The *In-Vivo* Behaviour Of Erodible Tablets: A Gamma Scintigraphic Study

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Bio-images

INTRODUCTION

An approach employed in improving treatment of circadian-dependent diseases is to coat conventional tablets with materials that act as barrier layers that slowly erode to expose the inner tablet, thereby delaying drug release [1]. In this study, placebo tablets consisting of materials conventionally used as barrier layers were manufactured in three different ways to investigate how the method of preparation affected the erosion behaviour *in-vivo.*

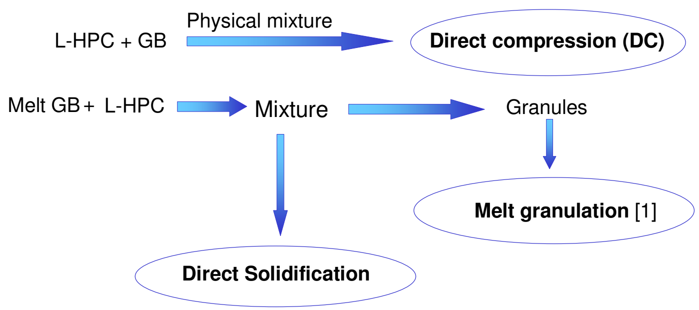
Erodible tablets (ET) containing glyceryl behenate (GB) (wax) and low-substituted hydroxypropylcellulose (L-HPC) (disintegrant) were manufactured using direct compression (DC), melt granulation (MG) and direct solidification (DS). A small amount of radioisotope was dispersed throughout the tablet. This allowed the behaviour of the tablet within the gastrointestinal tract to be assessed using gamma scintigraphy.

The aim of this study was to characterise the *in-vivo* behaviour of these ETs as barrier layers in view of developing wholly time-dependent controlled release tablet systems.

EXPERIMENTAL METHODS

PREPARATION OF ERODIBLE TABLETS

For all methods, the ratio of GB:L-HPC was maintained at 65:35%(w/w) and the target tablet weight was 500mg with dimensions of 13mm (diameter) and 4mm (thickness). Three manufacturing methods assessed are shown below.



CLINICAL STUDY AND SCINTIGRAPHIC IMAGING

Design Single centre, open-label, three arm study.

Subject 6 healthy male volunteers (range 22-46 years).

Dosing Subjects were dosed with one ET per study day with 240ml water 30 minutes after a light snack (500kJ).

Imaging Imaging was performed with the subject in a standing position using a Siemens E-Cam gamma camera. At each set interval, anterior and posterior static acquisitions were collected.

SCINTIGRAPHIC DATA ANALYSIS

The scintigraphic images were analysed to determine the time and site of onset and completion of tablet erosion as well as to establish gastric emptying of the tablet core, if applicable. Tablet erosion profiles were determined by drawing regions of interest around the tablet core in anterior and posterior images and the geometric mean of the background and decay-corrected counts was calculated.

RESULTS AND DISCUSSION

All subjects completed all three arms of the study. Scintigraphic images obtained allowed the visualisation of the ETs' erosion behaviour. Sample images of ET-DC erosion are shown in Fig 1. Onset of tablet erosion was observed from 10 min post-dose and progressed within the stomach until complete erosion of the tablet.

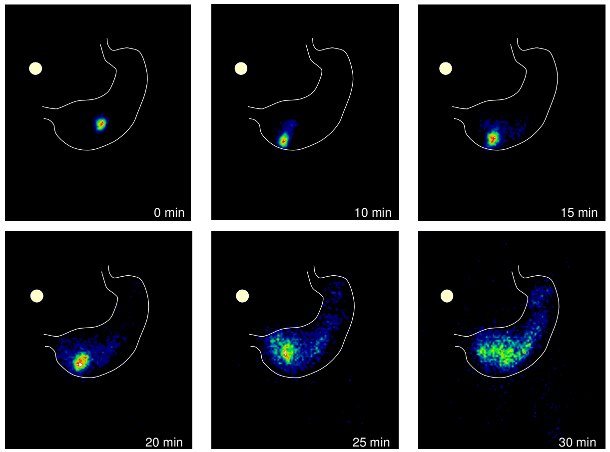


Fig 1. Sample images of ET-DC erosion *in-vivo.* A white circle represents the marker used for alignment of sequential images. A stomach outline is provided for visualisation of the tablet location.

The *in-vivo* tablet erosion profiles are shown in Fig. 2. The in-vivo erosion parameters are summarised in Table 1.

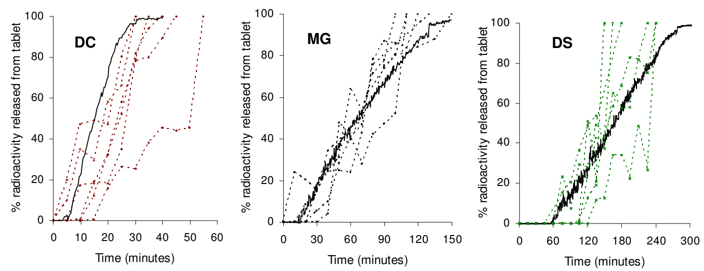


Fig 2. Comparison of mean (n=6) *in-vitro* scintigraphic erosion profile [2] (▬) to individual *in-vivo* erosion profiles.

In five subjects, erosion of the ET-DC was complete in the stomach. For the remaining subject, erosion commenced in the stomach and the tablet core gastric emptied at 32.5 min. The times of onset and completion of erosion were 6.4±3.8 min and 36.6±9.7 min respectively for ET-DC. All ET-MG tablets began to erode in the stomach (18.3±8.1 min), followed by gastric emptying of the tablet core (70.0±18.3 min) prior to completion of erosion in the small intestine 114.9±16.8 min post-dose. Two ET-DS tablets began to erode in the stomach, and the remaining four in the small intestine with a mean onset time of 67.0±18.9 min. Mean gastric emptying time for the ET-DS tablet core was 57.6±20.5 min. Complete erosion of the ET-DS (192.5±39.9 min) was observed in the small intestine in all ET-DS except one, which showed completion of erosion in the ascending colon

Table 1. Summary of *in-vivo* erosion parameters and transit data of ETs.

Formulation	Subject	Onset of erosion		Complete erosion		GE time
		Time	Site	Time	Site	
	1	7.5	S	32.5	S	-
	2	7.5	S	42.5	S	-
	3	2.5	S	27.5	S	-
ET-DC	4	12.5	S	52.5	S	-
	5	2.5	S	27.5	S	-
	6	7.5	S	37.0	SI	32.5
	Mean (SD)	6.7(3.8)	-	36.6 (9.7)	-	-
	1	15.0	S	142.5	SI	95.0
	2	25.0	S	105.5	SI	65.0
	3	5.0	S	105.5	SI	85.0
ET-MG	4	25.0	S	115.5	SI	45.0
	5	15.0	S	95.5	SI	55.0
	6	25.0	S	125.0	SI	75.0
	Mean (SD)	18.3(8.1)	-	114.9(16.8)	-	70.0(18.3)
	1	52.5	SI	232.5	SI	52.5
	2	97.5	SI	217.5	SI	82.5
	3	52.5	S	232.5	SI	67.5
ET-DS	4	82.5	SI	157.5	SI	67.5
	5	67.5	SI	142.5	SI	22.5
	6	53.0	S	172.5	AC	53.0
	Mean (SD)	67.0(18.9)	-	192.5(39.9)	-	57.6(20.5)

Note: Time is represented in minutes; GE: gastric emptying; S: stomach; SI: small intestine; AC: ascending colon.

The lag-time prior erosion and *in-vivo* erosion profiles of the tablets were dependent upon the method of tablet manufacturing. The rate of erosion decreased in the order of ET-DC>ET-MG>ET-DS. All ET-DCs displayed similar near linear erosion profiles except in one subject where the tablet eroded very quickly after the 50 min image and could not be detected in the 60 min image. Erosion profiles obtained from all volunteers were reproducible for MG i.e. near-linear release following a lag time. For DS, fragmentation of the tablet core was observed in four volunteers prior to complete erosion.

CONCLUSIONS

Gamma scintigraphy was successfully used to describe and differentiate the erosion behaviour of these tablets. Reproducible erosion profiles were exhibited by ET-MG, suggesting that this method of manufacture would be the choice for further development.

ACKNOWLEDGEMENTS

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