

TARGETING THE COLON WITH PECTIN-HPMC COMPRESSION-COATED TABLETS



M. Turkoglu¹, T. Ugurlu¹, L.A. Hodges² and H.N.E. Stevens^{2,3}

¹ Marmara University, Faculty of Pharmacy, Pharmaceutical Technology Department, 34668 Haydarpasa-Istanbul, Turkey ² Bio-Images Research Ltd., Bio-Imaging Centre, Within Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, U.K. ³ Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, U.K.

INTRODUCTION

Colon specific drug delivery formulations have applications both in local treatment of colonic disease and also for systemic treatment. The colon is thought to be a suitable site for systemic delivery of proteins and peptides due to its lower proteolytic activity. The pectin-hydroxypropyl methylcellulose (HPMC) combination with a potential for colonic drug delivery was first reported in 1999 [1]. The pectin-HPMC coating protects the core tablet until arrival in the colon, where colonic flora starts to degrade the excipient pectin exposing the core tablet allowing release of the incorporated drug. The *in-vitro* evaluation and optimisation of such a system using 5-aminosalicylic acid and nisin as marker drugs were also reported in the literature [2,3].

For this clinical study in healthy volunteers, the core tablet did not contain any active drug. Instead this was replaced by a technetium-99m-diethylenetriamine-pentaacetic acid (^{99m}Tc-DTPA) radiolabelled lactose marker. This allowed time and site of release and gastrointestinal transit to be determined by gamma scintigraphic methods.

OBJECTIVES

- To characterise release of a scintigraphic marker from the radiolabelled pectin-HPMC compression-coated tablets
- To assess gastrointestinal (GI) transit of the radiolabelled pectin-HPMC compression-coated tablets

EXPERIMENTAL METHODS

Formulation of radiolabelled pectin-HPMC compression-coated tablets

The core tablet mixture was prepared by wet granulation of polyvinylpyrrolidone and lactose, with water as the granulating fluid. The wet granulate was dried in an oven for 2h, then pressed through a 1mm sieve. Resultant granules were dried for another hour. Stearic acid (1% weight of dried granules) was added and mixed. ^{99m}Tc-DTPA-labelled lactose (4MBq at time of dosing) was then added to the resultant mixture and compressed into 100mg tablets. The tablet diameter was 6mm.

The coating mixture was prepared by mixing HPMC and pectin in a 1:4 weight ratio. The tablet was assembled by centralising the core tablet on a 200mg bed of the coating mixture contained in a punch and die set prior to addition of a further 200mg of the coating mixture, followed by compression. The complete tablet was approximately 500mg in weight with dimensions of 10mm (diameter) X 5mm (thickness). Figure 1 shows the configuration of the assembled tablet.

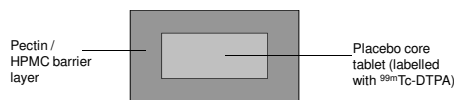


Figure 1: Pectin-HPMC compression-coated tablet.

Clinical study

Design Single-centre, open-label, single-dose study.

Subjects 6 healthy male volunteers (mean age 32.5±9.4, range 24 to 47 years).

Dosing Fasted subjects were dosed with one tablet on the study day with 240mL water.

Imaging schedule Scintigraphic imaging was performed with the subject in a standing position using a Siemens E-Cam gamma camera fitted with a low-energy high-resolution collimator. Anterior and posterior static acquisitions of 25-second duration were collected immediately after dosing then every 15 minutes. Imaging continued until complete release of the ^{99m}Tc radiolabel from the dose had been observed to a maximum of twelve hours post dose. Images were analysed using the WebLink image analysis software.

RESULTS AND DISCUSSION

Table 1 shows that the tablets arrived in the colon intact in all subjects. Release occurred in the ascending colon in three subjects and in the transverse colon in the other three subjects. The HPMC-pectin coating was sufficiently robust and successfully protected the core tablet from premature release in the upper GI tract. The coating only began to degrade in the presence of colonic flora thereby allowing release of the radiolabel upon exposure of the core tablet. Mean time of onset of release was 395.1±64.6min post-dose. Release of radiolabel from the tablet was complete within 110.0±33.8min after onset.

Subject	Release of radiolabel				
	Site of onset of release	Site of complete release	Onset (min)	Completion (min)	Time Taken (min)
001	AC	AC/TC	337.5	502.5	165.0
002	TC	TC	487.5	577.5	90.0
003	AC	AC	352.5	442.5	90.0
004	AC	AC	337.5	442.5	105.0
005	TC	TC	457.5	532.5	75.0
006	TC	TC	398.0	533.0	135.0
Mean			395.1	505.1	110.0
Min			337.5	442.5	75.0
Max			487.5	577.5	165.0
SD			64.6	54.1	33.8
n			6	6	6

Table 1: Radiolabel release parameters.

The mean gastric emptying time of the tablet was 72.5±41.0min (range 22.5 – 142.5min). This large variation in values may be attributed to dosing in the fasted state as the phases of the migrating myoelectric complex cycle (MMC) were not standardised. This increased the possibility of fortuitous emptying during a housekeeper wave in Phase 3 of the MMC. Mean colon arrival time was 272.5±82.0min, giving a mean small intestinal transit time of 200.0±78.6min.

For subjects in which the tablet entered the transverse colon, the mean transit time through the ascending colon was 25.2±17.2min (n=3). Example scintigraphic images obtained from the study are shown in Figure 2. Gastric emptying was first noted at the 90min image. Entry into the ascending colon and onset of radiolabel release were seen at the 360min image. Release was complete in the 450min image.

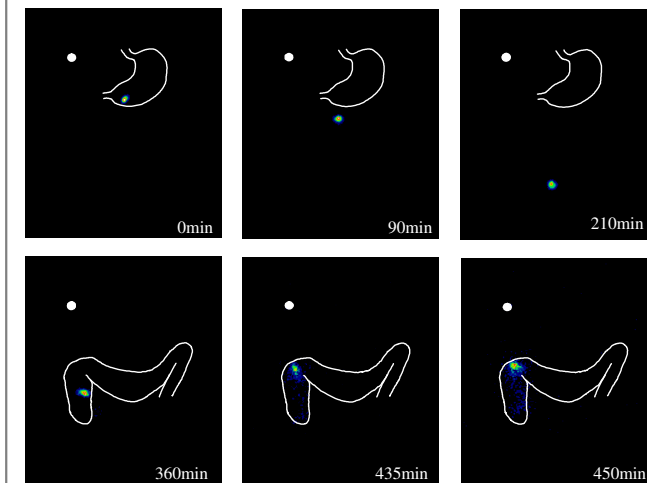


Figure 2: Scintigraphic images of tablet GI transit (Subject 003). All times shown are post-dose. Outlines of the stomach and colon are provided for reference. The reference marker for image alignment is shown as a filled white circle.

CONCLUSION

Gamma scintigraphy was used successfully in this study to track the gastrointestinal transit of tablets in all six subjects. Release of the radiolabel was clearly visualised. Each tablet dosed in this study remained intact until arrival in the colon, where release of the radiolabel occurred. The HPMC-pectin coating proved sufficiently robust, preventing premature release prior to colon entry.

ACKNOWLEDGEMENTS

This project was supported by the Scientific and Technological Research Council of Turkey (Project Number:105S405 SBAG-3212).

REFERENCES

1. Turkoglu, M. et al., *Pharm. Ind.*, 61 (1999) 662-665
2. Turkoglu, M and Ugurlu, T. *Eur. J. Pharm. Biopharm.*, 53 (2002) 65-73
3. Ugurlu, T. et al., *Eur. J. Pharm. Biopharm.*, 67 (2007) 202-210