EVALUATION OF A TIME-DELAYED RELEASE SLEEP TABLET USING SCINTIGRAPHIC METHODS

A.B. Mullen[2], K. Sime[1], D. Pecek[1], V. Ronaldson[1], LA Hodges[1], S.J. Eccleston[2], H.N.E. Stevens[1, 2]

[1] Bio-Images Research Ltd, Glasgow G4 0SF, UK; [2]Strathclyde Institute for Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE

www.bddpharma.com | enquiries@bddpharma.com

INTRODUCTION

Sleep maintenance insomnia is characterised by frequent and prolonged nocturnal awakenings, typically in the second half of the night. Sleep maintenance insomnia is a common problem for which incidence increases with age and detrimentally impacts on the quality of life of individuals. The clinical needs of sufferers could be addressed by the development of time-delayed hypnotic formulations.

OBJECTIVES

The *in vivo* gastrointestinal performance of a time-delayed hypnotic drug tablet designed to treat sleep maintenance insomnia was assessed using gamma scintigraphy in healthy male volunteers. A pharmacokinetic profile for the drug was constructed using blood samples taken from the volunteers.

EXPERIMENTAL METHODS

Tablet Manufacture and dissolution performance: A barrier layer tablet containing a hypnotic drug was constructed to provide a 2 h *in vitro* time-delay in drug release. Each tablet was radiolabelled with approximately 4 MBq ^{99m}Tc-DTPA to allow scintigraphic imaging. Dissolution performance was evaluated in USP type II apparatus.

Scintigraphic study: The study was performed in six healthy male volunteers. Each subject was dosed with a single tablet 4 h after consuming a dinner of roast chicken with salad, low fat yoghurt and a cup of decaffeinated coffee or tea (approximately 1115 kJ). The tablet was swallowed whole with 240 mL of water. Scintigraphic imaging, with the subjects lying supine, was performed immediately after dosing at 15 minute intervals until complete radiolabel release. The subjects' vital signs (arterial blood pressure and pulse) were monitored at regular intervals throughout the study visit.

Pharmacokinetic profile of drug: Plasma concentrations of drug were determined from volunteer blood samples using an HPLC method with fluorescence detection.

RESULTS

In vitro dissolution studies confirmed that pulsatile release was achieved after 2.5 h (Figure 1). The *in vivo* performance of the dosage form was highly reproducible with onset of release at approximately 2 h and induction of sleep in volunteers observed shortly afterwards (Figure 2).

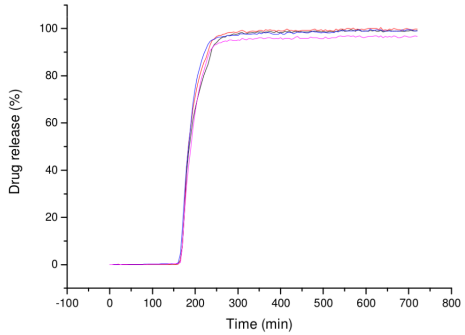

Figure 1. *In vitro* dissolution profile of delayed release tablets (n=6: USP Type II apparatus; 900mL distilled water, 37± 0.5℃, paddle speed 50rpm).

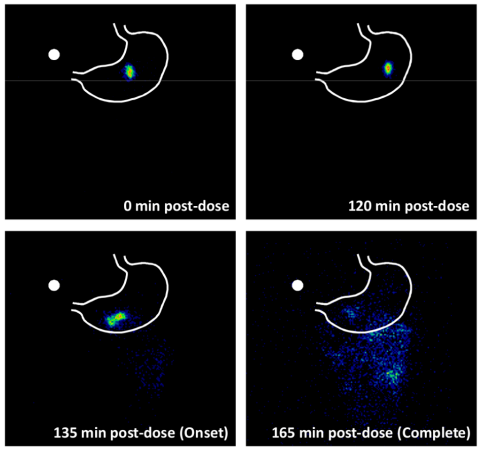

Figure 2. Scintigraphic images of ^{99m}Tc-labelled delayed release tablet demonstrating onset of release 2 hours after administration.

The pharmacokinetics following drug release from the time-delayed tablets in volunteer subjects is shown in Figure 3.

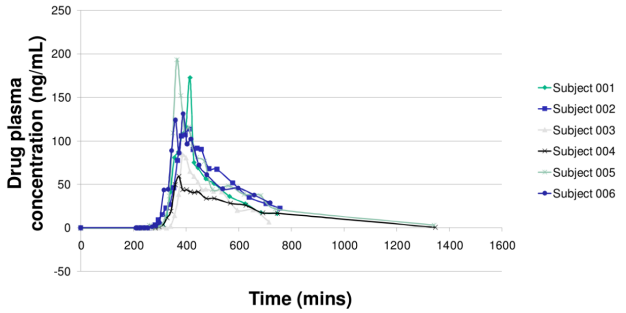

Figure 3. The pharmacokinetic profile of hypnotic drug in volunteers post-ingestion of a 2h time-delay tablet.

DISCUSSION

The results of the *in vivo* gamma-scintigraphic study demonstrated the onset of drug release to occur *in vivo* at around 2 hr after dosage and was consistent with the *in vitro* dissolution performance. PK analysis and induction of sleep in the volunteers confirmed the consistency of the *in vivo* drug release and absorption parameters.

CONCLUSION

The formulated tablet proved successful in delivering the drug after a predicted time-delay. The release parameters were comparable among the six subjects, indicating robustness of the formulation to provide accurate time-delayed release. The pharmacological induction of sleep coincided with the scintigraphic confirmation of drug release.