Rapid Fabrication and Characterization of Pediatric Nitric Oxide (NO) Releasing Catheters

Biomedical Engineering

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Introduction

Intravascular (IV) catheters used in clinical practice can activate platelets, leading to thrombus formation and stagnation of blood flow. Currently, there are 500,000 admissions to neonatal intensive care units each year. Most of these babies require management through central venous, umbilical venous, or umbilical artery for the administration of parental nutrition, chemotherapy, blood products, fluids and life-saving medications through IV catheters. Catheter fabrication platforms for experimental research usually rely on slow (turnaround time =up to a 4-day) dip-coating methods that also unfortunately produce non-uniform catheter wall thickness and high surface roughness. The aim of this research was to fabricate silicone catheters using an automated spin-casting platform (turnaround time =0.015 days) to ensure uniform wall thickness and reproducibility. Furthermore the catheters were modified to release nitric oxide, an anticlotting and antibacterial biological molecule.

Materials and Methods

A spin casting method shown in **Figure 1** was used to cast silicone resin into hollow cylinder shapes. A casting die into which the polymer resin was dispensed was driven by a high rpm motor. Centrifugal forces acting on the resin from the die spinning at 2600 to 3600 rpm creates an axial hollow core within the resin. Heat at 70ºC was applied to cure the resin in approximately 20 minutes followed by a 5 minute cool down. To functionalize the catheter to release NO, a mixture of diazeniumdiolated dimethyl-1,6-hexadiamine (DMHD-N_2O_2) NO donor and polydimethylsiloxane (PDMS) resin was spin-casted onto the cured catheter's luminal surface. A final layer of PDMS was casted onto the catheter. A pH stabilizing agent, polylacticglycolic acid (PLGA), was added into the catheter to aide NO release and analyze its release kinetics. NO release from the catheters were measured using a GE 280i Nitric Oxide analyzer. Samples were submerged in phosphate buffer saline (PBS) (pH 7.34, 37 ºC) for one hour measurements. PLGA and the NO donor used for this study are shown in **Figures 2A** and **2B** respectively.

Results and Discussion

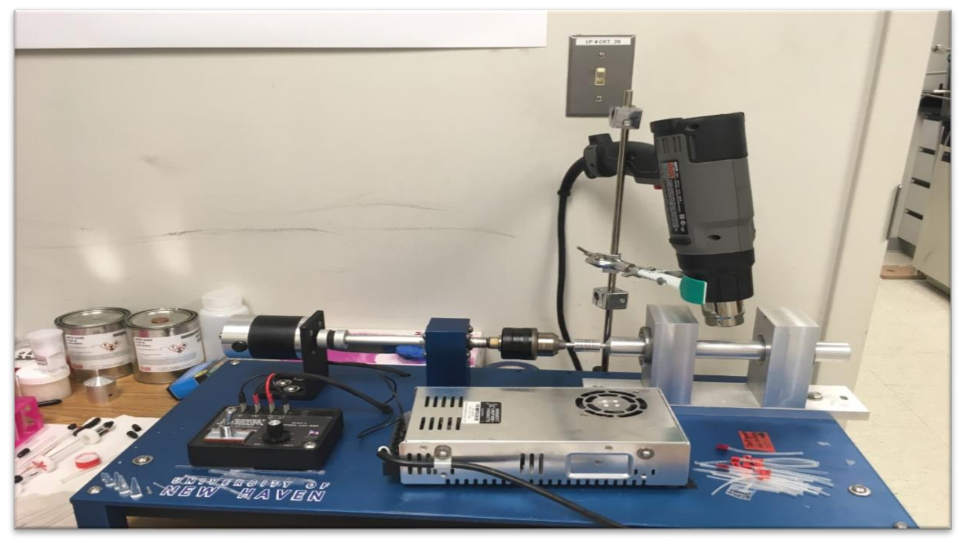

Figure 1: **Casting apparatus responsible for converting silicon resin into hollow catheters showing motor(left) and mechanical die(right)**

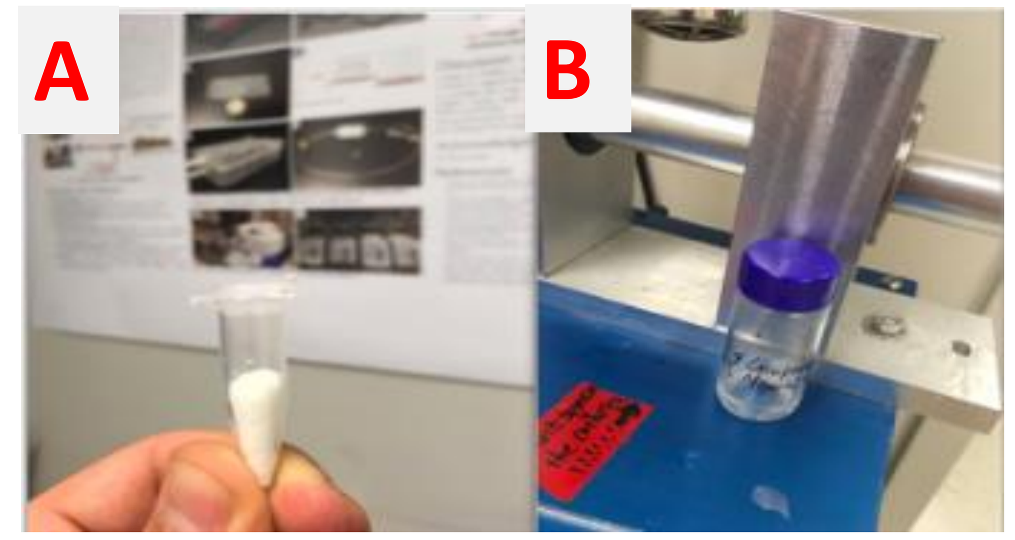

***Figure 2:* PLGA Stabilizer sample A) Compound containing charged NO conjugates mixed with mineral spirit B)**

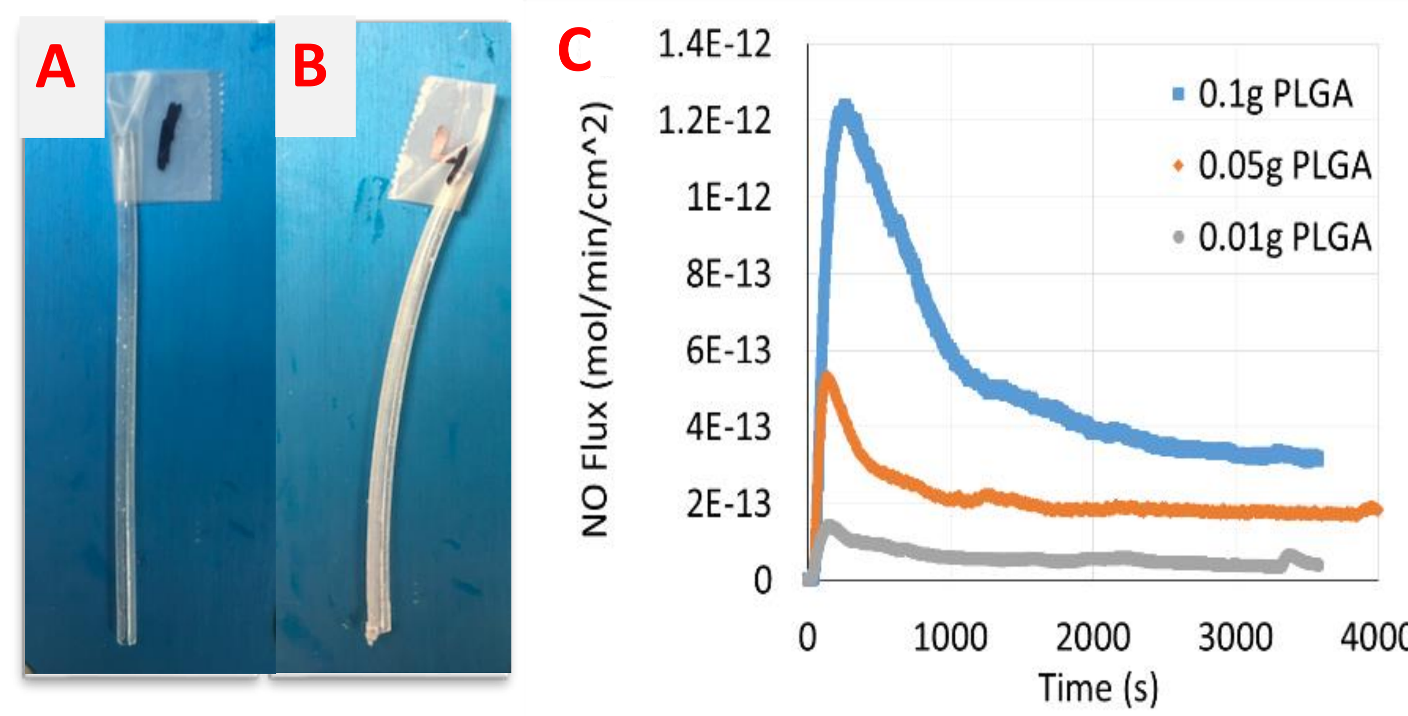

***Figure 3*: Control catheter A) and nitric oxide releasing catheter B) and one hour nitric oxide flux profiles of catheters modified with either 0.1 g, 0.05 g or 0.01 g of PLGA C).**

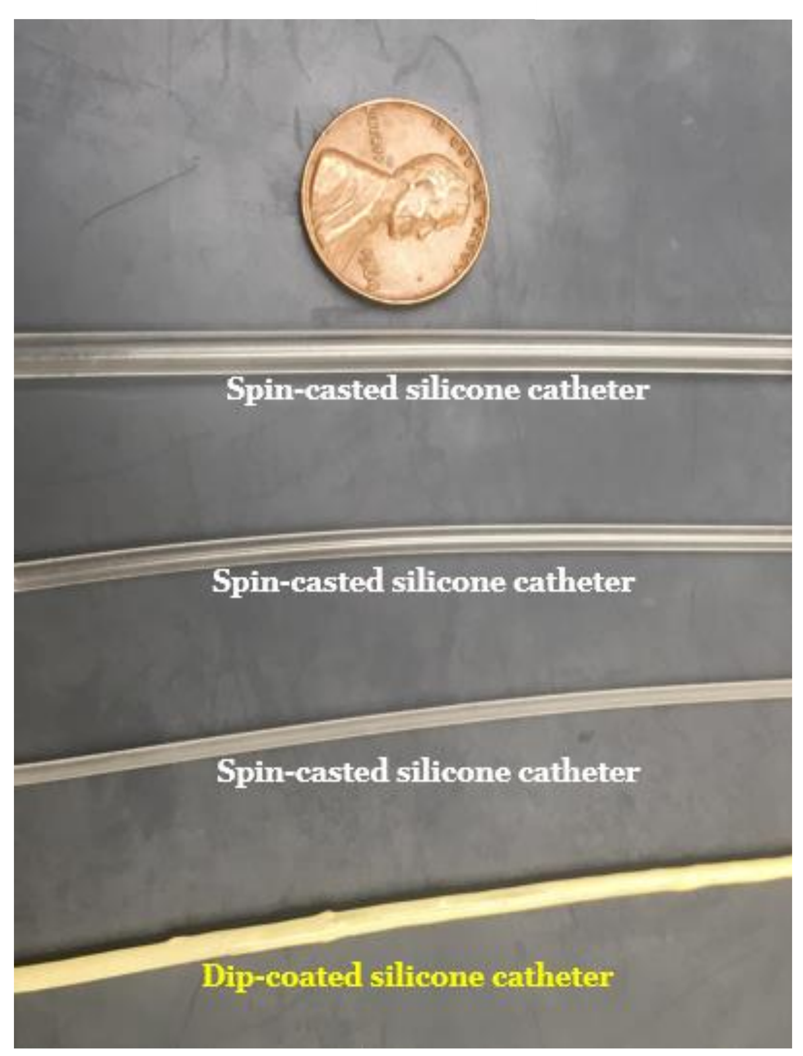

***Figure 4:* Comparison between spin-casted catheter versus dip-coated catheter**

Catheters fabricated measured 4.9 ± 0.7 cm long with 0.11 ± 0.01 cm outer diameter and 0.07 ± 0.01 cm inner diameter. The wall thickness measured 0.02 ± 0.003 cm. The composition of NO releasing catheters all had 3.4% of DMHD-N_2O_2 with either 0.1 g or 0.05 g or 0.01 g of PLGA. A control catheter**(figure 3A)** and nitric oxide releasing catheter**(figure 3B)** are shown in **Figure 3.** Three samples were analyzed for each catheter group containing the above PLGA additive. As shown in **Figure 3(C)**, the level of NO flux was a function of PLGA amount and time. Catheters with higher PLGA content released higher NO levels within the measurement timeframe.

The representative release profile shows 0.01 x 10^{-10} mol/min/cm² peak flux for 0.1g PLGA catheter compared to 0.005 x 10^{-10} mol/min/cm² for 0.05 g PLGA catheter. A schematic in **Figure 4** demonstrates the comparison between the spin-casted method versus the dip-coated catheter method. The spin-casting catheter obtained a more uniform wall thickness along with a smoother outer surface.

Conclusions

The spin-casting platform provided an easy-to-use method to rapidly fabricate silicone catheter with different material compositions. Catheters generally had uniform wall thickness, but however misalignment of the casting die can lead to small variations in wall thickness. It was observed that the PLGA content had an effect on the NO released rate. Further studies are needed to modulate NO release from catheters by optimizing the material composition. Ultimately a long-term NO releasing catheter can limit complications such as blood coagulation and bacterial colonization associated with indwelling catheters.

Acknowledgements

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