Correlating formulation behaviour with physiological effects for a time-delayed sleep tablet

AB Mullen,[1,3] SJ Eccleston,[3] LA Hodges,[2] VE Ronaldson,[2] CH Ordoyno,[1] KA Sime,[2] D Pecek,[2] HNE Stevens[1,2,3]
[1]Drug Delivery International Ltd, Glasgow, G4 0SF, UK; [2]Bio-Images Research Ltd, Glasgow, G4 0SF, UK; [3]Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow, G4 0RE, UK

INTRODUCTION

Sleep maintenance insomnia is characterised by frequent and prolonged nocturnal awakenings, typically in the second half of the night. This common problem has increased incidence 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. This study evaluated the properties of a delayed-release hypnotic sleep tablet, using gamma scintigraphy to monitor the *in vitro* and *in vivo* performance of the formulation.

EXPERIMENTAL METHODS

TABLET MANUFACTURE

The tablet was prepared by compressing a barrier layer around a smaller tablet containing 10 mg of the API. This barrier layer was designed to provide a 2 hour time delay prior to release of drug from the inner tablet.

IN VITRO

Tablets were radiolabelled with ^{99m}Tc (approx. 1 MBq) and subjected to USP Apparatus II dissolution in sodium phosphate buffer (pH 7), at 37±1 °C, 50 rpm, until complete radiolabel dispersion within the vessel was observed. The dissolution process was monitored using a gamma camera, acquiring static images at regular intervals.

IN VIVO

A clinical study was carried out in six healthy male volunteers. The tablet was radiolabelled with ^{99m}Tc-DTPA (approx. 4 MBq). Each subject was dosed 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 with 240 mL of water. Scintigraphic imaging, with the subjects lying supine, was performed immediately after dosing and subsequently at 15 minute intervals until complete radiolabel release was observed. Subjects' vital signs (arterial blood pressure and pulse) were monitored at regular intervals throughout the study visit.

PHARMACOKINETIC ANALYSIS

Blood samples were taken from the volunteers every 15 minutes until burst release was observed by scintigraphy, then every 15 minutes for the next 2 hours. Following this, samples were then taken every 30 minutes for 1 hour and then hourly until the end of the study day (9 hours post-dose). From this, plasma samples were analysed by HPLC to give drug plasma concentration.

RESULTS AND DISCUSSION

IN VITRO

The mean time to onset of radiolabel release was 95 min (n=3) and the mean time to completion of radiolabel release was 172±15 min (n=3).

IN VIVO

The mean time to onset of radiolabel release was 98±10 min post-dose and the mean time to completion of radiolabel release was 153±8 min post-dose. This gave a mean time of 55±16 min for complete dispersion, from onset to completion. This correlates with the *in vitro* results and shows the barrier layer successfully prevented drug release until close to the target time of 2 h. Onset of radiolabel release occurred in the stomach in five subjects and in the small intestine in the remaining subject. Complete release was noted in the stomach for four subjects and in the small intestine for two. Figure 1 shows scintigraphic images of key events in the GI transit of a tablet in Subject 001. No clinically significant deviations from normal blood pressure and pulse ranges were noted.

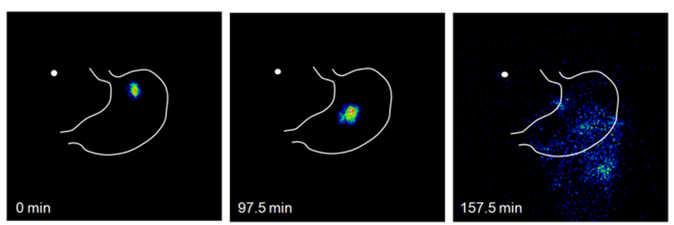

Figure 1. Scintigraphic images of Subject 001 at various times post-dose: 0 min (immediately post-dose); 98 min (onset of ^{99m}Tc release); 158 min (complete ^{99m}Tc release). Outline of the stomach is drawn for visualisation only.

PHARMACOKINETIC ANALYSIS

In addition to the scintigraphic images, API pharmacokinetics and induction of sleep in the volunteers was monitored. The onset of sleep in the volunteers was observed after the scintigraphic confirmation of drug release, while pharmacokinetic sampling (Figure 2) allowed correlation of the scintigraphic images with drug plasma concentrations. The *in vivo* pharmacokinetic parameters were comparable among the six subjects, indicating robustness of the formulation to provide accurate time-delayed release.

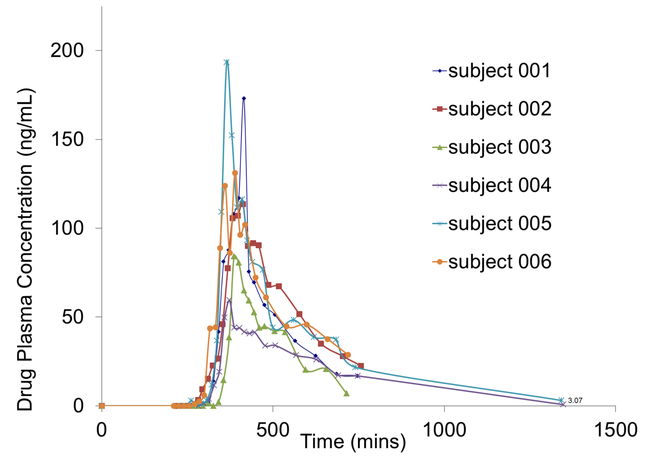

Figure 2. Plasma hypnotic drug concentration in six subjects, following administration of time-delayed sleep tablet.

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. Pharmacokinetic analysis of drug plasma concentrations further confirmed minimal variability among the six subjects.

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