SITE-SPECIFIC RELEASE WITH THE HS CAPSULE

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INTRODUCTION AND OBJECTIVES

Compounds with challenging biopharmaceutical properties, such as limited or narrow oral absorption windows, require evaluation of their absorption profiles prior to development in controlled release systems. The basic structure of the Hydrophilic Sandwich (HS) capsule is shown in Figure 1. The inner capsule is placed within the outer capsule and the inter-capsule space is filled with a layer of the hydrophilic polymer, hydroxypropyl methylcellulose (HPMC). The outer capsule is coated with a gastroresistant material.

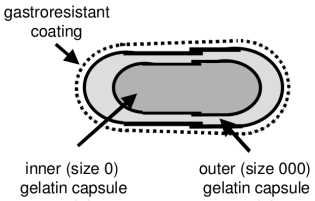

Figure 1: Configuration of HS capsule

An *in vitro* study was conducted to investigate the effect of the composition of the hydrophilic polymer layer on time of burst release. Following this study, three HS capsule variants were administered to healthy volunteers in a clinical trial.

EXPERIMENTAL METHODS

In vitro dissolution studies

HS capsules containing methylene blue as a marker in the inner capsule and ^{99m}Tc-DTPA-charcoal in the HPMC layer were prepared with the following ratios of HPMC layer: E15:E50 75:25%(w/w) [**A**], E15:E50 50:50%(w/w) [**B**] and E50 100%(w/w) [**C**]. These capsules were spray coated with an organic coating of Eudragit L100.

Capsules were subjected to 900 mL JP 1st fluid for 2 h, followed by 900 mL JP 2nd fluid in a USP II dissolution apparatus (37 ℃, 50 rpm). Release of ^{99m}Tc was monitored scintigraphically. Release of methylene blue was observed visually and the time of burst noted.

Clinical study

This was a single centre, open label, three-way crossover study in six healthy male volunteers. HS capsules (**A**-**C**) were prepared as described above but contained 0.3 MBq ^{111}In-DTPA-labelled lactose instead of methylene blue within the inner capsule. Each capsule was dosed with 240 mL water 30 min after a light snack of a slice of crispbread and jam with apple juice. Anterior and posterior static acquisitions were taken immediately after dosing, with the subject in a standing position, using a Siemens E-Cam gamma camera fitted with a low-energy, high-resolution collimator. Imaging was stopped when complete release of ^{111}In was observed.

RESULTS AND DISCUSSION

In vitro dissolution studies

Release of ^{99m}Tc-DTPA-charcoal from the HPMC layer was successfully determined using gamma scintigraphy. Quantitative analysis of the radiolabel release was performed and graphically depicted. Figure 2 shows the decrease of ^{99m}Tc activity from three HS capsules **B**.

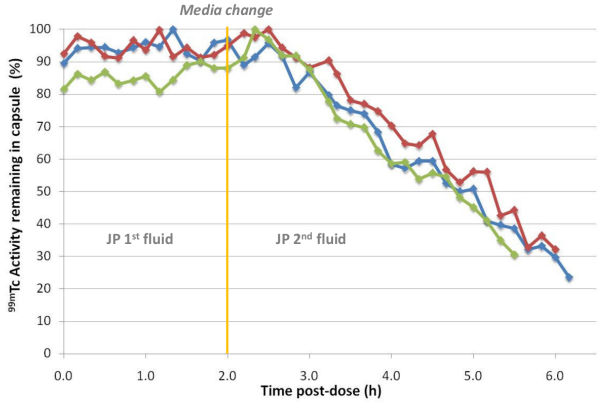

Figure 2: Release of ^{99m}Tc-DTPA-charcoal from HS capsule B

Scintigraphic monitoring clearly showed that the gastroresistant coat remained intact in the acidic, JP 1st fluid. Disintegration of the coat and subsequent onset of ^{99m}Tc release occurred only after immersion in JP 2nd fluid (pH 6.8). Exposure of the HPMC layer to aqueous medium resulted in gelling and subsequent erosion, which was manifested in the gradual release of ^{99m}Tc-DTPA-charcoal from the capsule.

Time to release of the inner capsule, as determined by visual observation of methylene blue release, is summarised in Table 1.

Table 1: Inner capsule *in vitro* release times.

HS capsule variant	n	Release time (Mean ±S.D.) (min)
A	2	235.0±3.5
B	5	267.8±33.5
C	3	324.0±26.0

Release behaviour of these formulations *in vitro* were relatively consistent within the same capsule variant. Time to onset of release increased from **A** to **C** as a result of increasing HPMC viscosity.

Clinical study

Five subjects completed all three arms of the study; one subject was only dosed with HS capsules **B** and **C**. Figure 3 shows scintigraphic images of HS capsule **A** behaviour in Subject 003.

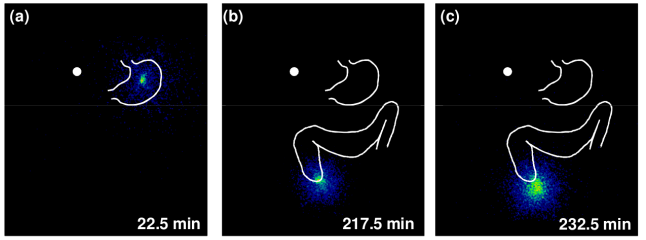

Figure 3: Scintigraphic images of HS capsule A (Subject 003) where (a) intact capsule in the stomach; (b) onset of ^{111}In release and (c) complete ^{111}In release. The white circle represents the marker used for alignment of sequential images. Stomach and colon outlines are provided for visualisation of tablet location. Times shown are post-dose.

Mean gastric emptying (GE) times for the three HS capsule variants were 106.5±34.5 min, 107.3±31.3 min and 88.3±17.2 min for **A**, **B** and **C** respectively. Release of the radiolabel was only seen post-gastric emptying, indicating the robustness of the gastroresistant coat.

HS capsule **A** (E15:E50 75:25%(w/w) in the inter-capsule space) proved the most successful in delivering the inner capsule radiolabel to the ileocaecal junction (ICJ)/proximal colon, as shown in Table 2. HS capsules **B** and **C** mainly released in the small intestine, except on two occasions where they released in the ascending colon and once in the ICJ.

Table 2: GI transit and ^{111}In release parameters for HS capsule A.

Subject	GE (min post-dose)	Release onset (min post-dose)	Site of onset	Complete release (min post-dose)	Site of complete release
001	112.5	247.5	AC	262.5	TC
002	67.5	142.5	SI	157.0	ICJ
003	112.5	217.5	ICJ	232.5	ICJ
004	82.5	187.5	SI	217.5	ICJ
005	157.5	262.5	ICJ	262.5	ICJ
Mean	106.5	211.5	NA	226.4	NA
S.D.	34.5	48.1	NA	43.4	NA

CONCLUSION

Delivery to the distal intestine (ICJ/proximal colon) was successfully achieved with HS capsule **A**. This is a simple, easily assembled delivery system with potential for use in regional absorption studies.