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Fabrication and characterization of medical grade polyurethane composite catheters for near-infrared imaging

André T. Stevenson Jr. [a], Laura M. Reese [f], Tanner K. Hill [c], Jeffrey McGuire [d], Aaron M. Mohs [c], Raj Shekhar [e], Lissett R. Bickford [b, d, f], Abby R. Whittington [a, b, g, *]

[a] Department of Materials Science and Engineering, Virginia Tech, Collegiate Square, Suite 302, Blacksburg, VA 24061, USA
[b] School of Biomedical Engineering and Sciences, Virginia Tech, Kelly Hall, Blacksburg, VA 24061, USA
[c] School of Biomedical Engineering and Sciences and Wake Forest Institute for Regenerative Medicine, Wake Forest University Health Sciences, Winston-Salem, NC 27157, USA
[d] Department of Mechanical Engineering, Virginia Tech, Randolph Hall, Blacksburg, VA 24061, USA
[e] Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Medical Center, Washington, DC 20010, USA
[f] Department of Biomedical Engineering and Mechanics, Virginia Tech, Kelly Hall, Blacksburg, VA 24061, USA
[g] Department of Chemical Engineering, Virginia Tech, Randolph Hall, Blacksburg, VA 24061, USA

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ABSTRACT

Peripherally inserted central catheters (PICCs) are hollow polymeric tubes that transport nutrients, blood and medications to neonates. To determine proper PICC placement, frequent X-ray imaging of neonates is performed. Because X-rays pose severe health risks to neonates, safer alternatives are needed. We hypothesize that near infrared (NIR) polymer composites can be fabricated into catheters by incorporating a fluorescent dye (IRDye 800CW) and visualized using NIR imaging. To fabricate catheters, polymer and dye are dry mixed and pressed, sectioned, and extruded to produce hollow tubes. We analyzed surface roughness, stiffness, dye retention, NIR contrast intensity, and biocompatibility. The extrusion process did not significantly alter the mechanical properties of the polymer composites. Over a period of 23 days, only 6.35 ± 5.08% dye leached out of catheters. The addition of 0.025 wt% dye resulted in a 14-fold contrast enhancement producing clear PICC images at 1 cm under a tissue equivalent. The addition of IRDye 800CW did not alter the biocompatibility of the polymer and did not increase adhesion of cells to the surface. We successfully demonstrated that catheters can be imaged without the use of harmful radiation and still maintain the same properties as the unaltered medical grade equivalent.

1. Introduction

Catheters offer a variety of uses in the clinical setting, including the delivery of chemical agents (such as drugs and imaging dyes), nutrients and blood to patients [1]. Peripherally inserted central catheters (PICCs), which are inserted into veins not in the chest or abdomen, are widely used in neonatal and pediatric intensive care units (ICUs) for long-term delivery of therapeutics with lower infection rates compared to central venous catheters [2–4]. However, the long-term placement of PICCs increases the likelihood of migration of the catheter from the target location, resulting in adverse effects to the patient [2,5]. These side effects include vascular perforation (pierced blood vessel), venous thrombosis (blocked blood vessel), and pericardial tamponade (pressure on the heart), all of which can result in death [2,6]. In addition to PICC migration, insertion can be difficult and often requires multiple adjustments in order for the tip of the catheter to be correctly placed [3]. Only 66% of catheters are inserted correctly the first time and 2–10.5% of catheters dislodge throughout the course of implantation [3,6]. To determine and monitor the location of the catheter, clinicians utilize X-ray imaging. Despite X-ray being the gold standard, neonates are particularly at an increased risk from prolonged radiation exposure involved in X-ray imaging, including proclivity to develop lymphoma and other forms of cancer at a later stage of their life [7–12]. Thus, there is a clear medical need for catheters that can be imaged without the use of ionizing radiation in order to avoid any inherent risks to the developing child.

* Corresponding author. Department of Materials Science and Engineering, Virginia Tech, Collegiate Square, Suite 302, Blacksburg, VA 24061, USA. Tel.: +1 540 231 0665; fax: +1 540 231 8919.
E-mail address: awhit@mse.vt.edu (A.R. Whittington).

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An attractive alternative to X-ray imaging is near infrared (NIR) imaging that allows images to be acquired without harmful side effects [13]. The main tissue components that absorb light are hemoglobin and melanin which have high absorption bands at wavelengths shorter than 600 nm and water which begins to absorb significant amounts of light at wavelengths above 1150 nm [14,15]. Thus, there is a window (between ~ 650 nm–950 nm) where biological tissue components do not absorb significant light, allowing imaging at depths ranging from 1 to 4 cm [13,16,17]. In this article, we report the fabrication of NIR fluorescent enhanced catheters through the integration of a near-infrared sensitive agent, IRDye 800CW, within a polymer matrix. The objective of this study is to demonstrate fluorescent-polymer composites as improved PICC materials, which we anticipate will provide physicians with a safe and effective substitute to imaging catheters without the use of ionizing radiation.

We provide details of the integration of medical grade thermoplastic polyurethane (TPU) with IRDye 800CW extruded as a PICC. Surface and mechanical testing results are reported to show the influence of the fluorescent agent incorporated within the TPU matrix. To test the safety of these altered PICCs in a biological setting, biocompatibility studies were conducted to analyze any adverse effects of the new PICC on endothelial cells.

2. Materials and methods

2.1. Materials

Aromatic polyether-based medical grade TPU pellets (Texin RxT90A) was provided as a gift from Bayer Material Science (Pittsburgh, PA). IRDye 800CW Carboxylate infrared dye was obtained from LI-COR Biosciences (Lincoln, NE). Phosphate buffered saline powder (PBS, pH 7.4) was purchased from Fisher Scientific and a 1X solution was prepared in milli-Q deionized water (EMD Millipore). A fabricated medical grade PICC (Hospital TPU) was provided as a gift from Cook® Medical (Winston Salem NC, USA). Human Umbilical Vein Endothelial (HUVEC) cells and complete endothelial growth medium (EGM Bulletkit) were obtained from Lonza and prepared according to manufacturer's instructions. Alamar Blue, Calcein AM and Propidium Iodide were purchased from Fisher Scientific.

2.2. Thermal analysis characterization and catheter fabrication

The thermal degradation temperatures were analyzed to verify that both the TPU and IRDye 800CW would not decompose during the extrusion process. The temperature at which the samples began to decrease sharply in weight was determined to be the onset of degradation. Thermal degradation temperatures were evaluated using a Q50 Thermogravimetric Analyzer (TGA) (TA Instruments, New Castle, DE). Analysis was conducted in nitrogen gas at 20 °C/min (n = 3).

Thin films of TPU with and without IRDye 800CW (TPU Composite and Plain TPU) were fabricated using a hydraulic platen press (PHI, City of Industry, CA). As illustrated in Figs. 1 and 5 grams of TPU with 0.025 wt% IRDye 800CW was pressed for 30 s, sectioned into 5 mm squares, and fed into a Haake Minilab Micro Compounder (Thermo Fisher Scientific, Waltham, MA). Catheters were extruded at 100 rpm at 195 °C using a custom die fabricated via additive manufacturing (Solid Concepts Inc., Austin, TX). Extruded sections of Plain TPU and TPU Composites were imaged and outer diameter measurements were obtained using calipers (n = 3). Inner diameter measurements were obtained using scanning electron microscopy (SEM), and thickness measurements were calculated by subtracting the inner radius from the outer radius.

2.3. Surface analysis and mechanical testing

Scanning electron microscopy (Field Emission SEM, LEO Zeiss 1550, Tokyo, Japan) was used to examine the outer surface and cross-sectional features of the catheters. Outer surfaces and cross-sectional features were imaged before and after retention studies of the extruded tubes. Atomic force microscopy (Veeco MultiMode AFM, Plainview, NY) was used to obtain quantitative outer surface roughness measurements of the Hospital TPU, Plain TPU, TPU Composite, and Leached TPU Composite samples. Surface roughness was measured using contact mode (n = 3). Tensile testing was performed using an Instron 5500R (Instron, Norwood, MA) at a cross head speed of 50 mm/min on Hospital TPU, Plain TPU, TPU Composite, and Leached TPU Composite (n = 3) samples. To prevent slipping, an Instron clamp with grooved indentations was used. Uniaxial tensile testing was performed on all samples until material failure. The elastic modulus was determined to be the slope from the linear low strain region (0–10%) of the curve. The point of fracture was determined to be the ultimate tensile strength (UTS).

2.4. Retention studies, fluorescence imaging, and photodegradation analysis

To simulate the long-term effect of being implanted *in vivo*, catheters were leached in PBS for 23 days to determine the amount of dye retained within the matrix. TPU Composite tubes were cut into thin slices, weighed, and added to a black 96 well plate containing 200 μl PBS. Leaching of IRDye 800CW from the TPU Composite (n = 8) was analyzed under physiological conditions (pH ~7.4, 37 °C, with gentle agitation) in a water bath. The water bath was covered to prevent photobleaching. Each day, tube slices were transferred to the successive well containing fresh PBS, and the previous day's saline was analyzed using a microplate reader (BioTek Multi-Mode, Winooski, VT) with excitation at 765 nm, emission at 794 nm, and sensitivity at 100. To determine the amount of IRDye 800CW retained, a calibration curve containing serial dilutions of IRDye 800CW in PBS was used (0–0.00030 wt%) ($R^2 = 0.99$).

In order to ensure measurements were sensitive, uniform, and low in noise interference, imaging was performed using a LI-COR Pearl® Impulse NIR Imaging System (Lincoln, NE) with analysis conducted in LI-COR Pearl® Impulse Software to compute the signal-to-noise ratio (SNR) (Mean of Sample/Standard deviation of Background). All imaging was performed using a thermoelectrically cooled charged cooled detection camera with the following specifications: laser wavelength was 785 nm, resolution was 85 μm, and acquisition speed was less than 30 s per scan. To determine the optimal loading concentration, thin films of TPU containing 0.025, 0.075 and 0.125 wt% IRDye 800CW were placed in the LI-COR Pearl® and imaged. Superflab® tissue mimic (Radiation Products Design Inc. Albertville, MN) was placed on top of the thin films (up to 2 cm thick) to determine the imaging resolution.

For fluorescence imaging of Plain TPU and TPU Composite samples, Plain TPU (n = 1) and TPU Composite (n = 4) was placed in the LI-COR Pearl®, automatic shape

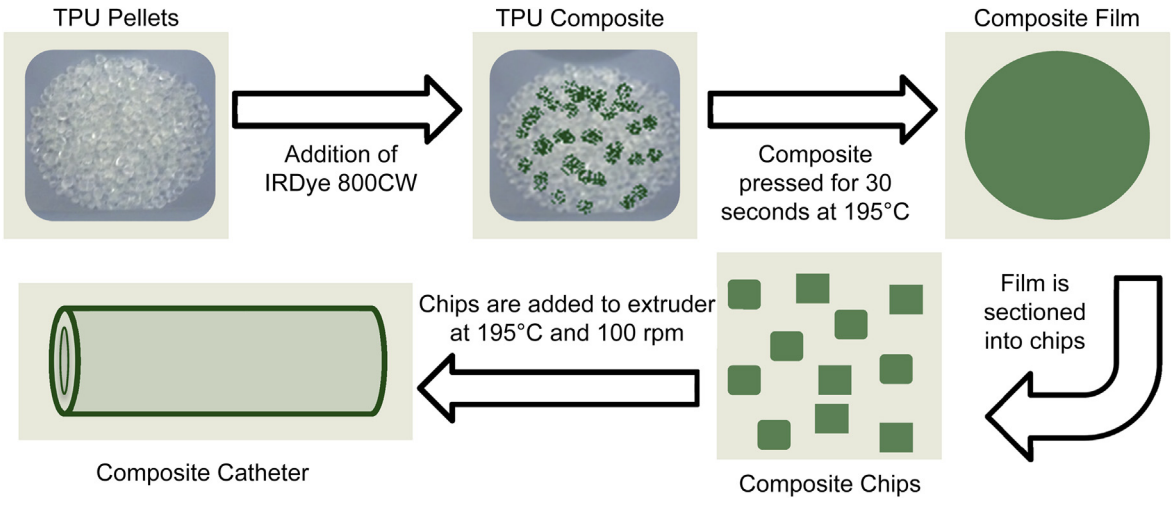

Fig. 1. . Schematic of the fabrication process for composite catheters.