Injectable Biodegradable Bi-layered Capsule for Sustainable Delivery of Protein Therapeutics

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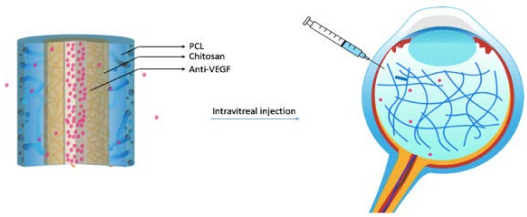
Statement of Propose:

Wet age-related macular degeneration (AMD) is one of the leading causes of blindness in humans over fifty[1]. Choroidal neovascularization induced by the overexpression of vascular endothelial growth factor (VEGF) can leak fluid and blood into the intraocular region and eventually cause irreversible retinal damage[2,3]. The current treatment requires monthly intravitreal injection of anti-VEGF such as bevacizumab or ranibizumab to block VEGF from initiating angiogenesis. However, frequent injection often leads to infection, elevated intraocular pressure, rhegmatogenous retinal detachment[4], and low patient compliance. Various drug delivery devices have been widely developed to create a more facile and efficient treatment of AMD[5] but these devices do not provide sustained drug release due to characteristic burst release and rapid degradation. To address this, we have developed an injectable and biodegradable drug delivery system which can provide drug release for months to potentially improve patient compliance and outcomes, while reducing the need for frequent injections.

Methods:

Bi-layered structured capsules were produced via electrospinning. The chitosan inner layer was prepared following the reported method[6] with minor changes. Either a 1.645 mm or 260 µm stainless steel rod was used as the drum collector. Polycaprolactone (PCL) outer layer was prepared according to the reported method[7]. HEPES sodium salt was mixed in the PCL solution to generate porous structure. The PCL fibers were collected on as-prepared chitosan layer and then followed by sintering and salt leaching. Afterwards, bovine serum albumin (BSA) (model drug) or bevacizumab was loaded, and capsules were sealed. Scanning electronic microscopy (SEM) and fourier-transform infrared spectroscopy (FTIR) were used to characterize morphological and chemical properties. Drug releasing profiles were determined by UV-Vis spectrophotometry at 562 nm and 277 nm. Human retinal pigmented epithelial (ARPE-19) cells were used to assess *in vitro* cytotoxicity. The *in vitro* anti-angiogenesis study was conducted by treating human umbilical vein endothelial cells (HUVECs) with free and released bevacizumab.



Scheme 1. Injectable bi-layered structured capsule

Results:

The positively charged chitosan layer can ionically interact with the negatively charged bevacizumab therapeutic to slow down drug diffusion. The nanoporous shell was designed to resist erosion and achieve zero-order release kinetics, which provided a constant intraocular drug concentration and promised the therapeutic efficacy over time. Based on the release profile, 4.16 µg and 1.67 µg bevacizumab were eluted from the PCL mono-layered capsule and bi-layered capsules per day, respectively. Furthermore, the outer diameter of each capsule was below 450 µm and could facilitate intravitreal injection. Both PCL and chitosan are FDA approved, and showed negligible cytotoxicity with RPE cells. The *in vitro* anti-angiogenesis study showed that released bevacizumab maintained its anti-angiogenic bioactivity for at least 3 months.

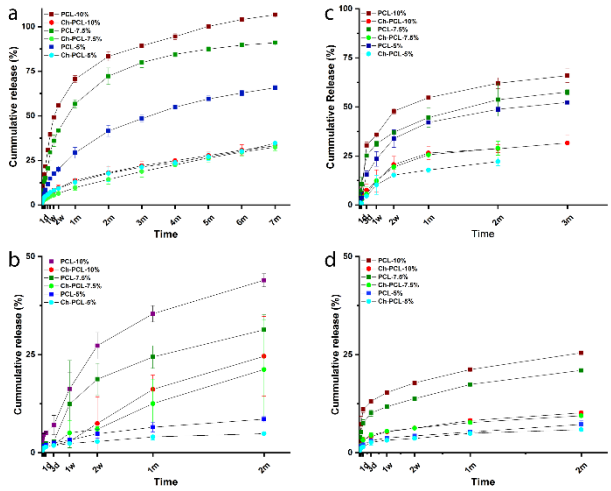


Figure 1. Release profile of (a) BSA (b) bevacizumab from 1.645 mm inner diameter capsule; (c) BSA (d) bevacizumab from 260 µm inner diameter capsule

Conclusion:

To address critical challenges in treating wet AMD, we developed a novel injectable bi-layered capsule that could provide constant anti-VEGF release for six months. Preliminary *in vitro* investigations of cytotoxicity and anti-angiogenic bioactivity yielded positive results.

References:

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