

Abstract Summary

A press-coated tablet formulation based on controlled erosion of a wax-disintegrant layer was investigated by *in vitro* and *in vivo* studies. *In vivo* release from the core tablet was determined by gamma scintigraphy and *in vitro* and *in vivo* lag-times compared. Erosion of the coating layer appeared slower *in vivo* than *in vitro*.

Introduction

A compression coating based on hydrophobic wax glyceryl behenate (GB) (*Comprit*[®] 888 ATO, *Gattefosse*) and the disintegrant low-substituted hydroxypropylcellulose (L-HPC) (*LH-21*, *ShinEtsu*) has been shown to provide an effective means of achieving time-delayed drug release *in vitro* (Leokittikul *et al.*, 2002a, 2003). Alteration of the wax-disintegrant ratio or the thickness of the coat provided a convenient means of controlling lag-time. Due to active control of the erosion process based on the interaction between fluid and the disintegrant, *in vitro* performance is relatively independent of dissolution hydrodynamics (Leokittikul *et al.*, 2002b). In this present study the *in vivo* performance of three formulations designed to release at 1.5, 2.5 and 4 hour post dose were assessed using gamma scintigraphy to determine core disintegration following a lag-time.

Experimental Methods

Preparation of ^{99m}Tc-DTPA labelled placebo core tablets

A powder blend was prepared by mixing lactose Fast flo (88.10 g) with Ac-Di-Sol (0.959 g) in a Turbula mixer for 30 min. Magnesium stearate was added (0.950 g) and mixed for a further 5 min. The quantity of the blend required for one tablet (90 mg) was weighed out into a glass vial. Five milligrams of lactose radiolabelled with 4 MBq (at time of dosing) technetium-99m diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA), was incorporated into the blend during manufacture to facilitate scintigraphic imaging. The mixture (95 mg) was placed in the tablet die (6.75 mm diameter) and compressed using a Spex CertiPrep 3628 bench press. The activity of the compressed tablets was checked using a Capintec CRC[®]-15R dose calibrator.

Preparation of compression coated tablets

Each coating formula (Table 1) was prepared by a melt granulation method and compressed (600mg) manually around the core tablets using a 13-mm diameter die and Spex CertiPrep 3628 bench press.

Table 1. Coating formulations for press-coated tablets

Formulation	Composition ratio (w/w)	
	Glyceryl behenate	L-HPC
A	50	50
B	60	40
C	65	35

Core containing propranolol HCl (42.75 mg) were prepared for comparative determination of *in vitro* release, using the USP II (paddle) apparatus at 50 rpm in distilled water.

Clinical study

Design

Single centre, double-blind, randomised, three-way cross-over study.

Subjects

8 healthy (4 males, 4 females), non-smoking volunteers age 22 to 34 years (mean 26.6 +/-3.7).

Dosing

Subjects received the formulations with 240ml water.

Meal Schedule

Fasted subjects received a light snack 30 minutes prior to dosing. All subjects received lunch (1300 kJ) 4 hours post-dose, an afternoon snack (600 kJ) 7 hours post-dose

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 complete release of the scintigraphic marker was observed up to a maximum of 8 hours

Scintigraphic analysis

Images were analysed using the WebLink[®] image analysis program. Gastric emptying time, time and site of release and gastrointestinal transit were determined.

Results and Discussion

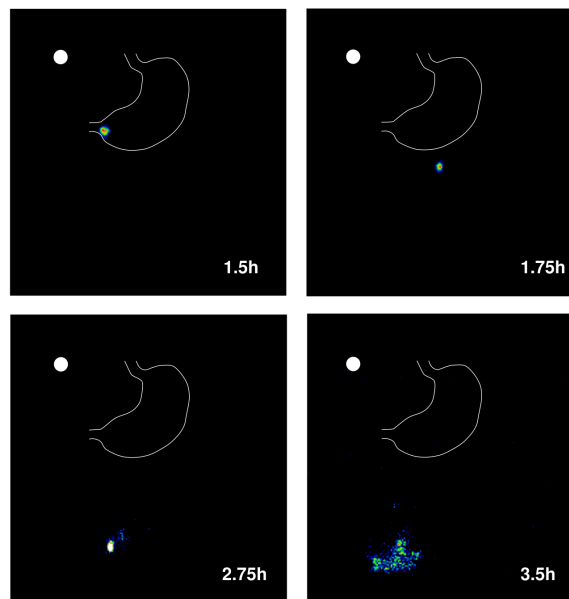


Figure 1. Gamma scintiscans showing gastrointestinal site and dispersal of ^{99m}Tc from formulation A (Subject 003). Tablet in the stomach at 1.5h, gastric emptying at 1.75h, onset of dispersion at 2.75h and complete dispersion at 3.5h.

The mean gastric emptying times are 1.25+/-0.99 hours, 1.44+/-1.04 hours and 1.28+/-0.95 hours for formulations A, B and C respectively (all n=8). This difference was not significant. This is entirely consistent with literature values for gastric emptying of fairly large (≥ 10 mm diameter) single unit dosage forms.

The shortest lag-time formulation A released successfully in 7 of the 8 subjects at times ranging from 2.75 h – 5.50 h (mean 4.43 h). The tablets were observed to release the radiolabelled marker in the small intestine (n = 5) and the ascending colon (n = 2). Formulation B released in 4 subjects, in the small intestine, at times ranging from 4.75 h – 5.25 h (mean 5.13 h), while formulation C released only in 1 subject (7.00 h) in the ascending colon. These release times showed good correlation with *in vitro* dissolution data.

The calculated mean small intestinal transit times for formulations A, B, and C: (A) 3.31 \pm 0.52 h (n = 4), (B) 3.69 \pm 0.90 h (n = 4) and (C) 4.38 \pm 1.12 h (n = 6) respectively. This difference was not significant.

Equally as expected the sites of release are randomly distributed through the gastrointestinal tract location. As erosion of the outer coating is caused by the interaction between fluid and the disintegrant, this process is likely to be reduced once the formulations reach the colon. Similar effects in the distal intestine have been observed for other time-delayed formulations releasing drug in the lower intestine (Stevens *et al.*, 2002).

Conclusions

An erodible coating comprising GB and L-HPC compressed around a core tablet provides an effective means of achieving time-delay *in vivo* where the lag-time of the formulation can be adjusted by variation of the wax content.

References

- Leokittikul, D., Eccleston, G.M., Stevens, H.N.E. Investigation of factors controlling the erosion of press-coated pulsed-release tablets. *J. Pharm. Pharmacol.* **54** (suppl), #039 S-15 (2002a).
- Leokittikul, D., McConnell, G., Girkin, J., Eccleston, G.M., Stevens, H.N.E. Erosion and confocal microscopy studies of compression coatings for pulsatile drug delivery. *AAPS Pharm Sci.* **5** (4), #W5127 (2003).
- Leokittikul, D., McConnell, G., Girkin, J., Eccleston, G.M., Stevens, H.N.E. The influence of dissolution hydrodynamics on drug release from a press-coated tablet. *AAPS Pharm Sci.* **4** (4), #W4086 (2002b).
- Stevens, H.N.E., Wilson, C.G., Welling, P.G., Bakhshae, M., Binns, J.S., Perkins, A.C., Frier, M., Blackshaw, E.P., Frame, M.W., Nichols, D.J., Humphrey, M.J., Wicks, S.R. Evaluation of PulsincapTM to provide regional delivery of dofetilide to the human GI tract. *Int. J. Pharm.* **236**, 27-34 (2002).

Acknowledgements

We thank the Royal Thai Government for the scholarship given to DL. Financial support from Shin-Etsu Japan (RW Unwin, UK) is gratefully acknowledged.