Pharmaceutical Sciences Seminar

“Coated PLGA Implants for Controlled Release of Bevacizumab”

Presented by:

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Wet age-related macular degeneration (AMD) is a condition in which new abnormal blood vessels grow behind the macula. This growth leads to displacing the macula from its normal position, which finally results in rapid central vision loss. In wet AMD, growth of abnormal blood vessels under the retina is stimulated by overexpression of vascular endothelial growth factor (VEGF), therefore, anti-VEGF therapies have been developed to neutralize the overexpressed VEGF. The current dosing regimen of the anti-VEGF agents is monthly intravitreal injection, but it is very inconvenient for patients and repeated injections introduce risk of infection and hemorrhage. Therefore, sustained release formulations are needed to reduce administration frequency for improved patient compliance and convenience and to minimize the risks by maintaining the therapeutic concentration longer in the target site.

Poly (lactic-co-glycolic acid) (PLGA) is the most common and extensively researched polymer for long-term controlled release, which has been used in several FDA-approved medical long-acting release depots due to its biodegradability, biocompatibility, and ability to provide continuous drug release. In this research, therefore, PLGA millicylindrical implants suitable for intravitreal injection were employed as sustained release formulations of the anti-VEGF full-length monoclonal antibody (mAb), bevacizumab (Avastin®). To stabilize the encapsulated mAb against the acidic microenvironment inside the PLGA implants during release period MgCO₃ was co-encapsulated. To prevent irreversible aggregation of bevacizumab from stress during powder preparation process, trehalose was co-lyophilized with the mAb above a critical level. The presence of excipients necessary to stabilize the mAb also caused a rapid uncontrolled release due to osmotic pressure. To offset this effect, the implants were coated with pure PLGA. The optimized coated implants demonstrated continuous release kinetics in vitro over six weeks with high (>80%) total cumulative release. The released bevacizumab over this entire period retained > 90% monomer content as well as excellent preservation of immunoreactivity and secondary structure. These data provide a new paradigm for controlled release of stable bevacizumab from PLGA, which both supports further development of this approach for AMD treatment and a generalizable application to site-specific controlled release of therapeutic mAbs.

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