GASTROINTESTINAL TRANSIT AND RELEASE OF TIME-DELAYED DELIVERY CAPSULES

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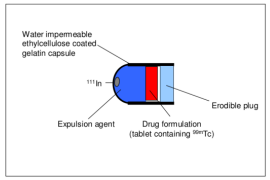
INTRODUCTION

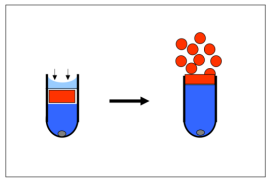
The purpose of this study was to investigate the relationship between gastrointestinal transit and site of release of a novel oral time-delayed release capsule[1].

The capsule comprises an insoluble capsule body sealed with erodible tablet plug. A swellable expulsion system is used to push the drug-containing tablet out of the capsule. The drug tablet was radiolabelled with ^{99m}Tc-DTPA and the capsule body was labelled with ^{111}In-DTPA. The capsules investigated were designed to release at 2, 3 and 4 hours post-dose.

The mechanism of action is summarised below.



The drug tablet (^{99m}Tc labelled) is sealed inside an insoluble capsule body (^{111}In labelled) by an erodible plug. Altering the composition of this plug allows variation in the release times.



GI tract fluids cause controlled erosion of the plug. After complete erosion, GI fluids enter the capsule body causing the expulsion system to swell pushing the drug tablet out into the surrounding environment.

METHODS

CLINICAL STUDY

Design
Single-centre, open-label, randomised, three-way crossover study.

Subjects
8 healthy, non-smoking males age 22 to 35 years (mean 27.9 +/-4.5).

Dosing
Subjects received one of three formulations (designed to release at 2, 3 and 4 hours) with 240ml water according to a randomisation schedule. Each study arm was separated by a seven-day washout period.

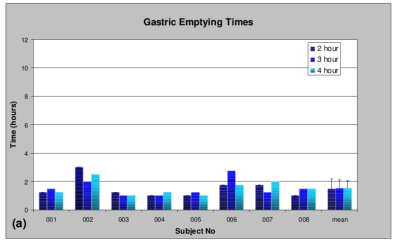
Imaging Schedule
Subjects were imaged in a standing position with the gamma camera. Anterior and posterior static acquisitions of 30 second duration were collected every 15 minutes until burst was observed then hourly to 12 hours post dose.

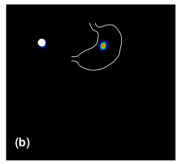
Scintigraphic analysis
Images were analysed using the WebLink® image analysis program. Gastric emptying time, time and site of release and gastrointestinal transit were determined by two independent trained operators.

RESULTS

GASTRIC EMPTYING TIMES

Gastric emptying times (Figure 2a) were not significantly different between treatments (range 1 to 3 hours).





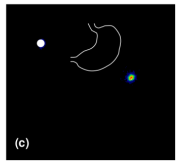
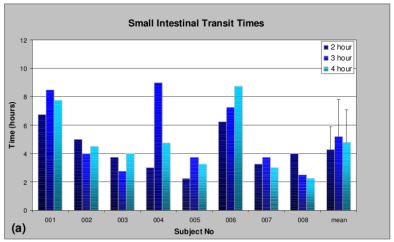
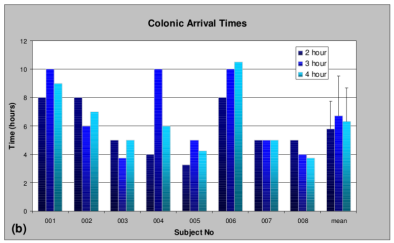


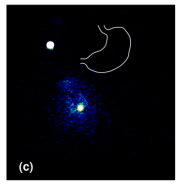
Figure 2 (a) Graph showing gastric emptying times (hours) for all subjects, all formulations. (b) & (c) Representative scintigraphic images showing a formulation pre- and post-gastric emptying

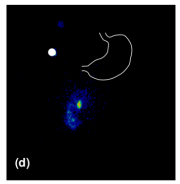
SMALL INTESTINAL TRANSIT AND COLONIC ARRIVAL TIMES

Both SI transit times (Figure 3a) and colonic arrival times (Figure 3b) were highly variable between subjects.









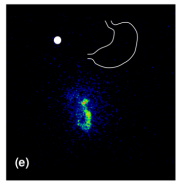


Figure 3 (a) Graph showing small intestinal transit times (hours) for all subjects, all formulations. (b) Graph showing colonic arrival times (hours) for all subjects, all formulations (c), (d) & (e) Representative scintigraphic images showing release from the 2, 3 and 4 hour formulations respectively.

TIME AND SITE OF RELEASE

The time and site of release of each formulation is shown in Table 1.

Subject No	Release time (hours)			Site of release		
	2 hour	3 hour	4 hour	2 hour	3 hour	4 hour
001	2.75	3.00	4.25	SI	SI	SI
002	3.50	2.75	4.75	SI	SI	SI
003	2.75	NR	3.25	SI		SI
004	2.75	NR	3.75	ICJ		SI
005	2.00	3.00	NR	SI	ICJ	
006	NR	3.75	5.25		SI	SI
007	2.50	3.25	3.75	SI	SI	SI
008	3.50	NR	NR	SI		

18 (out of a total of 24) formulations released in vivo with mean release times of 2.82 hours (+/-0.53, n=7), 3.15 hours (+/-0.38, n=5) and 4.17 hours (+/- 0.74, n=6) for the 2, 3 and 4 hour formulations respectively. All formulations released in the small intestine (SI).

DISCUSSION

Erosion of the plug to allow swelling of the expulsion system and hence release of the contents is dependant on the availability of water and the degree of stirring or tumbling.

Release is therefore unlikely to occur in an environment such as the colon and rapid transit through the small intestine, resulting in early arrival in the colon will reduce the likelihood of release.

The majority of formulations (5 out of 6) which failed to release exhibited either rapid SI transit (<3.5 hours) or were observed to exhibit prolonged stasis within the small intestine.

CONCLUSION

The feasibility of time-delayed release *in vivo* has been demonstrated. However variability still exists due to inter and intra subject variability in gastrointestinal transit times.

REFERENCES

[1]Ross AC *et al* (2000) *Journal of Pharmacy and Pharmacology* **52***:* 903-909

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