Development of dual stimuli-responsive hydrogels for colon target drug delivery system.

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Background: Target drug delivery systems aim to target localized, and prolonged drug delivery to the desired site of action. The colon has many features that make it an attractive site for drug targeting, as it's the ideal site for the treatment of local diseases such as Crohn's disease and ulcerative colitis. Enzymes produced by anaerobic bacteria of the colon, such as azoreductase, can be exploited for drug targeting to the colon and improve drug release profiles of peptides, proteins, and poorly absorbed drug for enhanced drug absorption. pH-responsive hydrogels can be exploited to control the release of drugs within the gastrointestinal system and have been commonly used to produce gastro-resistant oral formulations. However,the slight differences in the pH value between the small intestine and the colon trigger limit the ability of these systems to provide colon-specific drug release. This project aims to develop dual (pH-enzyme) stimuli-responsive hydrogels using pH-responsive polymers and enzyme-responsive cross-linking agents for specific colonic delivery of mesalazine.

Methods: A free radical polymerisation method was used to prepare hydrogel' copolymer films of hydroxyethyl methacrylate (HEMA) and methacrylic acid (MAA) using conventional crosslinking agents ethylene glycol dimethacrylate (EGDMA) and enzyme-sensitive crosslinking agent 4,4'-Di(methacryloylamino) azobenzene (DMAAB).

The swelling test was used to investigate the swelling degree of prepared hydrogels in different pH solutions mimicking conditions of the stomach, colonic region, and small intestine of the gastrointestinal tract (GIT) (pH 1.2, pH 6.5, pH 7.4) respectively.

An *in situ loading* method was used for loading of mesalazine in the polymeric networks andin *vitro* release studies of mesalazine from the prepared hydrogels were examined in buffer conditions mimicking the pH environment of stomach, colon, and small intestine (pH 1.2, pH 6.5, and pH 7.4) respectively. Ex *vivo* releases study of Mesalazine was investigated in the presence of the rat cecal content to investigate the efficacy of a dual-responsive hydrogel system.

Results: pH-responsive hydrogels and dual responsive hydrogels were successfully synthesized.

A significant difference in the swelling behavior of the prepared hydrogels in the different buffer conditions was obtained, where the maximum swelling was reached at pH 7.4 and the lowest swelling was obtained at pH 1.2 (69.63 % versus 32.51 %)respectively. In vitro release studies showed that both hydrogels have a slow release of mesalazine in three different buffer with less than 30% cumulative release obtained over 6 hrs. Dual hydrogels show a significantly higher release of mesalazine at pH 6.5 in the presence of the rat cecal content compared to the pH-responsive hydrogels in the three different buffer solutions without cecal content.

Conclusions: Developing colon target drug delivery system is essential to manage diseases affecting the colon such as Crohn's disease and ulcerative. The results show that the dual (pH-enzyme) responsive hydrogels are a potential carrier for colon targeted delivery of clinically relevant poorly water-soluble drugs, such as mesalazine. Further studies will assess the potential of this platform to improve delivery of acid-labile and poorly water soluble drugs.