Polymer Testing 71 (2018) 312–317

Contents lists available at ScienceDirect

Polymer Testing

journal homepage: www.elsevier.com/locate/polytest

Product Performance

Additive Manufacturing of PE/fluorouracil/progesterone intrauterine device for endometrial and ovarian cancer treatments

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ARTICLE INFO

Keywords:
Polyethylene
5-Fluorouracil
Progesterone
Intrauterine device
Cancer treatment

ABSTRACT

Progesterone and fluorouracil loaded-intrauterine drug delivery systems were prepared using selective laser sintering (SLS). PE/FU/PG IUDs had small particles of fluorouracil spread over the IUD surface and progesterone was dispersed within the porous PE matrix. The existence of additional peaks related to the fluorouracil and progesterone confirm their presence at 10% concentration by both DSC and FTIR. The PE/FU/PG IUDs prepared using higher laser power (5 W) had the highest flexural modulus, probably due to better PE particle coalescence. The PE/FU/PG IUDs initially showed rapid drug release due to the hydrophilic characteristics of fluorouracil. This is a desirable profile as it provides a high initial concentration of the drug locally to the cancer cells following implantation. The slow and controlled release of the progesterone presented by PE/FU/PG IUDs is interesting for sustained levels of the hormone therapy agent in the region of the tumor with the potential to enhance the cancer treatment.

1. Introduction

Endometrial and ovarian cancers are common types of gynecological cancer and they affect more than 60,000 and 20,000 women, respectively, every year [1]. Endometrial cancer results from the anomalous growth of cells in the endometrium due to a hormone imbalance that causes sustained unopposed estrogen action. Estrogen regulates the proliferation of the endometrial lining while progesterone antagonizes estrogen driven growth. When there is either deficient progesterone action or excess estrogen action, pathologies such as endometrial adenocarcinoma or endometrial hyperplasia may be triggered [2,3]. Endometrial cancer is most frequently diagnosed among menopausal women from 55 to 64 years old, although, around 7% of cases are found in younger and reproductive-aged women [1,4]. The conventional therapy for endometrial cancer is staging laparotomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy, followed by adjuvant radiation for patients with elevated risk for local recurrence. However, hysterectomy may not be an acceptable option for young women who have not yet reached childbearing age as well as for patients with multiple comorbidities. Furthermore, radiotherapy and chemotherapy usually use systemic approaches, which are known to cause side effects such as cardiopathy and respiratory problems [4,5].

Ovarian cancer is usually referred to as the “cancer that whispers”, because of late stage detection. The diagnosis is often made after the cancer cells have metastasized and the cancer is advanced. Known for being the most lethal gynecological malignancy, this cancer is the fifth-leading cause of cancer deaths among women. Although, the causes of ovarian cancers are unknown, genetic factors, reproductive history, age, body size and personal medical history have all been associated with this pathology [3,6]. Despite the improvements in cancer treatments, including surgery and chemotherapy, the mortality rate is still high because the current therapies for ovarian cancer are not very effective. Chemotherapy has led to a response rate from 3 to 30% while the average survival rate of 5-years for radiation therapy is 10%. The patients with less-than-25% and greater-than-75% cytoreduction have an average difference in survival of 11 months [7]. Therefore, new therapies for ovarian cancer are extremely desirable.

In order to preserve childbearing potential and avoid surgery, progesterone-based hormone therapy has demonstrated a protective role for both endometrial and ovarian cancer. However, side effects such as nausea, vomiting and headaches are associated with the oral treatment [2,6]. An alternative route for the administration of progesterone via an intrauterine drug delivery system has been proposed. Previous results have shown that an intrauterine system containing levonorgestrel (LNG) is more effective in suppressing endometrium cancer than the oral treatment. Furthermore, the dosage can be reduced significantly,

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https://doi.org/10.1016/j.polymertesting.2018.09.023
Received 7 August 2018; Accepted 18 September 2018
Available online 19 September 2018
0142-9418/

which minimizes the side effects and optimizes patient compliance [2]. 5-Fluorouracil (5-Fluoro-1H, 3H-pyrimidine-2,4-dione, 5-FU) is an anticancer drug used in the treatment of several kinds of cancer in both the early and advanced stages. The efficacy and absence of any effects on fertility make this drug a good candidate for endometrial and ovarian cancer treatment via an intrauterine drug delivery system [8]. In this study, progesterone and fluorouracil loaded-intrauterine drug delivery systems were prepared using selective laser sintering (SLS). SLS is a type of Additive Manufacturing that enables fast processing of three-dimensional devices from different materials and blends of materials, including high density polyethylene which is already used as a carrier due to its biocompatibility and inertness [9]. This technology is also known for overcoming geometry limitation characteristics of conventional manufacturing techniques and can produce more complex architectures [10].

This study details for the first time the production and characterization of an intrauterine device loaded with two distinct drugs for synergic activity in cancer treatment. SLS was used due to the greater facility for achieving an optimum mixture of raw materials and produce controlled porous matrix. Combining the promising effects of hormone therapy using progesterone with the well-established efficacy of 5-FU, we developed a new product with promising potential use in endometrial and ovarian cancer treatments. Here, we describe the manufacturing process, the physical-chemical and mechanical properties of the device as well as the drug release profile of progesterone and 5-FU.

2. Experimental

2.1. Materials

The materials used in this study were as follows: the polymeric powder to build the PE-based intrauterine device was commercial polyethylene (HD 7555, Ipiranga S.A.) with an average molecular weight of 140,000 to 250,000 g/mol, melting temperature (Tm) of 133 °C, melt flow index of 2.65 g/10 min and density of 0.89 g/cm − 3 at 25 °C. The particle size of the powder was from 125 to 212 μm. The fluorouracil (5-FU) was manufactured by Hubei Gedian Pharmaceutical Co. and has a melting temperature of 282 °C. The progesterone (PG) was manufactured by IFFECT CHEMPHAR and provided by Henrifarma Chemicals and Pharmaceuticals. It has a melting temperature of 130 °C. The powder blend was prepared by mechanical mixing using a Y-type rotator for 10 min at 30 rpm.

2.2. Manufacturing IUDs by selective laser sintering

The pure PE and PE/FU/PG IUDs (dimensions of 35 × 5 × 1.4 mm) were sintered (Fig. 1) in a selective laser sintering system with a 9 W power CO_2 laser and laser beam diameter of 250 μm. This study was performed in the open air and the powder bed temperature was 45 °C. The laser scanning speed was maintained at 350 mm/s. The building layer thickness used was 250 μm and the spacing between the laser scans was 125 μm. The laser density energies used to obtain the IUDs are shown in Table 1.

2.3. Infrared spectroscopy

Infrared spectra of the polymers were obtained using a Perkin-Elmer Frontier MIR/NIR spectrophotometer in the attenuated total reflectance (ATR) mode, performing 20 scans at a resolution of 4 cm^{-1}, in order to characterize the polymer and blend absorbance peaks.

2.4. Scanning electron microscopy and differential scanning calorimetry

The morphology of the IUDs were examined by scanning electron microscopy (SEM), using an XL 30 Phillips microscope. The specimens were coated with gold in a Bal-Tec Sputter Coater SCD005. Differential scanning calorimetry (DSC) curves were obtained using a differential scanning calorimeter (Perkin Elmer) from 0 to 300 °C at a heating rate of 10 °C/min. The average sample size was 5 mg and the nitrogen flow-rate was 25 cm^3/min.

Fig. 1. PE/FU/PG IUD manufactured by selective laser sintering.

Table 1
Pure PE and PE/FU/PG IUDs manufactured with different laser energies.

IUD	PE/FU/PG content (%)	Laser power (W)
PE	100/00/00	3.0
PE	100/00/00	5.0
PE/FU/PG	80/10/10	3.0
PE/FU/PG	80/10/10	5.0

2.5. Mechanical tests

A DMA Q800 system of TA instruments with a single cantilever clamp was used for the mechanical tests of the SLS IUDs (dimensions 30 × 5 × 1.4 mm). A ramp of 2N/min from 0 to 18N was applied for the quasi-static flexural tests. The fatigue test was performed applying an oscillatory deformation. The amplitude used was 750 μm in both directions, at a frequency of 1 Hz, at 35 °C.

2.6. Drug release and recovery of the incorporated fluorouracil and progesterone

The drug release tests were performed by placing a sample of 1 × 0.5 cm (~0.120 g) in a vial containing 20 mL of phosphate buffer pH 7.4. The tests were performed at 37 ± 0.5 °C using a Dubnoff bath (Quimis SA, Brazil) with horizontal shaking at *(the rate of)* 60 rpm. At predetermined intervals, the total solution was withdrawn and replaced by fresh solution to maintain unimpaired dissolution. The simultaneous quantification of progesterone and 5-FU was determined by High Performance Liquid Chromatography (HPLC) (Agilent 1100 Chromatography system). The separations were achieved by gradient elution (Table 2) with a Luna C18 column 4.6 μm (150 × 4.6 mm) from Phenomenex® (USA), mobile phase A: water, and B: methanol, temperature 30 °C, injection volume of 20 μL, and detection at 239 nm. The amount of progesterone and 5-FU released was expressed as a % over time (see Table 3).