COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar

Wednesday, November 3, 2021
4:00pm
2548 NUB or Zoom

"Metal-HisTag Coordination for Remote Loading of Very Small Quantities of Biomacromolecules into PLGA Microspheres"

Presented by:

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Abstract: Challenges to discovery and pre-clinical development of long-acting release (LAR) systems for protein therapeutics include protein instability, use of organic solvents during encapsulation, specialized equipment and personnel, and high costs of proteins. We sought to overcome these issues by combining remote-loading self-healing encapsulation with binding HisTag protein to transition metal ions. Porous, drug-free self-healing microspheres of copolymers of lactic and glycolic acids (PLGAs) with high molecular weight dextran sulfate (HDS) and immobilized divalent transition metal (M^{2+}) ions were placed in the presence of proteins with or without HisTags to bind the protein in the pores of the polymer before healing the surface pores with modest temperature. Using human serum albumin (HSA), insulin-like growth factor 1 (IGF-1), and granulocyte-macrophage colony-stimulating factor (GM-CSF), encapsulated efficiencies of immunoreactive protein relative to non-encapsulation protein solutions increased significantly with the inclusion of Zn^{2+} and HisTags. These three proteins were continuously released in immunoreactive form over seven to ten weeks to 73-100% complete release, and GM-CSF showed bioactivity >95% relative to immunoreactive protein throughout the release interval. Increased encapsulation efficiencies were also found with other divalent transition metals ions, but not with Ca^{2+}. Ethylenediaminetetraacetic acid (EDTA) was found to interfere with this process, as was hypothesized due to EDTA's chelating properties. In further studies, the direct encapsulation of $ZnCO_3$ was found to increase the Zn loading and the protein loading capacity of the microspheres. Optimization experiments showed that the time and temperature of protein loading and self-healing encapsulation could be substantially decreased. Varying the pH of the loading conditions showed that the difference between the encapsulation efficiency of the HisTagged vs. un-tagged protein disappeared below pH 6, as hypothesized due to the pK_a of histidine. These results indicate that M^{2+}-immobilized self-healing microspheres can be prepared for simple and efficient encapsulation by simple mixing in aqueous solutions. These formulations provide slow and continuous release of immunoreactive proteins of diverse types by using a fraction of protein (e.g., <10 μg), which may be highly useful in the discovery and early pre-clinical development phase of new protein active pharmaceutical ingredients, allowing for improved translation to further development of potent proteins for local delivery.

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