

51b Mucoadhesive Oral Insulin Delivery Systems Using Lectin Functionalized Complexation Hydrogels

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The main advantage of oral protein delivery is that it improves patient compliance and comfort over other routes of administration (i.e. injection), thus leading to a more effective treatment regimen. Although oral protein delivery could benefit many individuals, maintaining the functionality of the protein and low bioavailability of the delivered drug have prevented it from becoming a successful therapy.

We have developed a class of environmentally responsive complexation hydrogels composed of methacrylic acid grafted with ethylene glycol chains (P(MAA-g-EG)) functionalized with wheat germ agglutinin (WGA) to overcome these challenges. The drug carriers were designed to (1) minimize the effects of the harsh environment of the gastrointestinal tract and (2) target delivery of the protein drug to the upper small intestine by exploiting the pH shift between the stomach and the upper small intestine. In addition, functionalization of PEG chains with WGA will allow for specific binding to carbohydrate moieties present in the intestinal mucosa to improve residence time of the carrier at the delivery site.

Hydrogel microparticles were prepared by UV-initiated free radical solution polymerization. PEG chains were then functionalized with WGA through a biotin-avidin interaction. Insulin, a model protein, was used to determine if the functionalization process affected the loading and release behavior of the microparticles. In vitro mucoadhesive characteristics of the functionalized polymer were evaluated using a mucus secreting co-culture of Caco-2 and HT29-MTX cells. Biodistribution of the functionalized microparticles within the small intestine of male Wistar rats was determined over the course of 4 hours.

Insulin entrapment in the polymer network was unaffected by the WGA functionalization and loading efficiency was determined to be 75% in both functionalized and unfunctionalized microparticles. A release study was done to mimic the conditions of the pH shift between the stomach and the small intestine. The hydrogel carriers prevented release at a low pH (3.2) and rapidly released insulin when the pH was increased to 7.0. WGA functionalized microparticles displayed a higher adhesion to a mucus secreting co-culture than non-functionalized microparticles. In addition, a competitive carbohydrate assay was used to demonstrate that there was a specific interaction between the WGA and the carbohydrate groups present within the secreted mucus layer. The final study examined the transit of functionalized microparticles when administered directly to the small intestine of rats. After 1 hour almost 100% of the microparticles remained in the mucus layer of the small intestine and after 2 hours 64% of the microparticles were still present in the small intestine.

Functionalizing complexation hydrogels with WGA improved the mucoadhesive properties of this polymer. Future work is focused on determining bioavailability of the orally delivered insulin using the WGA functionalized hydrogels.