Technical Summary, PhD Thesis

Development and Evaluation of Glucose-Responsive Biomaterials as Self-Regulated Insulin Delivery Systems

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Motivation: Diabetes mellitus is a disease characterized by poor glycemic control which often leads to severe complications including retinopathy, cardiovascular disease, and kidney failure. Many diabetic patients must continually monitor their blood sugar and self-administer multiple daily doses of exogenous insulin to combat hyperglycemia. To reduce this patient burden, limit the occurrence of hypoglycemic events, and better mimic native insulin activity, therapies which can self-regulate insulin delivery are an attractive option. Existing technologies, however, lack fine sensitivity to glucose changes at physiologically relevant concentrations and fail to respond on therapeutically relevant timescales. This work begins to address such limitations by developing novel biomaterial-based insulin delivery systems.

Results: This thesis presents several novel glucose-responsive insulin delivery systems based on the enzymatic sensor glucose oxidase. Glucose oxidase converts glucose to gluconic acid and reduces the pH of the microenvironment when glucose levels are high. This change in pH acts as a trigger, enabling the on-demand release of insulin. The first delivery system discussed uses the pH-responsive polymer acetalated-dextran to formulate nanoparticles that physically encapsulate both insulin and glucose oxidase. The nanoparticles rapidly degrade in the presence of acid, making this system a fast acting therapeutic that responds an hour after administration and is able to maintain normoglycemia in a diabetic mouse model for at least 16 hours. The second system is comprised of porous alginate microgels that encapsulate nanoparticles to create a depot of insulin for sustained glucose-responsive release *in vivo* for over 3 weeks with just 2 doses. The third system is based on the electrostatic complexation of insulin to positively charged polymers, such as polyethylenimine. When the pH is reduced below the isoelectric point of insulin, the complex dissociates and releases insulin only in response to elevated levels of glucose. These complexes are afforded a prolonged functional lifetime by decreasing the rate of insulin release under normal glucose concentrations. The synthesis, formulation, *in vitro* characterization, and *in vivo* evaluation in both healthy and diabetic animals is discussed for each of these systems.

Conclusion: The development and characterization of the glucose-responsive insulin delivery systems described here marks an important step in the advancement of self-regulated insulin delivery. Furthermore, these formulations may provide generalized strategies for the development of future stimuli-responsive drug delivery systems.