

IN VITRO – IN VIVO CORRELATION OF EROSION OF MATRIX TABLETS: A GAMMA SCINTIGRAPHIC STUDY

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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]. In this scintigraphic study, *in vitro* gravimetric erosion studies were correlated with *in vivo* erosion behaviour of HPMC matrix tablets (MT).

EXPERIMENTAL METHODS

Formulation of radiolabelled matrix tablets

Two MT formulations, A and B, were prepared consisting of HPMC (100cp):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 diethylenepentaacetic acid (^{99m}Tc-DTPA) radiolabelled charcoal and compressed at 1 ton for 10s to form flat-faced tablets (8.0mm diameter and 3.7mm thickness). Each tablet contained 4MBq ^{99m}Tc-DTPA at the time of dosing.

In vitro erosion studies

Tablets were prepared as above using non-radiolabelled charcoal and gravimetric erosion studies were performed in 1L distilled water as previously described [2].

Clinical study

This was a single centre, randomised, two way crossover study in 6 healthy male volunteers (range 21-35 years; BMI 22.5±2.3 kg/m²). Subjects were dosed with one MT per study day 30 minutes after a light snack. Each MT was given with 240 mL 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.

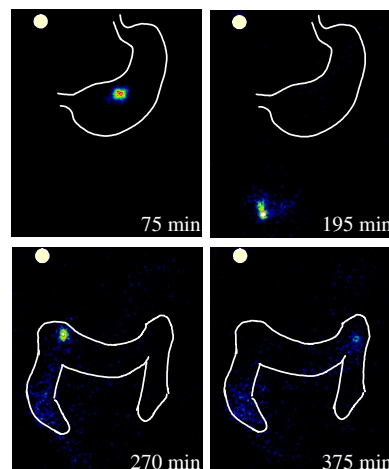


Figure 1: Sample images of MT(B) erosion *in vivo*. A white circle represents the marker used for alignment of sequential images. Stomach and colon outlines are provided for visualisation of tablet location.

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 for MT(A) for all subjects in the small intestine. In contrast, 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 2: 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 *in vitro* profiles and the behaviour of the MTs following exposure to gastrointestinal fluids were dependent on the composition ratios of HPMC:lactose. The erosion of MT(A) was faster than MT(B). Dissolution of the water-soluble component, lactose, forms porous channels which expedite water penetration to the tablet core. The increase in water content may dilute the gel layer in MT(A), thereby detrimentally affecting the gel structure leading to faster erosion (Table 2).

MT(A) showed good correlation between *in vitro* and *in vivo* results with the exception of Subject 001. Release of radiolabel corresponding to *in vivo* erosion for MT(A) was observed over a two hour period, which was consistent with the *in vitro* erosion profile. This rapid erosion rate can be attributed to the formulation composition of the tablet, 69%(w/w) lactose and 20%(w/w) HPMC. The dissolution and consequent diffusion of lactose from the tablet occurred at a higher rate than HPMC erosion, leaving behind a porous and diluted gel layer. Poor tablet integrity reduced the ability of the tablets to withstand shearing forces within the GI tract.

MT(B) also showed good correlation between *in vitro* and *in vivo* erosion profiles, although over a much longer (>6hr) time-scale. The higher HPMC concentration in MT(B) increased the strength of the gel layer that formed upon hydration and retarded the penetration of water into the dry core. This enabled the tablet to better withstand *in vivo* hydrodynamic forces, resulting in slower erosion.

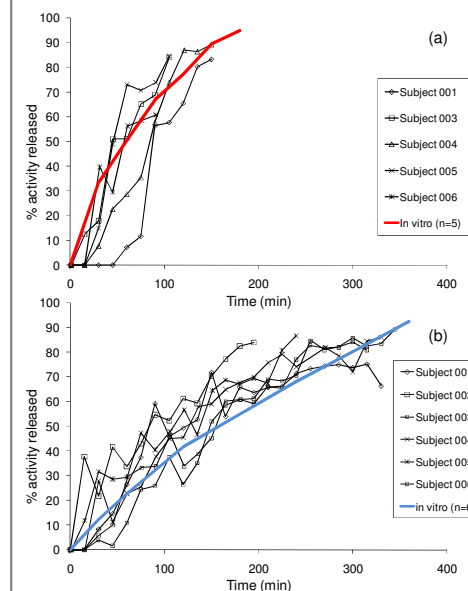


Figure 2: Individual *in vivo* radiolabel release profiles with *in vitro* gravimetric erosion profile for (a) MT(A) and (b) MT(B).

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. Correlation with *in vitro* data was also achieved. Differences in erosion profiles were attributed to the formulation composition and strength of the gel layer formed.

REFERENCES

1. Alderman D.A. (1984) *Int. J. Pharm. Tech. & Prod. Mfr.* 5(3), 1-9
2. Ghimire, M. et al. (2007) *Proc 33rd Int Symp Cont Rel Bioactive Mat*, 708.