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In vitro and in vivo evaluation of alginate-based microparticles for oral delivery of active entities to sites of inflammation in the colon

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Abstract

Treatment options for inflammatory bowel diseases (IBD) involving aminosalicylates, corticosteroids, imunomodulators and biologics are associated with severe side effects including osteoporosis, adrenal insufficiency, and hypertension. Efficient drug delivery to sites of inflammation in the colon has the potential to increase the bioavailability, and thus reduce the dose and side effects. Alginate hydrogels have been investigated extensively for controlling drug delivery, due to their biocompatibility, and gelation by divalent metal ions under mild aqueous conditions. Thus the research presented in this thesis explored the potential of alginate microparticles for oral delivery of the anti-inflammatory compounds hydrocortisone hemisuccinate (HCHS) and Nigella sativa extract (NSE) to the colon.

Alginate microparticles prepared by the drop method or homogenization technique (Chapter 2) were spherical with an average size of 1mm and 45μm, respectively. Alginate microparticles prepared by homogenization and loaded with HCHS by diffusion released 7% of the drug content in SGF in 2h and a further 10% in SIF in 4h. An additional 75% of the initial content was released from the microparticles during incubation in SCF over 12h, demonstrating the potential for delivery of high concentrations of drug at sites of inflammation in the colon. Direct encapsulation of HCHS in alginate microparticles using the homogenization method was less effective in restricting drug release, where 36% of the HCHS content was released following immersion in SGF (2h) and SIF (4h) and 40% was released over 6h in SCF.

HCHS-loaded alginate microparticles produced by aerosolization and diffusion loading (Chapter 3) exhibited an average size of 65μm and high drug loading of 43% w/w. Microparticles released 5% of the initial HCHS load after incubation in SGF for 2h and SIF for 4h. A further 75% of the drug load was released in SCF over 12h, indicating the potential for delivery of high concentrations of drug to sites of inflammation in the colon. HCHS-loaded microparticles prepared by direct drug encapsulation resulted in much lower drug loadings of 11%, but a highly efficient colon targeting potential was exhibited since 10% of the initial HCHS load was released after incubation in SGF for 2h and SIF for 4h, allowing a further 80% HCHS to be released in SCF in 6h.

HCHS-loaded alginate microparticles were coated with Eudragit® to explore the effect of a pH-responsive coating on drug release behaviour (Chapter 4). HCHS-loaded alginate microparticles prepared by aerosolization and drug diffusion were coated using 3% and 6% Eudragit® S100 resulting in a total weight gain of 12% and 20%. However, drug release behaviour in SCF was not significantly different from that recorded for uncoated microparticles.

Freeze drying of drug-loaded alginate hydrogel microparticles is essential for storage or prior to formulation as capsules, tablets or suspensions. Freeze-dried alginate microparticles loaded with

HCHS (Chapter 4) suppressed drug release in SGF and SIF, allowing 80% of the load to be released in SCF over 18h. This finding was significant in confirming that freeze drying did not result in fragmentation of the microparticles with exposure of the drug.

HCHS-loaded alginate microparticles (2.5mg HCHS/kg) were administered orally to mice presenting DSS-induced colitis, to investigate anti-inflammatory activity (Chapter 5). Mice treated with HCHS-loaded microparticles showed significantly lower Disease Activity Index and percentage weight loss compared with mice treated with HCHS solution of equivalent concentration. Investigation of intestinal permeability using oral FITC-dextran revealed similar permeability for mice treated with HCHS-loaded microparticles and HCHS solution of 4-fold higher concentration (10mg/kg dose) Histological examination revealed showed significant enhancement in mucosal structure and decrease in inflammation in groups treated with HCHS-loaded microparticles compared with HCHS solution. These results demonstrated that alginate microparticles produced by aerosolization provided a high local HCHS concentration at sites of inflammation in the colon and enhanced therapeutic activity.

Nigella sativa extract (NSE) is known to possess anti-oxidant and anti-inflammatory activity in colitis models. NSE was encapsulated in alginate hydrogel microparticles using aerosolization and homogenization methods respectively (Chapter 6), resulting in high loadings up to 42%w/w and entrapment efficiency up to 63%. The microparticles suppressed NSE release in SGF and SIF and released 80% of the load in SCF over 18h. NSE released in SCF after 12h exhibited antioxidant scavenging activity (DPPH assay) comparable with unencapsulated extract demonstrating the potential for release of high concentrations of naturally-derived active entities at sites of inflammation in the colon.

Overall, the results of the research demonstrate the ability of alginate hydrogel microparticles produced by aerosolization and homogenization techniques to act as carriers for efficient, site-specific delivery of drugs to the colon for treatment of IBD. Significantly, a major improvement of efficacy was demonstrated when HCHS was delivered in alginate microparticles in the DSS-induced colitis mouse model compared with HCHS solution of 4-fold higher concentration. This finding indicates that drug reaches the target site in high concentrations, resulting in increased therapeutic activity with an expectation of reduced side effects.

Declaration by author

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