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Controlled Drug Delivery from 3D Printed Two-Photon Polymerized Poly(Ethylene Glycol) Dimethacrylate Devices

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Abstract

Controlled drug delivery systems have been utilized to enhance the therapeutic effects of many drugs by delivering drugs in a time-dependent and sustained manner. Here, with the aid of 3D printing technology, drug delivery devices were fabricated and tested using a model drug (fluorophore: rhodamine B). Poly(ethylene glycol) dimethacrylate (PEGDMA) devices were fabricated using a two-photon polymerization (TPP) system and rhodamine B was homogenously entrapped inside the polymer matrix during photopolymerization. These devices were printed with varying porosity and morphology using varying printing parameters such as slicing and hatching distance. The effects of these variables on drug release kinetics were determined by evaluating device fluorescence over the course of one week. These PEGDMA-based structures were then investigated for toxicity and biocompatibility *in vitro*, where MTS assays were performed using a range of cell types including induced pluripotent stem cells (iPSCs). Overall, tuning the hatching distance, slicing distance, and pore size of the fabricated devices modulated the rhodamine B release profile, in each case presumably due to resulting changes in the motility of the small molecule and its access to structure edges. In general, increased spacing provided higher drug release while smaller spacing resulted in some occlusion, preventing media infiltration and thus resulting in reduced fluorophore release. The devices had no cytotoxic effects on human embryonic kidney cells (HEK293), bone marrow stromal stem cells (BMSCs) or iPSCs. Thus, we have demonstrated the utility of two-photon polymerization to create biocompatible, complex miniature devices with fine details and tunable release of a model drug.

Keywords: 3D Printing, Two-photon Polymerization, Controlled Drug Release, PEGDMA

Introduction

Recent advances in 3D printing, including the ability to construct complex structures with fine precision, open the door to rapid and facile production of controlled release devices (Acosta-Velez et al., 2018; Clark et al., 2017; Do et al., 2015; Fina et al., 2018; Goole and Amighi, 2016; Hollander et al., 2018; Khaled et al., 2018; Martinez et al., 2017; Zhang et al., 2017). Newly developed technologies such as two-photon polymerization (TPP) enable researchers to prototype micro- and nanostructures with high resolution. Compared to typical fused deposition modeling printing (50-200 μm resolution) and stereolithography (~20 μm resolution), TPP can be used to create structures with features of the order of approximately 100 nm resolution (Melchels et al., 2010). With such high resolution and precision, TPP enables the fabrication of complex nanoscale devices (Timashev et al., 2016; Worthington et al., 2017).