3D-Printed Antibacterial Silicone Devices Based Nitric Oxide Release from S-nitrosothiol Crystals

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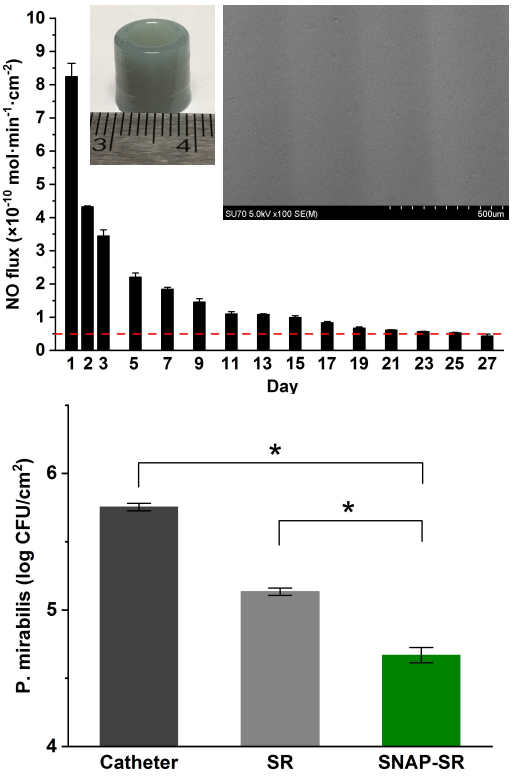
Statement of Purpose: Healthcare-associated infections (HAIs) are one of the leading threats to modern medicine because they significantly increase the morbidity and mortality of patients as well as their length of stay in the hospital. HAIs are caused by surgical procedures or the use of invasive medical devices. The device-associated infections account for 60-70% of HAIs. Therefore, prevention and reduction of medical device-associated infections are imperative.

As a natural anti-infective drugs, nitric oxide (NO) has potent bactericidal, anti-thrombus, anti-inflammatory, and pro-angiogenic properties. Release of NO from biomedical devices has the potential to significantly improve their biocompatibility and antimicrobial properties. Traditional methods to functionalize biomedical devices with NO donors include coating and impregnation. In the coating method, the NO donor solutions are applied onto the surface of a device. Generation of uniform coating from a solution is challenging especially for complex shapes. Due to the low thickness of coating, the amount of released NO is usually limited. In the impregnation method, NO donors are introduced into the polymer matrix of the device with assistance of an organic solvent that is able to swell the polymer. Swelling of the polymer typically changes the mechanical or surface property of the original devices. It also requires excessive solvents and drugs, and the swelling and drying processes are time-consuming. Herein, we devised the first 3D printing strategy for single-step fabrication of NO-releasing polymer devices.

Methods: S-nitroso-N-acetylpenicillamine (SNAP) is synthesized and used as the NO donor. A two-part silicone elastomer obtained from Momentive Performance Materials (Momentive 1520-030) is used as the silicone ink for 3D printing. The NO donor powder and silicone polymers are directly combined and mixed by a Thinky mixer (ARE-310) for 5 minutes at 2,000 rpm. Defoam is proceeded for 30 s in the mixer to remove any air bubbles inside the ink. Cylindrical tube structures are printed on a 3D printer (EnvisionTec, 3D Bioplotter) with the direct ink writing process. A smooth-flow tapered nozzle (22 Gauge, 400-μm inner diameter, Nordson) is used to print the drug-laden silicone tubes. NO release of the 3D printed tubes in phosphate buffered saline-EDTA (PBSE) at 37°C is measured by an ECO PHYSICS NO analyzer (nCLD 66). Inhibition of bacteria adhesion on 3D printed tubes is tested in a 24-h in vitro experiment using Proteus mirabilis (ATCC 29906) as an example strain.

Results: The Momentive silicone is moisture-curing and does not require any heat or light in 3D printing. However, direct printing of silicone-drug blends results in a rough and poorly defined surfaces due to the protruding microsized SNAP powders. Such irregular surfaces may be detrimental to biomedical applications as they attract bacteria and cells. To solve this problem, we added 10% PDMS in the Momentive silicone ink. PDMS is a Newtonian fluid with a viscosity of only 3 Pa·s, which is three orders of magnitude smaller than the Momentive silicone. The mixed ink displays a lower viscosity compared to the Momentive ink but retains the shearing thinning property. Upon deposition, the Momentive silicone forms the skeleton of the printed structure while a very thin layer of PDMS "oozes" out of the printed surface due to its low viscosity and long curing time at room temperature. As a result, the surface of the printed tube is highly smooth without exposed drug particles. This tube release 27 days of NO at a flux above 0.5 x 10^{-10} mol cm^{-2} min^{-1} in PBS at physiological temperature. In the 24-h biofilm experiments, the viable bacteria on the SNAP-loaded 3D-printed tube is lower than the 3D-printed tube and a commercial silicone rubber catheter by 66 % and 92 %, respectively.



Conclusions: We present the first NO-releasing device that is directly 3D printed. We will examine more polymeric materials and NO donors to further enhance the drug release capability and explore more medical applications for personalized healthcare.

Reference: Li W., et al. ACS Applied Bio Materials, 2021, 4, 10, 7653-7662. Permission granted from ACS.