured in liquid nitrogen (cryogenic fracture) to evaluate their cross-sectional area. Energy dispersive X-ray spectrometry (EDS) was employed to assess the chemical elements in three distinct areas of each tube. Samples were coated with a thin layer of gold before the SEM-EDS analysis.

Fourier Transform Infrared Spectroscopy and X-ray Diffraction

Fourier transform infrared (FTIR) spectroscopy was performed using a Frontier NIC/NIR Perkin-Elmer spectrophotometer in attenuated total reflectance (ATR) mode. FTIR spectra were recorded from 32 scans in the range 4000–450 cm\textsuperscript{-1} with a resolution of 4 cm\textsuperscript{-1}. X-ray diffraction (XRD) analysis was carried out on a Philips X’Pert diffractometer (40 kV and 30 mA). Data were obtained using monochromatic Cu K\textsubscript{α} radiation in the 20 region between 5° and 40°. XRD patterns were analyzed by deconvolution with the aid of OriginPro 8.5 software. Peak identification was conducted based on the first integration and peak fit parameters based on the Gaussian model. The crystallinity of the samples was calculated as the ratio of the areas of crystalline peaks to the area under the entire spectrum, as proposed by Weidinger and Hermans.\textsuperscript{18}

**Mechanical Analysis**

A dynamic mechanical analysis (DMA) Q800 analyzer (TA Instruments) with a single cantilever clamp was used for the mechanical tests. A force rate of 2 N/min from 0 to 18 N was applied for quasi-static tests. DMA was performed to obtain values for the storage modulus (\(E'\)), loss modulus (\(E''\)), and tan delta (\(\delta\)) at a frequency of 1 Hz in the temperature range 30–140°C. The heating rate and strain values used in the experiment were 3°C/min and 0.3%, respectively. Five samples for each condition were used to perform the mechanical tests.

**Drug Concentration in HDPE Tubes**

To determine potential loss of the drug during the manufacturing process, the drug concentration in each tube was evaluated and compared to the theoretical value (10 wt %). Segments in three distinct locations of the tube were collected to evaluate the amount of drug incorporated into the polymer. Each segment was weighed and cut into three smaller samples to increase the surface area in contact with the solvent. Each section was placed in a vial containing 10 mL of methanol. The vials were kept in an ultrasonic bath for 2 h. Subsequently, the amount of drug released in methanol was determined using a UV/Vis spectrophotometer (PerkinElmer, model Lambda 750) at \(\lambda_{\text{max}}\) of 265 nm. The results were expressed as experimental drug concentration.

**Drug Release Test**

Specimens with known dimensions and drug concentration were placed in sealed vials with 20 mL of phosphate buffer solution (PBS, pH = 7.4). The tube extremities were sealed to ensure that the drug release measured related only to the outer surface of the tube. The vials were placed horizontally in a
Dubnoff bath (Faalk, Brazil) and shaken at 37.0 ± 0.5°C and 60 rpm to minimize the boundary effect. PBS was collected at predetermined time intervals and, after suitable dilution, the solution was analyzed using at $\lambda_{\text{max}}$ 265 nm. The drug concentration in each aliquot was obtained from a calibration curve constructed for IBP in PBS (five dilutions between 0.050 and 0.40 mg/mL). After each experiment, an equal volume of fresh solution was added to the vials.

**RESULTS AND DISCUSSION**

**SEM**

Figure 1 shows the cross-sectional areas of HDPE and HDPE/IBP tubes processed at 160°C/25 rpm. Overall, the average values for the outer diameter and wall thickness were 1.50 mm (±0.12) and 0.48 mm (±0.12), respectively. No notable differences between the HDPE and HDPE/IBP samples were observed. Moreover, the macroscopic surface features of the two materials were similar.

The microstructure of the HDPE and HDPE/IBP cross-sectional areas can be seen in Figure 2. The surface morphologies of the HDPE samples were similar and are represented by HDPE 160°C/25 rpm in Figure 2(a). Flat crack propagation (black arrows in Figure 2) was verified across the entire surface, and this is associated with the cryogenic fracture procedure. The SEM results for the HDPE/IBP showed mixed characteristics, where the surfaces consisted of regions with flat cracks (black arrows in Figure 2) as well as rougher areas (red arrows in Figure 2). The latter may have resulted from agglomeration of the pure drug and outgassing or from the association between HDPE and IBP, which emerged as a distinct morphology. EDS analysis was performed to determine the chemical composition of different locations along the cross-sectional area of the HDPE/IBP 150°C/25 rpm. Only carbon was detected in the flat cracks whereas oxygen and carbon were observed in areas with more asperities (red arrows), which supports the hypothesis that these regions contain IBP. The EDS spectra for the flat cracks and rougher areas of HDPE/IBP 150°C/25 rpm.
cracks and particles of HDPE/IBP 150 °C/25 rpm are shown in Figure 2(f).

The outer surfaces of the HDPE 160 °C/25 rpm and HDPE/IBP tubes are shown in Figure 3.

The SEM images of the tubes manufactured with pure HDPE showed low surface roughness regardless of the processing conditions [Figure 3(a) and Supporting Information Figures S1a–S1c]. On the other hand, for the HDPE/IBP tubes [Figure 3(b–e)], there was a relationship between the roughness and the manufacturing parameters. HDPE/IBP prepared at 150 °C/25 rpm had the smoothest surface in comparison to the other drug-loaded samples. A greater homogeneity of the outer surface and the cross-sectional area of this sample [Figure 2(b)] indicated a better interaction between the polymer and the drug. More particles and irregularities were observed for the HDPE/IBP samples prepared at 150 °C/35 rpm, 160 °C/25 rpm, and 160 °C/35 rpm. Aggregate-like structures similar to the pure drug20 were identified in samples processed at the higher temperature, as indicated by black arrows in Figure 3(d,e). This phenomenon may be associated with the solidification of the drug on the polymer surface. Therefore, the higher temperature resulted in an uneven distribution of IBP with the accumulation of the drug on the tube surface [Figure 3(d,e)] and in the polymeric matrix [Figure 2(d,e)].

**FTIR Spectroscopy and X-ray Diffraction**

Figure 4(a–d) summarizes the FTIR-ATR spectra for the pure HDPE, pure IBP, and HDPE/IBP tubes obtained applying different processing conditions.

Characteristic bands of HDPE and IBP were observed in the ATR-FTIR spectra as demonstrated in Figure 4(e,f), respectively.15,21 Stretching vibrations at 2950 and 2850 cm⁻¹ in the HDPE spectrum indicate symmetric and asymmetric stretching.
of C–H in CH₂ groups. The vibration band between 1350 and 1450 cm⁻¹ is associated with the bending movement of CH₂, whereas the rocking vibration of CH₂ is located at 720 cm⁻¹. The manufacturing process did not alter the FTIR spectra obtained for the HDPE samples, as shown in the Supporting Information Figure S2. The IBP spectrum showed overlapping of vibration bands in the region 3300–2500 cm⁻¹, which corresponds to the stretching of OH groups present in carboxylic acids, and the C–H vibrations of CH₃ and phenyl functional groups. Stretching of the carbonyl bond (C=O) is located at 1720 cm⁻¹ and has a high intensity, which is characteristic of the IBP spectrum. The ATR-FTIR spectra for HDPE/IBU samples exhibited both HDPE and drug-stretching bands, consistent with the microscopic features observed in the SEM images.

X-ray analysis was performed to evaluate the crystallinity and bulk organization of the HDPE and HDPE/IBP samples. Figure 5 shows the XRD patterns obtained for the pure HDPE and HDPE/IBP samples processed under different conditions. The pure HDPE spectra presented a strong reflection peak at 21.6° and a less intense peak at 24.0°, and these are associated with the orthorhombic unit cell structure of the (110) and (200) reflection planes, respectively. The HDPE and HDPE/IBP samples provided similar spectra regardless of the processing conditions (Supporting Information Figure S3 and Figure 5). No shifts or new peaks were observed, which indicates that the manufacturing process did not alter the HDPE crystalline structure. On the other hand, the absence of IBP peaks in spectra for the HDPE/IBP samples reveals the amorphization of this compound. Table II summarizes the crystallinity values obtained by applying this technique.

In general, the HDPE/IBU samples presented lower crystallinity in comparison to the pure HDPE, which suggests that the drug reduces the intensity of the interactions between the polymer

<table>
<thead>
<tr>
<th>Sample</th>
<th>Crystallinity (%)</th>
</tr>
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<tbody>
<tr>
<td>Pure HDPE</td>
<td>58.9</td>
</tr>
<tr>
<td>HDPE 150°C/25 rpm</td>
<td>56.8</td>
</tr>
<tr>
<td>HDPE 150°C/35 rpm</td>
<td>50.8</td>
</tr>
<tr>
<td>HDPE 160°C/25 rpm</td>
<td>68.4</td>
</tr>
<tr>
<td>HDPE 160°C/35 rpm</td>
<td>60.1</td>
</tr>
<tr>
<td>HDPE/IBU 150°C/25 rpm</td>
<td>46.1</td>
</tr>
<tr>
<td>HDPE/IBU 150°C/35 rpm</td>
<td>45.2</td>
</tr>
<tr>
<td>HDPE/IBU 160°C/25 rpm</td>
<td>49.0</td>
</tr>
<tr>
<td>HDPE/IBU 160°C/35 rpm</td>
<td>47.5</td>
</tr>
</tbody>
</table>

Figure 5. XRD patterns for (a) HDPE/IBP 150°C/25 rpm, (b) HDPE/IBP 150°C/35 rpm, (c) HDPE/IBP 160°C/25 rpm, (d) HDPE/IBP 160°C/35 rpm, and (e) pure HDPE. [Color figure can be viewed at wileyonlinelibrary.com]

Figure 6. Storage modulus values for (a) (I) HDPE 150°C/25 rpm, (II) HDPE 150°C/35 rpm, (III) HDPE 160°C/25 rpm, (IV) HDPE 160°C/35 rpm, and (b) (V) HDPE/IBP 150°C/25 rpm, (VI) HDPE/IBP 150°C/35 rpm, (VII) HDPE/IBP 160°C/25 rpm, and (VIII) HDPE/IBP 160°C/35 rpm. [Color figure can be viewed at wileyonlinelibrary.com]
molecules. According to previous studies, the crystalline arrangement of polymers can be suppressed by a second component in the polymeric blend.\textsuperscript{23,24} Higher crystallinity was verified for the HDPE and HDPE/IBP samples processed at 160°C/25 rpm, which can be explained based on the slower cooling rate and increased time of the polymer in the extruder. These conditions could facilitate the molecular mobility, enabling the rearrangement of polymer chains and resulting in a material with a greater crystallinity. Furthermore, the crystallinity results are consistent with the SEM images, where the samples with greater homogeneity presented a lower degree of crystal organization. The IBP molecule has a hydrophobic portion that can interact with the HDPE chains, aiding the dissolution of the drug in the polymeric matrix, which in turn reduces the links between HDPE molecules and the material crystallinity.

Mechanical Analysis
The results for the flexural modulus and storage modulus values obtained for the HDPE and HDPE/IBP are summarized in Table III and Figure 6, respectively. The HDPE samples processed at 160°C had higher flexural modulus and storage modulus values whereas the opposite behavior was observed for the HDPE/IBP samples. The higher crystallinity of the HDPE 160°C/25 rpm and HDPE 160°C/35 rpm samples may be related to the better mechanical performance of these samples. On the other hand, a better distribution of the drug in the HDPE/IBU 150°C/25 rpm and HDPE/IBU 150°C/35 rpm samples could reinforce the polymer matrix, increasing its rigidity.\textsuperscript{25}

The loss tangent (\(\tan \delta\)) was calculated for each sample to evaluate the relationship between the storage modulus (\(E'\)) and loss modulus (\(E''\)). The results are shown in Figure 7. \(\tan \delta\) values reflect the ability of a material to dissipate energy and to recover after being deformed.\textsuperscript{26,27} HDPE is known to have two transitions between 0 and 100°C, referred to as \(\alpha'\) and \(\alpha\). The \(\alpha'\) transition corresponds to intralamellar movements in the unit cells whereas the second mode refers to intracrystalline movements. As expected, peaks located in the \(\alpha\) region were observed for the HDPE and HDPE/IBP samples with higher crystallinity. Moreover, less intense and wider peaks were obtained for the HDPE/IBP samples. It has been proposed that the presence of IBP reduces the mobility of the polymer matrix, decreasing the ability of material to dissipate the vibrational energy.\textsuperscript{26,27}

Drug Concentration in HDPE Tubes
The amount of IBP incorporated into the HDPE tubes under different processing conditions is summarized in Table IV.

<table>
<thead>
<tr>
<th>Samples</th>
<th>Experimental drug concentration (%)\textsuperscript{a}</th>
</tr>
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<tbody>
<tr>
<td>HDPE/IBU 150°C/25 rpm</td>
<td>81.3 ± 2.3</td>
</tr>
<tr>
<td>HDPE/IBU 150°C/35 rpm</td>
<td>82.6 ± 2.0</td>
</tr>
<tr>
<td>HDPE/IBU 160°C/25 rpm</td>
<td>80.0 ± 1.1</td>
</tr>
<tr>
<td>HDPE/IBU 160°C/35 rpm</td>
<td>83.1 ± 0.7</td>
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\textsuperscript{a}Percentage of drug relative to the 10 wt % used in the manufacturing process.

Figure 7. \(\tan \delta\) of (a) (I) HDPE 150°C/25 rpm, (II) HDPE 150°C/35 rpm, (III) HDPE 160°C/25 rpm, (IV) HDPE 160°C/35 rpm, and (b) (V) HDPE/IBP 150°C/25 rpm, (VI) HDPE/IBP 150°C/35 rpm, (VII) HDPE/IBP 160°C/25 rpm, and (VIII) HDPE/IBP 160°C/35 rpm. [Color figure can be viewed at wileyonlinelibrary.com]
polymer/drug mixture, reducing its availability in the middle and end portions of the equipment. The average amount of drug incorporated showed no significant differences according to the processing conditions, which verifies good reproducibility of the manufacturing process.

Drug Release Test
The results obtained for the IBP release from the HDPE/IBP tubes over the 28-day test period can be observed in Figure 8.

The IBP release profiles for the HDPE/IBP samples are not linear. A faster release was observed for all samples in the first 4 days followed by a slower release on subsequent days. Deposition of the drug on the tube surface and entrapment of drug in the tube matrix may explain these release profile characteristics. Furthermore, due to the reduced permeability of HDPE in the aqueous medium, a low diffusion rate for IBP is expected. After 24 h, more than 5% of the IBP had been released from all samples, which is the concentration employed in topical formulations for effective anti-inflammatory activity. The concentration after 7 days (6 mg/mL) is known to exhibit anti-bacterial growth against strains, which are clinically relevant to the urinary environment. The concentration (0 and 10 wt %) on the material properties was evaluated. The temperature was the main parameter affecting the material properties. Samples processed at the lower temperature resulted in a more homogeneous material with a smoother surface, lower crystallinity, and better mechanical properties. The degree of drug release was higher in the first 4 days, due to the accumulation of drug on the outer surface of the tubes. The IBP concentration released was similar to the drug contents of commercially available topical formulations (5%). Furthermore, after 2 days of immersion, the release achieved the concentration that is known to inhibit bacterial growth (6 mg/mL). These characteristics indicate that this material has significant potential for application as a urinary catheter.

CONCLUSIONS
HDPE urinary catheters loaded with IBP were prepared through the melt extrusion process. The influence of screw speed (25 and 35 rpm), temperature (150 and 160 °C), and drug concentration (0 and 10 wt %) on the material properties was evaluated. The temperature was the main parameter affecting the material properties. Samples processed at the lower temperature resulted in a more homogeneous material with a smoother surface, lower crystallinity, and better mechanical properties. The degree of drug release was higher in the first 4 days, due to the accumulation of drug on the outer surface of the tubes. The IBP concentration released was similar to the drug contents of commercially available topical formulations (5%). Furthermore, after 2 days of immersion, the release achieved the concentration that is known to inhibit bacterial growth (6 mg/mL). These characteristics indicate that this material has significant potential for application as a urinary catheter.

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