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

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Introduction

Targeted 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 (1).

Recently the prevalence of these conditions has dramatically increased around the globe with more than 6.8 million individuals worldwide suffering from inflammatory bowel disease (IBD) complications with an estimated 11 % increase in the prevalence by 2025 in the UK (2). Furthermore, IBD has considerable economic impact with patient treatment costs approximately 23,000$ annually in the US (3).

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 drugs 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 limit the ability of these systems to provide colon-specific drug release.

Project objectives and goals

- This project aims to develop a novel dual pH-enzymatic responsive hydrogel carrier for colon targeted drug delivery purposes.
- This approach was investigated by incorporating pH-responsive polymers with azoreductase-labile crosslinkers.
- This delivery system was investigated and characterised for the poorly water-soluble drug mesalazine.

Methods

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

Table 1: Monomer composition used to prepare 10 g films

Hydrogel symbol	HEMA	MAA	EGDMA	DMAAB	AIBN
HE	8.8 g	1 g	0.1 g	-	0.1 g
HZ	8.8 g	1 g	-	0.1 g	0.1 g

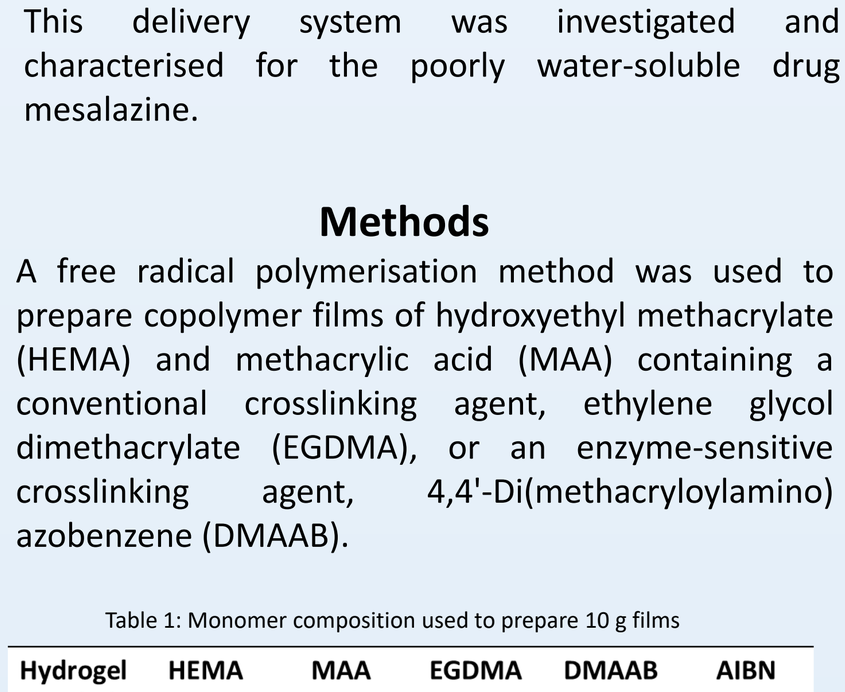

Figure 1: Schematic representation of the methodology of the hydrogel formulation.

Methods

- The swelling degree of prepared hydrogels in response to buffer solutions mimicking the pH conditions of the stomach, colonic region, and small intestine of the gastrointestinal tract (GIT) (pH 1.2, pH 6.5, pH 7.4) respectively was determined.

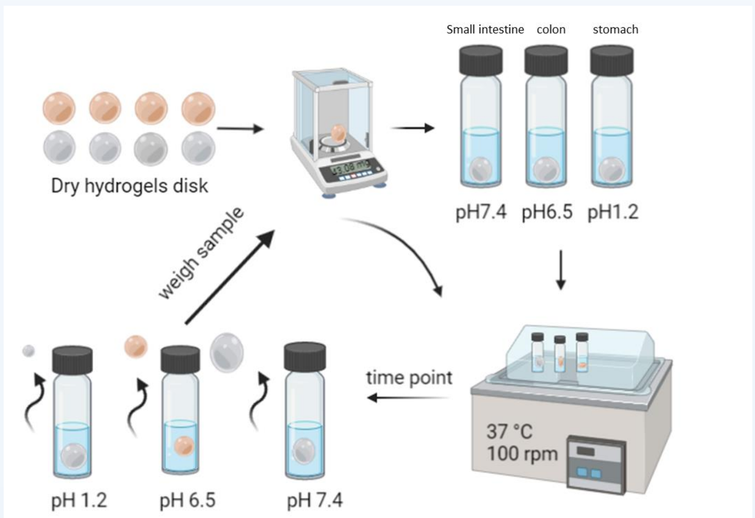

Figure 2: Schematic showing the process used in the swelling studies.

- An *in situ loading* method was used for loading of mesalazine in the polymeric networks.
- In *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.

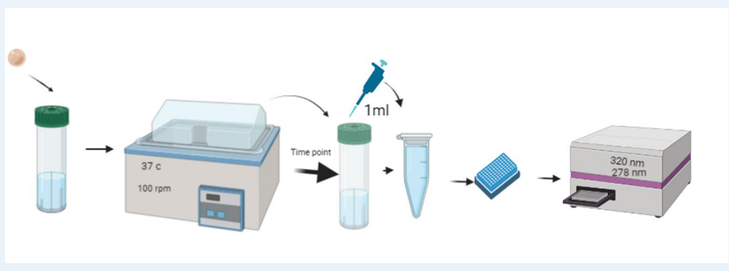

Figure 3: Schematic showing the process used in the drug release studies.

- 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.

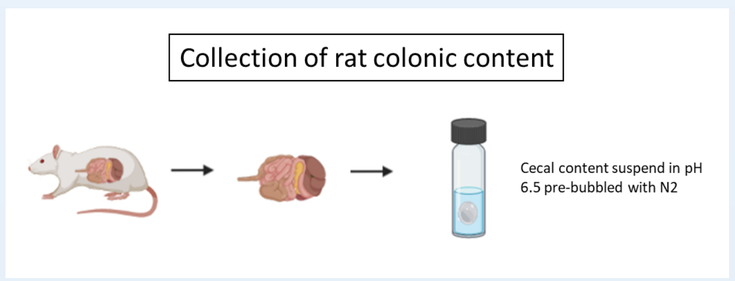

Figure 4: Schematic illustrates the collection of the rat cecal content.

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.

Figure 5: Time-dependent equilibrium water content (mean ± SD) of a) HE hydrogel film and b) HZ hydrogel film in three different buffers.

Results

- In vitro release studies showed that both hydrogels have a slow release of mesalazine in three different buffers 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.

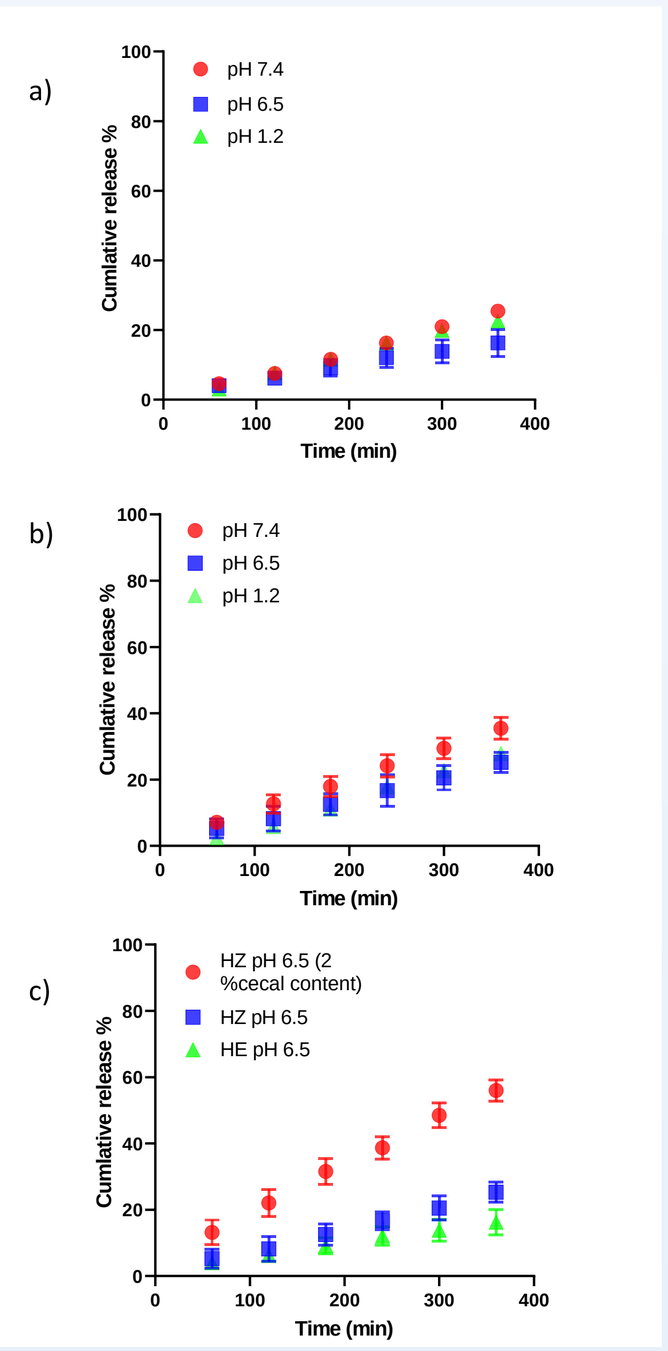

Figure 6: a) The release profile of mesalazine (mean ± SD) from HE hydrogel films at different pH conditions. b) The release profile of mesalazine (mean ± SD) from HZ hydrogel films in different pH conditions . c) The release profile of mesalazine (mean ± SD) of HZ and HE hydrogels film in different media.

Conclusions

Developing colon targeted drug delivery system is essential to manage diseases affecting the colon such as Crohn's disease and ulcerative colitis. The results show that 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 drug candidates.

Reference

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