In Situ Gel for Ocular Drug Delivery Synthesis, Characterization and Mathematical Modelling

By

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Date: 16 January 2020 (Tuesday)
Time: 09:00
Venue: Room 4582 (Lift 27-28)

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Abstract

Hydrogels have attracted much attention for long-term release of biomacromolecules for both tissue engineering and drug delivery. A better understanding of underlying principles in their behavior as biomaterials would be beneficial to the success of their final application. It would be possible with the help of mathematical modeling. In this thesis, effort has been made to (1) develop a theoretical framework to model the degradation behavior of hydrogels prepared by chemical cross-linking of pendant functional groups on long polymer chains and identify the influencing parameters, (2) explain the macromolecular release profile from degradable and non-degradable formulations and finally (3) study biomacromolecule distribution within ocular tissues after IVT bolus and degradable hydrogel depot as one application with the aid of CFD technique.

Degradation profile of these hydrogels can be modeled by tracking the number of small chains between cross-link nodes, responsible for the maintaining the network, over time and relate it to the macroscopic swelling ratio. Initial hydrogel compositions without changing the chemistry of cleavable cross-link nodes like polymer concentration and DM has a great impact on the swelling profile as well as life-time. As they are formed in a random cross-linking reaction, hydrogels bear a heterogeneous microstructure. This feature leads to a multiphase release profile with different slopes from non-degradable formulation. In this thesis, the observed multiphase release is explained by applying lattice based model with two discrete diffusion coefficients. For three macromolecules, unlike the single-diffusivity model, the dual-diffusivity model shows a good agreement with the experimental data. In the form of degradable formulations, this heterogeneity produces a combined diffusion and degradation controlling mechanism for macromolecular release. From mathematical point of view, it can be described by applying an initial heterogeneous distribution for diffusion coefficient into the hydrogel network in a lattice based approach. Lastly, one 3D transport model based on the physiology of the rabbit eye is constructed to test the efficacy of degradable hydrogel depot compared to the typical IVT bolus of Bevacizumab, an anti-VGEF protein. The distribution of protein is found to be very sensitive to the hydrodynamic parameters (IOP and aqueous flow) as well as transport properties and is more prolonged in the depot case.