Scintigraphic Study to Investigate the Effect of Food on a HPMC Modified Release Formulation of UK-294,315

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ABSTRACT: The objective of the study was to use the combined approach of gamma scintigraphy and pharmacokinetics, in order to understand the mechanisms explaining the pharmacokinetic differences observed for a modified release (MR) formulation, when administered either in the fed or fasted state. Ten healthy subjects were recruited into a randomized three period single dose study, each subject receiving UK-294,315 40 mg IR (fasted), 100 mg MR (fasted) or 100 mg MR (after a high fat meal). C_{max} values were markedly higher for the MR tablet in the fed state versus fasted and mean residence time was about 3 h longer for fasted versus fed; there was little difference in apparent oral clearance. In the fasted state, average gastric emptying of the intact tablet occurred at 1.2 h postdose, with gastric emptying of intact tablet observed in all subjects. In the fed state, rapid disintegration of the MR tablet was observed by scintigraphy, with 7/9 subjects showing complete disintegration in the stomach. Complete disintegration occurred 10.1 h postdose in the fasted state versus 5.9 h after a high fat meal. The study showed that in the fed state, the MR tablet eroded more rapidly than in the fasted state, leading to an overall increase in the rate of absorption. J Pharm Sci 98:1568–1576, 2009

Keywords: UK-294,315; scintigraphy; food effects; modified release; pharmacokinetics

INTRODUCTION

UK-294,315 is a potent antagonist of the human α_1 adrenoreceptor found in the prostate gland, cardiovascular system and other tissues. α_1-adrenoreceptor antagonists are well precedented in the effective treatment of prostatic hyperplasia. UK-294,315 has good intrinsic membrane permeability, aqueous solubility of 0.74 mg/mL, rising to >40 mg/mL at pH 5, log$P$ of 1.8 and pK_a of 8.5.[1]

In early phase 1 studies, single immediate release (IR) doses of UK-294,315 up to 40 mg were well tolerated. Consistent with its pharmacology, dose limiting adverse events in early clinical studies were postural hypotension and syncope (fainting). Effects on blood pressure appeared to be related to peak plasma concentration. In single dose studies, plasma concentrations of UK-294,315 below 30 ng/mL were associated with a lower incidence of postural hypotension and smaller reductions in systemic blood pressure than concentrations above this limit (Pfizer Global R&D, data on file). As a consequence, modified release (MR) formulations were developed, in order to minimize fluctuations in the plasma concentration–time profile. Encouraging clinical

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data were obtained for a wet-granulated hydroxypropylmethylcellulose (HPMC) MR matrix formulation (50% release after 6 h, 90% release after 18 h *in vitro*) in healthy subjects in the fasted state. However, following administration immediately after a high fat breakfast, mean C_{max} and AUC were increased significantly (by 112% and 39%, respectively). Inspection of the individual concentration–time profiles suggested that the absorption of UK-294,315 was much more variable in the fed state and suggested that, in some subjects, the formulation had failed to release the drug in the desired manner in the fed state, leading to 'dose dumping'.

The interaction between drug, dosage form and gut physiology plays a crucial role in determining the clinical potential of any new drug product. Scintigraphic techniques have been developed, which allow the visualisation of this dynamic in a noninvasive manner.[2]

The objective of the present study was to use the combined approach of gamma scintigraphy and pharmacokinetic evaluation (pharmacoscintigraphy) to investigate the single dose transit, erosion and absorption properties of the MR formulation in the fasted and fed state, in order to understand the mechanism for the apparent failure of this formulation in the fed state.

METHODS

Dosage Form Manufacture and Validation of Radiolabelling Methodology

UK-294,315 10 mg IR tablets contain UK-294,315, microcrystalline cellulose, calcium phosphate (dibasic anhydrous), croscarmellose sodium (Ac-Di-Sol®) and magnesium stearate. UK-294,315 100 mg MR tablets contain UK-294,315, hypromellose (Methocel®), lactose monohydrate, povidone (Kollidon®) and magnesium stearate. Both formulations contain 6.0 mg samarium oxide. UK-294,315 10 mg IR tablets were manufactured using conventional dry blending processes followed by compression to circular, convex tablets. UK-294,315 100 mg MR tablets were manufactured using conventional wet granulation processes, prior to samarium oxide extragranular addition and compression to circular, convex tablets. *In vitro* evaluation comprised testing tablets with USP I (basket) apparatus at 100 rpm, with 1000 mL pH 7.5 media (0.06 M KCI/0.03 M NaCI/0.006 M KH_2PO_4/0.005 M NaOH).

The technique of neutron activation was used to radiolabel the dosage forms for this scintigraphic investigation. This requires the addition of a stable isotope (samarium oxide) within the formulation. Subsequent irradiation in a neutron source converted the stable isotope (^{152}Sm) into a gamma emitting radionuclide (^{153}Sm). Dosage forms were irradiated for 2.5 min in a neutron flux of 10^{12} n $cm^{-2} s^{-1}$ and *in vitro* testing demonstrated that neither the addition of the samarium oxide nor the neutron activation process adversely affected the performance of the dosage forms or the stability of the drug.

Study Approval

The study was conducted in accordance with the Clinical Protocol, with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines approved by the Committee for Proprietary Medicinal Products (CPMP) on 17 July 1996, which came into force on 17 January 1997, and with the most recent version of the Declaration of Helsinki (Revised Edinburgh October 2000) and with all applicable regulatory requirements including an appropriate Administration of Radioactive Substances Advisory Committee (ARSAC) certificate.

Subjects

Ten healthy male subjects were recruited into the study, aged 37–54 years, height 168–184 cm and weight 65.6–91 kg. Mean body mass index was 25.2. Nine subjects completed all three periods of the study.

Blood Sampling and Bioanalytical/Pharmacokinetic Procedures

On each study day blood samples (approximately 6 mL) were taken to provide approximately 2.5 mL plasma for analysis of UK-294,315. Samples were collected in nonbeaded heparinised tubes. Samples were taken at the following times: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 36 and 48 h post dose.

The method for analysing UK-294,315 in plasma utilised the ASTED system for automatic sample preparation. Plasma samples were automatically mixed with monochloroacetic acid (MCA) and a reference compound (UK-298,108). The sample/reagent mixture was dialysed against potassium phosphate buffer/methanol (10 mmol/L, pH 7.0/20% methanol) and the resulting dialysate