DEVELOPMENT OF A CAPSULE SYSTEM FOR SITE-SPECIFIC DRUG DELIVERY

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

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.

This communication describes a simple, manually assembled 'capsule within a capsule' device which relies only on the controllable erosion of a gel layer to release drug at specific sites in the GI tract. The basic structure of this 'Hydrophilic Sandwich' (HS) capsule is shown in Figure 1.

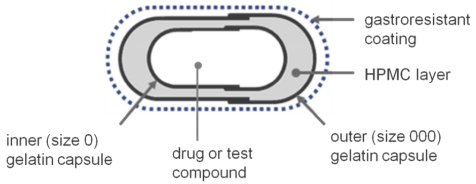

Figure 1: Configuration of HS capsule

The inner capsule, designed to hold test compounds, 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. 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.

EXPERIMENTAL METHODS

HS capsules containing methylene blue as a marker in the inner capsule, and technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) labeled 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 solution of Eudragit L100.

Capsules (n=3) were subjected to 900 mL JP 1st fluid (pH 1.2) for 2 h, followed by 900 mL JP 2nd fluid (pH 6.8) in a USP II dissolution apparatus (37 °C, 50 rpm). Release of ^{99m}Tc was monitored scintigraphically. Release of methylene blue was observed visually and the time of release noted.

RESULTS AND DISCUSSION

Release of ^{99m}Tc-DTPA-charcoal from the HPMC layer was determined using gamma scintigraphy. Figure 2 shows sample dissolution images obtained from HS Capsule **B**.

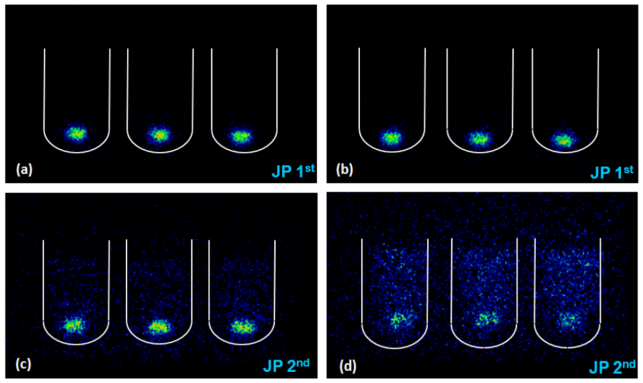

Figure 2: Gamma scintigraphic images of ^{99m}Tc release from HS capsule B after (a) 0 min; (b) 120 min; (c) 246 min and (d) 370 min. Outlines of dissolution vessels have been drawn for presentation only and are not to scale.

After 2 h in JP 1st fluid, all radioactivity remained concentrated in the capsule, indicating the robustness and integrity of the gastroresistant coat. Disintegration of the coat and subsequent onset of ^{99m}Tc release occurred only after immersion in JP 2nd fluid. 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.

The times to 50% release of ^{99m}Tc ($t_{50\%}$) and release of methylene blue from the HS capsules are shown in Table 1.

Table 1: $t_{50\%}$ for ^{99m}Tc release and times for methylene blue release

HS Capsule	$t_{50\%}$ (min)		Methylene blue release	
	Mean	S.D.	Mean	S.D.
A	266	13	355	4
B	374	5	388	34
C	385	8	444	26

The data in Table 1 shows that as the viscosity of the gelable layer increased, the ^{99m}Tc release rate decreased while the time to inner capsule (methylene blue) release increased.

In vivo, the gastroresistant layer would be expected to prevent disintegration in the stomach; indeed radiolabel release profiles from these *in vitro* studies are fairly linear after capsule exposure to higher pH media and show no erosion in JP 1st fluid (Figure 3).

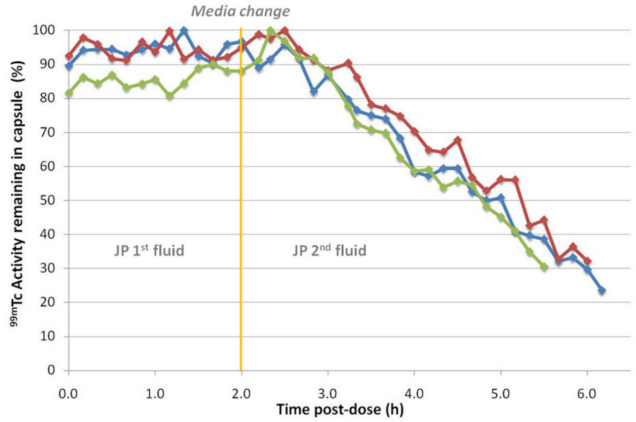

Figure 3: Release of ^{99m}Tc from HS Capsule B

Gelling, and subsequent erosion, of the HPMC layer would be expected only to commence in the higher pH environment of the small intestine. As small intestinal transit time has been well characterized as relatively constant (between 120 and 240 min [1]), it is highly likely that release of the contents of the HS capsule would occur either at the ileocaecal junction or upon entry into the proximal colon.

CONCLUSION

These *in vitro* studies showed that manually-assembled HS capsules exhibit reproducible dissolution profiles which can be monitored scintigraphically. These *in vitro* results, together with literature on small intestinal transit time, suggest that *in vivo* release of the capsule contents should occur in the distal small intestine or proximal colon.

REFERENCE

1. Davis, S.S., Hardy, J.G., Fara, J.W. (1986) Transit of pharmaceutical dosage forms through the small intestine. Gut. 27: 886-892.