Emerging Trends in Stimuli Responsive Nanocarriers for Oral Drug Delivery

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Site specific oral delivery of many biopharmaceutical classification system (BCS) class II and IV molecules is challenging due to their poor solubility, permeability and potential degradation in the gastrointestinal tract. The use of bio-responsive nanoparticles for improving the bioavailability of such drugs is gaining more and more attention. However, most nanoparticle-based drug delivery systems suffer from many disadvantages, such as low encapsulation efficiency (liposomes, polymeric nanoparticles), complex synthesis methods (silica, silicon based materials) and poorly understood biodegradability (inorganic nanoparticles). Recent studies have emerged an appreciation for the use of proteins and polypeptides, originated from food as potential nanocarriers with good biocompatibility, biodegradability, low cost and low toxicity. Hence, in this project nanoparticles were fabricated using succinylated β-lactoglobulin (Succ. BLG) or β-lactoglobulin (BLG) to achieve high loading capacity, high solubility and site-specific delivery of two model nutraceuticals (curcumin and resveratrol), improving their physicochemical properties and biological activity *in-vitro*, *ex-vivo* and *in-vivo*. Our results show spherical nanoparticles of around 200 nm which are capable of encapsulating curcumin with ~100% encapsulation efficiency and ~10% w/w drug loading. Results revealed that encapsulation with BLG increases the solubility, whereas Succ. BLG provides additional protection to nutraceuticals when subjected to gastric fluids as it is resistant to breakdown in acidic pH and pepsin. By forming nano complexes of curcumin with BLG and Succ. BLG, the solubility of curcumin was markedly increased by ~ 100 fold. Additionally, the apparent permeability in an in-vitro Caco-2 cells monolayer model was significantly enhanced compared to curcumin solution (dissolved in 1% DMSO). In a mouse-derived intestinal epithelial 3D organoid culture stimulated with IL-1β, curcumin encapsulated nanoparticles showed significant reduced production of inflammatory cytokines and chemokines such as TNFα and Cxcl10 compared to curcumin solution and suspension. To demonstrate the applicability of the nanoplatform, it was next applied to a slightly more soluble nutraceutical – resveratrol. Complexation of resveratrol with BLG and Succ. BLG increased the solubility of resveratrol by ≈ 3 times and ≈ 2 times, and significant enhancement in dissolution. Furthermore, resveratrol loaded nanoparticles (BLG-RES) were administered via oral route to Winnie mice with spontaneous colitis. Histology and decreases in expression levels of inflammatory cytokines (Il1b, Il10, Il17 and Tnfa) confirmed a significantly greater reduction in inflammation due to the potentially due to increased solubility and stability of resveratrol by complexation with BLG. Our results suggest that, nutraceutical-based nanocarriers such as BLG, and Succ. BLG, have great potential as an alternative nanocarrier in improving solubility, permeability and intestinal delivery of hydrophobic nutraceuticals such as curcumin, resveratrol and opened doors for delivering many small molecules orally with BCS class II and IV.