

SCINTIGRAPHIC EVALUATION OF HPMC MATRIX TABLET EROSION IN MAN

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INTRODUCTION

In contact with water, hydroxypropyl methylcellulose (HPMC) swells to form a gel, which serves as a barrier to drug diffusion. Drug release from the HPMC-drug matrix involves solvent penetration into the dry matrix, gelatinisation of the polymer, dissolution of the drug and diffusion of the solubilised drug through the gel layer. Concomitantly, outer layers of the tablet become fully hydrated and dissolve, a process generally referred to as erosion [1].

OBJECTIVE

This study evaluated the release of radiolabelled insoluble marker from two tablets containing HPMC to improve understanding of drug release from these matrices.

EXPERIMENTAL METHODS

Formulation of radiolabelled matrix tablets

Two matrix tablet (MT) formulations, A and B, were prepared consisting of HPMC (Metolose, 90SH-100SR):lactose in ratios of 20:69 and 40:49%(w/w) respectively. The tablets also contained 10%(w/w) dicalcium phosphate and 1%(w/w) magnesium stearate (MgS). All the excipients except MgS were mixed in a Turbula® mixer for 20 min followed by addition of MgS and further mixed for another 5 min. 250mg of the resultant powder was mixed with technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA)-labelled charcoal and compressed at 1 ton for 10s to form flat-faced tablets (8.0mm diameter and 3.7mm thickness). Each tablet contained approximately 3mg activated charcoal labelled with 4MBq ^{99m}Tc-DTPA at time of dosing.

Clinical study

This was a single centre, randomised, two-way crossover study in 6 healthy male volunteers (range 21-35 years; BMI 22.5±2.3kg/m²). Subjects were dosed with one MT per study day 30 minutes after a light snack. Each MT was given with 240mL water. Imaging was performed immediately after dosing and then every 15 minutes with the subject in a standing position using a Siemens E-Cam gamma camera fitted with a low-energy, high-resolution collimator. At each timepoint, anterior and posterior static acquisitions were collected until complete release of the radiolabel was observed.

Scintigraphic data analysis

The scintigraphic images were analysed to quantitatively describe the tablet erosion, to determine the time and site of onset and completion of tablet erosion as well as to establish gastric emptying and colonic arrival of the tablet core, if applicable. Tablet erosion profiles were determined by drawing regions of interest around the tablet core. Anterior and posterior images were analysed in this manner and the geometric mean of the background and decay-corrected counts was calculated.

RESULTS AND DISCUSSION

Five subjects completed both arms of the study; one subject was unable to attend for dosing of MT(A). Scintigraphic images obtained allowed the visualisation of MT erosion behaviour. Sample images of erosion of MT(B) are shown in Figure 1.

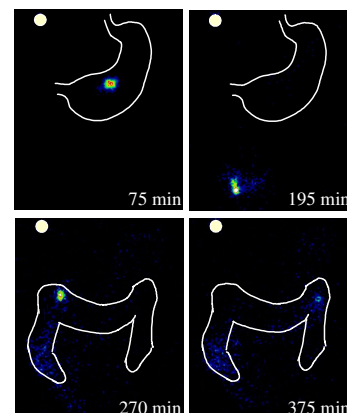


Figure 1: Sample images of MT(B) erosion in-vivo. A white circle represents the marker used for alignment of sequential images. Stomach and colon outlines are provided for visualisation of tablet location.

Onset of erosion for MT(A) and MT(B) was in the stomach, for all except one subject in both study arms. Erosion was complete in the small intestine for MT(A) for all subjects. MT(B) arrived in the colon in five out of six subjects, with approximately 20% of the maximum activity remaining in the tablet core.

Table 1: Erosion parameters of MT in vivo. The values represented are mean (S.D.)

| Parameter | MT(A); n=5 | MT(B); n=6 |
|----------------------------|--------------|--------------|
| Onset (min post-dose) | 19.8 (12.3) | 20.1 (5.9) |
| Completion (min-post-dose) | 139.9 (24.3) | 322.6 (37.8) |
| Erosion time (min) | 120.1 (27.7) | 302.5 (34.7) |

The behaviour of the MTs following exposure to gastrointestinal fluids were dependent on the composition ratios of HPMC:lactose. No difference was observed in mean time of erosion onset between the two tablets (Table 1). Initial radiolabel release was probably due to dissolution and diffusion of lactose from the tablet surface, creating porous channels allowing detachment of radiolabelled charcoal.

The erosion of MT(A) was faster than MT(B) as seen by the mean erosion completion times of 139.9±24.3min and 322.6±37.8min respectively. Lactose dissolution forms porous channels expediting water penetration into the tablet core. The gel structure of Tablet A was more adversely affected by this phenomenon due to higher lactose content, thereby reducing tablet integrity and resulting in higher and more erratic erosion rates. The higher HPMC content of Tablet B increased the strength of the hydrated gel layer, improving resistance to in-vivo shearing forces.

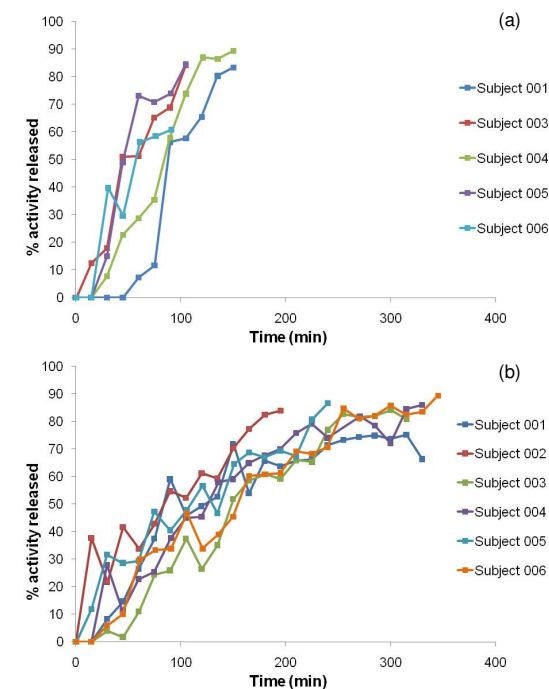


Figure 2: Individual in-vivo radiolabel release profiles (a) MT(A) and (b) MT(B).

CONCLUSION

This study succeeded in characterising the in-vivo erosion behaviour of two HPMC matrix tablets in a quantitative manner based on radioactive counts remaining in the tablet core. Differences in erosion profiles were attributed to the formulation composition and strength of the gel layer formed.

REFERENCE

1. Alderman D.A. (1984) *Int. J. Pharm. Tech. & Prod. Mfr.* 5(3), 1-9