Fabrication and characterisation of Axitinib-loaded 3D printed ocular implants for the treatment of posterior ocular disease

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Background: Visual impairment and blindness can significantly impact many people's social lives and become a global problem. The primary cause of blindness and vision impairment is retinal dysfunction, which includes diabetic retinopathy (DR), age-related macular degeneration (AMD), and retinal vein occlusion (RVO). Current treatments for AMD, DR, and RVO typically involve anti-VEGF drugs administered through intravitreal injections, costing thousands of dollars per year. These high costs can limit access to adequate healthcare (6). Therefore, alternative therapies are needed. Tyrosine kinase inhibitors (TKIs) offer promise for treating posterior ocular diseases. Unlike anti-VEGF monoclonal antibodies, TKIs can effectively permeate the cells, interacting with intracellular signaling molecules to inhibit angiogenesis. Axitinib (AX), a second-generation TKI, shows promise due to its potency and selectivity for VEGF receptors. Unlike multitargeted TKIs, AX offers targeted anti-angiogenesis activity with fewer off-target toxicities. In this study, sustained-release AX intravitreal implants were developed using 3D printing technology, incorporating poly(ε-caprolactone) (PCL) and glyceryl distearate (GDS) as matrix polymers and characterized.

Methods: The implants were printed using GeSiM 3.2 Bioscaffolder 3D Bioprinter (Radeberg, Germany). The different molecular weight of PCL (5 kDa and 500 Da) in the ratio of 60:40 %v/v was combined with GDS as the matrix polymer. Different drug loadings of AX (10 and 20% w/w) were tested in this experiment. AX-loaded implants were characterized for their morphology, thermal behaviors, in-vitro release, and biocompatibility. To maintain the sink condition, the in-vitro study was conducted in 20 mL of PBS pH 7.4, containing 0.05% sodium azide and 0.5% sodium lauryl sulfate. The release mechanism of AX from the implants was evaluated using various mathematical models with the help of DDSolver software, and the biocompatibility of AX-loaded implants was tested using ARPE-19 cells.

Results: The sustained release of AX implants was successfully fabricated using SSE 3D printing technology. Implants were printed at 70°C with an applied pressure of 300 kPa and a printer nozzle diameter of 0.4 mm. The FTIR confirmed that no chemical interaction occurred amongst the components of implants with AX. The DSC and TGA data supported FTIR data, confirming no chemical interaction between AX and the matrix polymer. SEM results showed a uniform implant surface without aggregates or drug crystals, proving that AX was uniformly distributed in the polymer matrix. Pores and rough surfaces were visible on the implants' surface on day 180. All implants were successfully released AX for 180 days, with a daily release rate of >0.01 µg/day. The release mechanism study confirmed that AX-loaded PCL implants have two primary release mechanisms, first-order and Korsmeyer-Peppas models, depending on the drug loading. The addition of GDS had a significant role in the implants' degradation with a higher drug loading. The biocompatibility study using ARPE-19 cells demonstrated that AX-loaded PCL implants were safe for ocular application.

Conclusions: AX-loaded implants successfully showed sustained release of AX for 180 days above the desired therapeutic range and were also found safe when tested in the preliminary safety studies. The 3D printed implants offer significant tailorability to engineer implants for sustained release of drug molecules. Overall, AX-loaded implants have the potential to replace monthly anti-VEGF injections used in the treatment of AMD, DR, and RVO.