A NOVEL ANTIPROLIFERATIVE DRUG FORMULATION FOR GLAUCOMA DRAINAGE DEVICE


*Department of Chemical and Biomolecular Engineering, Tulane University and **Department of Biochemistry and ***Ophthalmology, Tulane University School of Medicine, New Orleans, LA

Purpose: Many disease processes in the body are treated by the frequent topical or systemic application of a medication. Such traditional treatment regimes are often ineffective and can, on occasion, lead to severe side effects. In this project, an interdisciplinary team is developing a series of drug-delivery systems that will allow the physician to “tune” the rate of drug delivery to suit therapeutic requirements.

Methods: A series of thin film coatings are being developed for glaucoma drainage devices that will act as biodegradable drug delivery vehicles for the release of anti-fibrotic agents. The films coatings are made of poly(lactic-co-glycolic acid) (PLGA); the spin-coating technique employed in their manufacture also produces an asymmetric pore structure that can exploited to control the rate of dissolution, which can range from a sharp initial burst of the drug to an initial slow delivery followed by an accelerated delivery as the film degrades. A cell culture system was used to test the efficacy of these polymers in vitro before animal testing.

Results: Mitomycin C (MMC) is highly potent antiproliferative drug that is highly sensitive to degradation when incorporated directly into a PLGA film. The degradation was confirmed by UV spectroscopy and FTIR analysis. We have developed a new MMC--cyclodextrin complexation system that stabilizes the drug and allows its release from the PLGA film in an active form. A less potent antiproliferative drug, 5-Fluorouracil (5-FU), remained stable when incorporated directly into PLGA films and the in vitro release was studied for a 4 week period. The release pattern showed an initial burst followed by a lag phase for a 2 week period. Beyond this period, there was a sharp increase in drug release that continued till the end of a 4 week delivery period. To achieve the continued release of drug to prevent fibrosis, the synergistic effect of the highly potent MMC and less active 5-FU is being investigated by dispersing both the drugs into the PLGA film. All drug-film preparations are also evaluated for cytotoxicity using COS-1 cells. A dose response curve was obtained for MMC, both loaded onto the surface of PLGA films and incorporated into the PLGA film. Polymers with a surface coating of MMC were acutely toxic to the cultured cells, while those with MMC incorporated in the polymer matrix showed a delayed toxicity.

Conclusions: These experiments have demonstrated that the controlled release can be effected through the encapsulation of antiproliferative drugs in biocompatible and biodegradable polymer films formulated with novel pore structure morphologies. The experiments indicate promising materials that can be incorporated into glaucoma drainage devices. After additional experiments to establish a dose-response in culture, the PLGA films will be incorporated into glaucoma drainage devices for animal studies and ultimately for clinical trials.
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