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Dual stimuli-responsive hydrogels for colon targeted drug delivery.

Mohmmad Rabeh, Matthew P. Wylie, Colin P. McCoy*

School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, UK.

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*Corresponding author.
Tel.: +99 1234 567 890
Fax: +99 1234 567 890
E-mail: c.mccoy@qub.ac.uk

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SUMMARY

Colon targeted drug delivery systems are promising for the treatment of local diseases. The colon possesses a diverse microbiome that secretes a number of biomolecules, such as enzymes, that can be exploited for targeted drug delivery. Here, we report the synthesis of 2-hydroxyethyl methacrylate and methacrylic acid copolymer hydrogels crosslinked with an enzyme-sensitive crosslinking agent. The swelling and drug release properties of hydrogels were observed in pH 1.2, pH 6.5 and pH 7.4, and in the presence of rat cecal content. Swelling studies revealed pH responsivity of the hydrogels while the release kinetics of metronidazole from hydrogels containing an enzyme-labile crosslinker were faster in the presence of rat cecal content. The results show that dual responsive hydrogels could provide a promising platform for colonic drug delivery.

INTRODUCTION

Colon-targeted drug delivery systems are promising carriers to manage local diseases affecting the colon such as Crohn's disease and ulcerative colitis [1]. The physiology of the gastrointestinal tract (GIT), which has different pH values, has encouraged the development of pH-dependent systems to prevent drug release in the stomach [2]. In addition, other stimuli can be exploited to improve oral drug delivery. Various enzymes produced by anaerobic bacteria of the colon, such as azoreductase, can be exploited for targeted drug delivery. Metronidazole (MT) is widely used in the treatment of GIT infection and pseudomembranous colitis triggered by Clostridioides difficile infections, which might pertain to severe life-threatening illnesses [3]. This study aims to develop dual stimuli-responsive hydrogels using pH-responsive polymer and enzyme-labile crosslinking agents for colon-specific delivery of metronidazole.

MATERIALS AND METHODS

Hydrogel copolymer films of 2-hydroxyethyl methacrylate (HEMA) and methacrylic acid (MAA) using a conventional crosslinking agent ethylene glycol dimethacrylate (EGDMA) and enzyme-sensitive crosslinking 4,4'-Di(methacryloylamino) azobenzene (DMAAB), azobisisobutyronitrile (AIBN) was used as thermal free radical initiator. The specific compositions are shown in Table 1. The swelling behaviour of prepared hydrogels was investigated in different pH solutions mimicking conditions of the stomach, colonic region, and small intestine of the GIT (pH 1.2, pH 6.5, pH 7.4) respectively. The swelling method was used for loading of MT in the polymeric networks and in vitro release of MT from the prepared hydrogels was examined at 1.2, pH 6.5, and pH 7.4. An ex vivo release study of MT was investigated in the presence of the rat cecal content to examine the efficacy of a dual-responsive hydrogel system.

Table 1. *The hydrogels formulation to prepare 10 g films*

Hydrogel name	Component weight (g)				
	HEMA	MAA	EGDMA	DMAAB	AIBN
HE	8.8	1	0.1	-	0.1
HZ	8.8	1	-	0.1	0.1

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RESULTS AND DISCUSSION

pH-responsive hydrogels and dual responsive hydrogels were successfully synthesized. The swelling degree of prepared hydrogels was significantly higher at pH 7.4 compared to pH 6.5 and 1.2, this can be contributed to ionization of the carboxylic group of MAA in basic media leading to electrostatic repulsion, while its unionised form predominates in acidic solution [2]. In vitro release data of metronidazole from hydrogels is shown in Fig. 1. At pH 7.4 both formulations exhibited fast and total release with 100% cumulative release were obtained. Release of metronidazole was fast at pH 6.5 with an average cumulative release of 80%. This can be correlated to complete ionisation (de-protonation) of carboxylic group of MAA at pH 7.4, and partial ionisation at pH 6.5. In contrast, minimal release of metronidazole was observed at pH 1.2 due to unionized state of carboxylic group of MAA in acidic media.

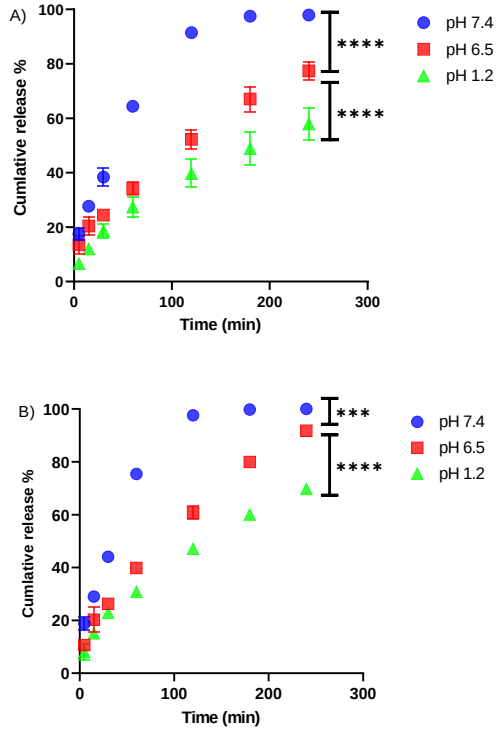

Fig. 1. *A) The release profile of metronidazole (mean ± SD) from HE hydrogel films at different pH conditions. B) The release profile of metronidazole (mean ± SD) from HZ hydrogel films at different pH conditions. At 37°C with shaking 100 rpm. n=3*

The data in Fig.2 show dual hydrogels have a significantly higher release of MT at pH 6.5 in the presence of the rat cecal content compared to the pH-responsive hydrogels in the same buffer solutions without cecal content. This can be justified by azoreductase activity produced by anaerobic bacteria in the colon.

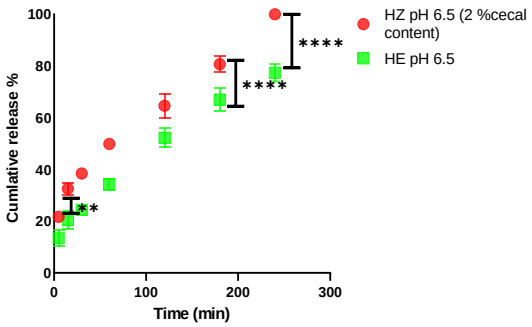

Fig. 2*. The release profile of metronidazole (mean ± SD) from HZ hydrogel films in the presence of the 2% rat cecal content compared to HE in buffer 6.5. n=3*

CONCLUSIONS

Developing colon targeted drug delivery systems is essential to improve treatment of colonic diseases such as Crohn's disease and ulcerative colitis, as well as bacterial infection of GIT. The results show that the dual (pH-enzyme) responsive hydrogels are a potential carrier for colon targeted delivery of clinically relevant water-soluble drugs, such as metronidazole.

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