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Sustained Delivery of Biologics to Back of the Eye

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Ocular drug delivery remains a challenging task due to restrictive barrier functionalities of the eye structure. Dynamic and static ocular barriers impede transport and efficacy of various topically or systemically administered medications. New technologies for delivery of small molecules and biologics are of growing interest among clinical pharmacologists and pharmaceutical scientists for treating both anterior and posterior segment disorders. The major challenge is to deliver drugs and biologics at therapeutic concentrations to the targeted ocular tissues with minimal side effects. A better understanding of physiological and pathological conditions of the eye, along with various methods of delivery, would aid in the development of novel therapeutics. Nevertheless, delivery systems that can efficiently target the diseased ocular tissues, generate high drug levels and maintain prolonged and effective concentrations are highly desirable [1]. Such emerging drug delivery technologies have the potential to maintain, and/or improve therapeutic indices of active agents. It can also boost both patient adherence to chronic therapy and outcomes.

Non-invasive drug delivery to the back of the eye represents an important unmet therapeutic need [2]. Delivery of high molecular weight compounds such as proteins, peptides, antibodies, Fab fragments, growth factors and genetic material are currently a major focus of many researchers and pharmaceutical companies. Direct intravitreal injections of biologics allow for specific and targeted treatment of retinal disorders. Monthly intravitreal injection of Ranibizumab, an anti-VEGF Fab, has become the standard of care for wet AMD patients [3]. Though intravitreal route appears to be a promising route to attain high drug concentrations in back of the eye (retina/choroid), however, this route is often limited by post dosing adverse effects, such as development of endophthalmitis, blurred vision, increase in intraocular pressure, cataract formation and increased risk of retinal detachment [4]. Current momentum in the development of new drug delivery systems hold promise for improved therapies in the treatment of vision threatening vascular degenerative disorders of the posterior eye, such as age-related macular degeneration (AMD), diabetic macular edema (DME) and proliferative vitreoretinopathy (PVR). New technologies that can provide controlled, scalable and sustained release of therapeutic proteins (biologics), through non-invasive or minimally invasive routes for targeting intraocular tissues, are warranted. Drug delivery systems which can provide and maintain levels of therapeutic proteins within the therapeutic and safe windows, are to be preferred. The major hurdle in designing such delivery carriers is to ensure that the structure and activity of biologics are retained during the preparation, sterilization and release processes [3]. Subsequently, the drug delivery system should be biodegradable to minimize the potential side effects of surgical implantation and removal. Encapsulation of biologics in biodegradable polymeric nanoparticles may be an ideal strategy. Biodegradable polymers, such as poly (lactic-co-glycolic acid)(PLGA), poly (lactic acid) (PLA), poly (glycolic acid) (PGA), polyethylene glycol (PEG) and poly(caprolactone) (PCL), are widely studied for the preparation of nanoparticles. PLGA copolymer based system produces high molar mass of lactic and glycolic acids. Studies with PLGA suggest that acidic pH in the core of nanoparticles significantly induces protein aggregation, and reduces biological activity of therapeutic proteins [5-7]. Hence, there is an unmet need for development of alternate, safe and viable polymers capable of retaining the biological activity and providing minimally invasive controlled delivery of therapeutic proteins to back of the eye (retina-choroid).

Novel tailor-made pentablock copolymers have been developed in our laboratory, utilizing various FDA approved biodegradable and biocompatible polymer blocks, such as PGA, PEG, PLA and PCL. These novel copolymers can be optimized, with respect to molecular weight and ratios of each block, in order to develop a successful macromolecular (model proteins such as lysozyme, BSA, IgG, and IgG-Fab) drug delivery system. High molecular weight pentablock copolymers can be utilized to prepare protein encapsulated nanoparticulate formulations. Whereas, pentablock copolymers with low molecular weight and varied block arrangement could be used to formulate thermosensitive gel [8]. Nanoparticles prepared from pentablock copolymers cause minimum or no apparent burst release effect, and provide sustained release for longer duration at constant zero order rate [9]. Furthermore, burst release phase can be eliminated by dispersing nanoparticles in thermosensitive gel to provide a continuous zero-order drug release. These novel polymers are excellent biomaterials, and can act as a platform for ocular delivery of therapeutic biologics, which can minimize/eliminate side effects associated with frequent intravitreal injections. Moreover, these polymers produce significantly lower amounts of lactic acid, negligible tissue irritation and toxicity, optimize and prolong drug release profile, preserve structural integrity and immunogenicity of macromolecules. However, the applicability of these copolymers in the development of drug delivery systems may not be limited to ocular formulations. It is highly anticipated that these new polymer based technologies, as potential drug-delivery systems may receive US FDA approval for human use in the near future.

In conclusion, therapeutic proteins are now established biologics, with high activity against many ocular diseases. However, design of novel drug delivery systems to achieve a non-toxic, constant and efficient delivery with minimal doses of therapeutic proteins is still challenging. Several factors, such as the protein aggregation, unfolding can occur when injected into the vitreous. Importance of injection site for improving bioavailability of protein to the retina, interactions of biologics with the retina, diffusion in the vitreous, penetration inside the retinal layers, and finally elimination from the eye needs to be carefully studied. Fate of protein loaded drug delivery carriers in the vitreous and the consequences of increasing protein concentrations in the vitreous need to be critically examined. Nevertheless, development

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of new therapeutic stratagems, techniques and systems may not be possible without interdisciplinary efforts to delineate diffusion and kinetic parameters, interactions with vitreous and retina, in order to advance this promising field.

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