COMPARISON OF THE RATES OF DISINTEGRATION AND GASTRIC EMPTYING OF PARACETAMOL FORMULATIONS (PANADOL® AND PANADOL ACTIFAST®) USING GAMMA SCINTIGRAPHY

Kilian Kelly[1], Bridget O'Mahony[2], Blythe Lindsay[2], Tamara Jones[2], Tim J. Grattan[3], Clive G. Wilson[1,2], Howard N.E. Stevens[1,2]
[1]Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, G4 0NR, UK [2]Bio-Images Research Ltd, Glasgow, G4 0SF, UK,
[3]GlaxoSmithKline Consumer Healthcare, Surrey, KT13 0DE, UK

INTRODUCTION

Panadol Actifast® is a new rapidly absorbed paracetamol tablet containing sodium bicarbonate. Pharmacokinetic studies in man have shown a significantly shorter t_{max} (in both fed and fasted states) and a significantly higher C_{max} (in the fasted state) for Panadol Actifast® compared to conventional paracetamol tablets, following oral dosing[1,2]. Various physiological mechanisms have been proposed that might explain this phenomenon, including increased gastric emptying rate and increased *in vivo* dissolution rate. However, the previous studies measured serum paracetamol concentrations only, so the mechanism responsible for faster absorption remains elusive. We propose that enhanced gastric emptying and dissolution/disintegration mechanisms are responsible. To investigate this hypothesis, a combined scintigraphy and pharmacokinetic study was conducted to compare the rates of disintegration and gastric emptying and the serum-concentration time-profiles of the two formulations in fasted and fed states.

METHODS

STUDY DESIGN

This was a single centre, randomised, four-way, within subject study in 11 healthy, non-smoking males and females age 21 to 36 years (mean 27.0 +/-4.6).

5mg lactose, radiolabelled with 2MBq ^{99m}Tc-DTPA, was incorporated into each tablet during manufacture to facilitate scintigraphic imaging. For the purposes of this trial no film coating was applied to the tablets. In vitro dissolution tests were conducted to assess paracetamol release rate from each formulation, using the USP II paddle apparatus at 30 rpm in 0.5M HCl.

In each study arm, a two tablet dose of one formulation was dosed in either fed or fasted conditions as shown in Table 1, in accordance with the study randomisation.

Study Arm	Formulation	Conditions
A	Panadol®	Fasted state
B	Panadol®	Fed state
C	Panadol Actifast®	Fasted state
D	Panadol Actifast®	Fed state

Table 1. Dosing schedule.

IMAGING SCHEDULE

Following dosing the subjects were imaged in a reclining position with the gamma camera. Anterior static acquisitions of 30-second duration were collected every 5 minutes for a period of 30 minutes, then every 15 minutes to 2 hours. After this time the volunteers were imaged in a standing position, every 30 minutes to 4 hours then hourly to 10 hours.

SCINTIGRAPHIC ANALYSIS

Images were analysed using the WebLink® image analysis program. Tablet disintegration times and gastric emptying times were determined by two independent trained operators.

PHARMACOKINETICS

Blood samples were withdrawn at pre-defined intervals. They were then centrifuged and the serum fraction was removed and stored at –20°C. The results of HPLC analysis of serum paracetamol concentrations will be presented in a later report.

RESULTS

IN VITRO DISSOLUTION

Paracetamol release was significantly faster from Panadol Actifast® than from Panadol®. It was shown that there was good correlation between ^{99m}Tc-DTPA and paracetamol release and that the radiolabelling procedure did not affect tablet dissolution properties.

IN VIVO TABLET DISINTEGRATION

	Mean	SD	Median
Panadol Actifast® Fasted	10.2	9.3	7.5
Panadol Actifast® Fed	14.3	11.0	12.5
Panadol® Fasted	22.5	12.8	17.5
Panadol® Fed	46.4	38.0	37.5

Table 2. *In vivo* disintegration times

Table 2 shows the mean tablet disintegration times. Wilcoxon Matched Pairs Test was used to compare parameters from different treatments. Panadol Actifast® disintegrated significantly faster than Panadol® in both fasted and fed states (p=0.0488 (fasted), p=0.0156 (fed)). There was no significant difference in mean disintegration time for either formulation between the fasted and fed states.

GASTRIC EMPTYING – FASTED STATE

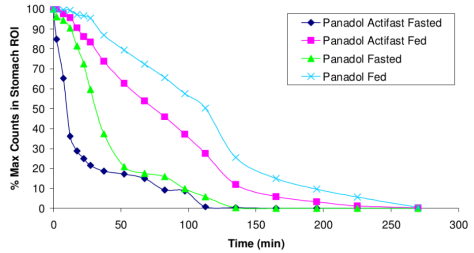

Fig. 1: Mean gastric emptying curves (n=11)

Fig. 1 shows mean gastric emptying curves for the four study arms. The gastric emptying (GE) curve for Panadol Actifast® in the fasted state is approximately mono-exponential, suggestive of a classical liquid emptying curve, while that for Panadol® approximates to a sigmoidal solid emptying curve. Panadol Actifast® tablets emptied from the stomach faster than Panadol®, but the differences were not significant.

However, in subjects 9 and 12, emptying of Panadol Actifast® in the fasted state was dramatically retarded. This may be due to the fact that both subjects were females who were menstruating at this stage of the study, as the menstrual cycle has been linked to changes in gastric emptying patterns[3]. If data from these two subjects is excluded, onset of emptying, t_{50} and t_{90} are all significantly faster for Panadol Actifast® than for Panadol® (p=0.0039 in all three cases).

GASTRIC EMPTYING – FED STATE

In the fed state onset of emptying, t_{50} and t_{90} were all faster for Panadol Actifast® than for Panadol® although the differences were not significant. The GE curves in both cases were linear (fig. 1), indicating that the formulation emptied with the meal. Since the meal will dominate the emptying process under these conditions, this is to be expected and is consistent with the findings of the recent pharmacokinetic study[1]. Representative scintigraphic images are shown in fig. 2.

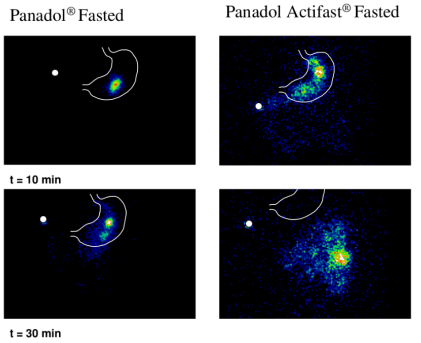

Fig. 2: Representative scintigraphic images (subject 7) showing gastric emptying of both formulations in the fasted state

CONCLUSION

The results of the present study suggest that the shorter t_{max} and higher C_{max} seen with Panadol Actifast® are due to faster disintegration and gastric emptying. While these effects exist in both the fed and fasted states, the differences in gastric emptying are more pronounced in the fasted state and the differences in disintegration are more pronounced in the fed state. It would seem that a combination of these factors is responsible for the shorter t_{max} and higher C_{max} seen with the new paracetamol formulation.

REFERENCES

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ACKNOWLEDGEMENT

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