VALIDATION OF A TARGETED RELEASE CAPSULE USING SCINTIGRAPHIC METHODS

D. Pecek[1], K.A. Sime[1], V.E. Ronaldson[1], S.M. Connolly[1], L.A. Hodges[1], F.J. McInnes[2], H.N.E. Stevens[1,2]

[1] Bio-Images Research Ltd., Glasgow G4 0SF, UK. [2]Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow G4 0NR, U.K.

INTRODUCTION AND OBJECTIVES

There currently exists a large range of compounds with challenging biopharmaceutical properties, such as limited or narrow oral absorption windows. In order to evaluate the behaviour of such compounds at specific sites in the gastrointestinal (GI) tract, various controlled release systems, triggered by external stimuli, have been developed. However, there have been instances of failure of these complex systems whereby the drug payload was not released after triggering.

The 'Hydrophilic Sandwich' (HS) capsule, as shown in Figure 1, is a 'capsule within a capsule', where the drug or test compound is placed in the inner capsule, and the inter-capsule space is filled with a layer of the hydrophilic polymer, hydroxypropyl methycellulose (HPMC). With judicious choice of the molecular weight and density of the gelling polymer layer, the time taken for its erosion, subsequent bursting of the inner capsule and release of drug, can be controlled. It was envisaged that by varying the grade and blend of erodible HPMC in the hydrophilic layer, the time of drug release from the inner capsule could be controlled.

Following extensive *in vitro* characterisation, a clinical study was conducted in healthy volunteers to evaluate the *in vivo* behaviour of this system with three HS capsule variants.

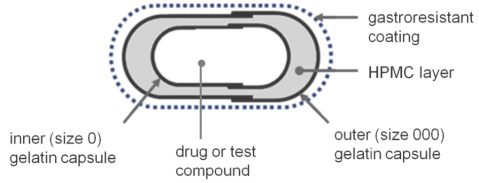

Figure 1: Configuration of HS capsule

EXPERIMENTAL METHODS

This was a single centre, open label, three-way crossover study in six healthy male volunteers. HS capsules were prepared with the following ratios of hydroxypropyl methylcellulose (HPMC) as the polymer layer: E15:E50 75:25%(w/w) [**A**], E15:E50 50:50%(w/w) [**B**] and E50 100%(w/w) [**C**]. The HPMC layer of each HS capsule was labelled with 4.0 MBq ^{99m}Tc-DTPA and the inner capsule contained 0.3 MBq ^{111}In-DTPA. Assembled capsules were spray coated with Eudragit L100 to confer gastroresistance. Each capsule was taken with 240 mL water 30 min after a light snack (approximately 550 kJ). Anterior and posterior static acquisitions were acquired 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. Imaging was stopped when complete release of ^{111}In from the inner capsule was observed.

RESULTS AND DISCUSSION

Five subjects completed all three arms of the study; one subject was only dosed with HS capsules **B** and **C**.

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 observed post-gastric emptying, indicating the robustness of the gastroresistant coat.

Onset of ^{99m}Tc release from the inter-capsule layer occurred in the small intestine (SI) for all subjects dosed with all variants of the HS capsule. The mean times to onset of HPMC layer erosion post gastric emptying are shown in Table 1 are in relatively good agreement for the three HS capsule variants. The mean onset of erosion of the capsules for all three capsules occurred after approximately 1.5 h in the higher pH of the SI.

Table 1: Mean Time to onset of release of ^{99m}Tc post gastric emptying

HS variant	n	Time to onset of ^{99m}Tc release post gastric emptying (Mean ± S.D.) (min)
A	5	87.2±12.3
B	6	94.9±18.2
C	5	102±6.7

^{111}In was used in the inner capsule as a marker to represent release of drug. Figure 2 shows scintigraphic images of HS capsule **A** behaviour in Subject 003.

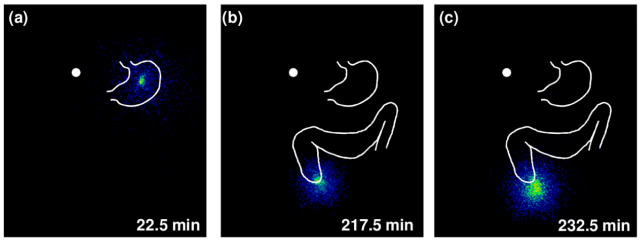

Figure 2: Scintigraphic images of HS capsule A (Subject 003) showing (a) intact capsule in the stomach; (b) onset of ^{111}In release and (c) complete ^{111}In release. The white circle represents the external marker used for alignment of sequential images. Stomach and colon outlines are provided for visualisation of capsule location. Times shown are post-dose.

HS capsule **A** (E15:E50 75:25%(w/w) in the inter-capsule space) proved consistent in delivering the inner capsule radiolabel to the ileocaecal junction (ICJ)/proximal colon, as shown in Table 2.

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

Where AC, ascending colon; TC, transverse colon; SI, small intestine; ICJ, ileocaecal junction; GE, gastric emptying

The site of release of Capsules **B** and **C** were much more variable compared to A. The site of complete ^{111}In release is shown in table 3.

Table 3: Site of complete ^{111}In release for the three HS variants

Location of Complete ^{111}In Release	HS Variant A (n = 5)	HS Variant B (n = 6)	HS variant C (n= 5)
SI		2	3
Distal SI			1
ICJ	4	2	1
AC		1	
AC/TC		1	
TC	1		

Where AC, ascending colon; TC, transverse colon; SI, small intestine; ICJ, ileocaecal junction; GE, gastric emptying

CONCLUSION

Delivery to the distal small intestine (ICJ/proximal colon) was achieved with HS capsule **A**. Capsule contents released in the ICJ or AC should, under normal GI transit conditions, move on to the colon and be absorbed from there. Based on this, HS Capsule **A** (E15:E50 75:25%) could prove very useful for targeting drug release to the colon. This is a simple, easily assembled delivery system with potential for use in regional absorption studies.