Comparison of the Rates of Disintegration, Gastric Emptying, and Drug Absorption Following Administration of a New and a Conventional Paracetamol Formulation, Using γ Scintigraphy

Kilian Kelly,[1,5] Bridget O'Mahony,[2] Blythe Lindsay,[2] Tamara Jones,[2] Tim J. Grattan,[3] Amin Rostami-Hodjegan,[4] Howard N. E. Stevens,[1,2] and Clive G. Wilson[1,2]

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Purpose. To investigate the hypothesis that faster drug absorption from a new paracetamol formulation containing sodium bicarbonate compared to that from a conventional formulation results from a combination of enhanced gastric emptying and disintegration/dissolution.

Methods. Each formulation was administered in both fasted and fed states to 12 healthy volunteers. Gastric emptying and disintegration times were assessed by γ scintigraphy, and serum paracetamol concentrations were determined by HPLC.

Results. The mean time to complete disintegration of the new tablets was faster than that for conventional tablets in both fasted (10.2 min vs. 22.5 min) and fed (14.3 min vs. 46.4 min) states, although this difference was statistically significant in the fed state only ($p = 0.0053$). Mean gastric emptying times for the new tablets, as measured by t_{50} and t_{90}, were also faster than those for conventional tablets in both fasted (t_{50} = 22.4 min vs. 47.5 min, t_{90} = 30.9 min vs. 64.1 min) and fed (t_{50} = 76.9 min vs. 106.4 min, t_{90} = 152.7 min vs. 155.5 min) states, although these differences were not statistically significant. Two subjects showed dramatically retarded gastric emptying of the new tablets in the fasted state: if these atypical data are excluded, the differences in both t_{50} and t_{90} in the fasted state are significant ($p = 0.0110$ and 0.0035, respectively). Rate of paracetamol absorption reflected the gastric emptying profiles as shown by significant correlation of emptying times with partial AUC.

Conclusions. It would seem that a combination of faster disintegration and gastric emptying of the new tablets is responsible for the faster rate of absorption of paracetamol from PA compared to P observed in both this study and in previous studies. The differences in gastric emptying are more pronounced in the fasted state, and the differences in disintegration are more pronounced in the fed state.

KEY WORDS: paracetamol; gastric emptying; dissolution; disintegration; γ scintigraphy.

[1] Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow G4 0NR, UK.
[2] Bio-Images Research Ltd., Glasgow, UK.
[3] GlaxoSmithKline Consumer Healthcare, Surrey, UK.
[4] The University of Sheffield Section of Medicine and Pharmacology, Royal Hallamshire Hospital, Sheffield, UK.
[5] To whom correspondence should be addressed. (email: kilian.kelly@strath.ac.uk)

ABBREVIATIONS: t_{max}, time to maximum serum concentration; C_{max}, maximum serum concentration; AUC, area under the serum concentration–time curve; t_{50}, time to 50% gastric emptying; t_{90}, time to 90% gastric emptying.

INTRODUCTION

Paracetamol is currently the most widely used analgesic and antipyretic on general sale for both adults and children. When taken at recommended doses it has an excellent safety profile, notably lacking the gastrointestinal side effects of aspirin and ibuprofen (1). Absorption of paracetamol from the stomach is negligible, but it is rapidly and almost completely absorbed from the small intestine (2). As a result, the rate of absorption is dependent on gastric emptying rate (3), and so it is highly variable following oral administration of conventional paracetamol formulations (4,5). This variability could lead to an unpredictable therapeutic effect. Because paracetamol is taken as required in response to pain, current research has been centered on the development of formulations with rapid and consistent onset of action.

Panadol Actifast® (PA) is a new rapidly absorbed paracetamol 500 mg tablet containing 630 mg sodium bicarbonate. Pharmacokinetic studies of PA in man have shown a significantly shorter time to maximum serum concentration (t_{max}) (in both fed and fasted states) and a significantly higher maximum serum concentration (C_{max}) (in the fasted state) compared to conventional paracetamol tablets (Panadol®, P) (6).

In an earlier study on a development formulation of similar composition, various physiologic mechanisms were proposed that might explain this phenomenon. These included increased *in vivo* dissolution rate and increased gastric emptying rate (7). *In vitro* studies have shown no difference in dissolution rate of paracetamol between the two formulations when dissolution testing was carried out according to the USP monograph in phosphate buffer at pH 5.8, with a standard stirrer speed of 50 rpm. However, in 0.05 M HCl and at lower stirrer speeds (i.e., 10–40 rpm), the rate of paracetamol dissolution was significantly faster from PA tablets compared to P tablets (8). These findings raise the possibility that the new formulation may exhibit an increased *in vivo* dissolution rate. This may be related to the altered hydrodynamic environment created by the release of gaseous carbon dioxide as a result of the reaction between sodium bicarbonate and hydrochloric acid. According to the Noyes-Whitney equation, dissolution rate is inversely proportional to the thickness of the boundary diffusion layer at the surface of the tablet. Therefore, turbulence caused by gaseous carbon dioxide could reduce the thickness of the diffusion layer and thus increase dissolution rate. In order to investigate further the influence of gaseous carbon dioxide on dissolution rate, *in vitro* dissolution studies were carried out using carbonated and degassed soda water as dissolution media.

Hunt and Pathak found that the gastric emptying rate of solutions of sodium bicarbonate increased with increasing concentration up to a maximum, which corresponded approximately to an isotonic solution (150 mM) (9). Two PA tablets (1260 mg sodium bicarbonate) dissolved in 100 ml water would form an approximately isotonic solution, which should have a maximal prokinetic effect. This provides evidence to support a mechanism of action based on increased gastric emptying rate.

A significant correlation has been demonstrated between *in vitro* dissolution of PA and P in 0.05M HCl at a stirrer speed of 30 rpm and *in vivo* release in both fed and fasted states (8). Furthermore, the differential between the rate of

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in vitro dissolution of PA and that of three other commercially available conventional paracetamol formulations under these conditions was similar to the differential observed between PA and P (10). This suggests that the differences in *in vivo* absorption rate between PA and P are likely to also be seen between PA and other conventional paracetamol tablets.

To investigate the hypothesis that faster absorption is a result of enhanced gastric emptying and disintegration/dissolution, a combined scintigraphy and pharmacokinetic study was conducted. This approach allows comparison of the *in vivo* rates of disintegration and gastric emptying with the serum concentration–time profiles of the two formulations in fasted and fed states. The clinical study was preceded by an *in vitro* investigation to validate the tablet manufacturing and radiolabeling procedures and to elucidate the effect of gaseous carbon dioxide on paracetamol dissolution rate.

MATERIALS AND METHODS

Materials

All raw materials for the manufacture of P and PA tablets were provided by GlaxoSmithKline, Dungarvan, Ireland. Technetium-99m diethylenetriaminepentaacetic acid (^{99m}TcDTPA) was provided by the West of Scotland Radionuclide Dispensary, Glasgow, UK.

Tablet Manufacture

Lactose was radiolabeled by adding 0.5 ml ^{99m}TcDTPA solution [activity 40 MBq at time of dosing (TOD)] to 100 mg of lactose in a glass vial. The ^{99m}TcDTPA was then dried onto the lactose using a hot-air drier. P and PA tablets were prepared using GlaxoSmithKline methodology, with minor modifications to allow for scaled-down batch sizes. Approximately 5 mg radiolabeled lactose was added to the granulates before compression to produce tablets labeled with 2 MBq ^{99m}TcDTPA at TOD. The tablets were compressed using standard punches and dies with a Spex CertiPrep Bench Press.

In Vitro Studies

Validation of Tablet Manufacture and Radiolabeling Procedures

Dissolution studies were carried out using a Caleva 7ST USP apparatus II at stirring speeds of both 30 and 50 rpm in 900 ml 0.05 M HCl maintained at a temperature of 37 ± 0.5°C. For each batch, dissolution was carried out on 12 tablets at each stirring speed. Then, 5 ml samples of dissolution medium were withdrawn at 5, 10, 15, 20, 30, and 60 min through a 10 μm probe filter. All sample volumes removed were replaced with 5 ml fresh dissolution medium. The sample was diluted 1 in 50 with 0.05 M HCl. Samples were analyzed by UV spectrophotometry at a wavelength of 249 nm. Dissolution profiles were compared using the similarity factor f_2 (11), which is a simple method for the comparison of dissolution profiles recommended by the FDA. Tablet hardness was assessed using an Erweka tablet hardness tester.

Comparison of the Effect of Carbonated and Noncarbonated Dissolution Medium on Dissolution Rate

Dissolution studies were carried out at 30 rpm as above but using soda water (Tesco, UK) as the dissolution medium. Studies were carried out on 12 factory-produced P tablets in freshly opened carbonated soda water and again in degassed soda water to assess the effect of carbonation on drug dissolution rate. The pH of carbonated and degassed soda water was measured using a Mettler Toledo MA235 pH/ion analyzer.

Clinical Study

Study Design

This was a single-center, randomized, four-way, within-subject crossover study. The study followed the tenets of the Declaration of Helsinki, was approved by the North Glasgow Universities NHS Trust Ethics Committee (Project No. 00PS007), and the Administration of Radioactive Substances Advisory Committee [Certificate No. RPC178-1748 (14999)] and was conducted to Good Clinical Practice. The following dosing conditions were studied:

Study arm A: Two P tablets in fasted conditions (1 g paracetamol)
Study arm B: Two P tablets in fed conditions (1 g paracetamol)
Study arm C: Two PA tablets in fasted conditions (1 g paracetamol)
Study arm D: Two PA tablets in fed conditions (1 g paracetamol)

Each tablet was radiolabeled with 2MBq [^{99m}Tc]DTPA at TOD.

Study Population

Twelve healthy volunteers (four male and eight female) were entered into the study. All volunteers gave written informed consent and underwent a medical examination to ensure compliance with study criteria. Volunteers were required to be nonsmokers, with no history of gastrointestinal (GI) tract disorders and taking no regular medication. Female volunteers were required to be of nonchildbearing potential or using an acceptable method of contraception. They were pregnancy tested before study entry and before dosing on each study day.

Study Day Procedure

Subjects fasted from 22.00 h the evening before each study day. In the two fed arms (B and D), a high-fat breakfast (2900 kJ) consisting of one fried egg, one slice bacon, one slice toast, 15 g butter, 5 g marmalade, 100 g hash browns, and 200 ml whole milk was given 30 min before dosing. On all study days a two-tablet dose was given at time zero with 100 ml of water, according to the randomization schedule. All volunteers were given 200 ml water 2 h postdose, lunch (1300 kJ) 4 h postdose, and an afternoon snack (600 kJ) 7 h postdose. Each study arm was separated by a 7 day washout period.

External radioactive markers were taped to the anterior abdomen to allow accurate alignment of sequential images.

Following dosing the subjects were imaged in a reclining position with the γ camera. Anterior static acquisitions of 30 s duration were collected every 5 min for a period of 30 min, then every 15 min to 2 h. After this time the volunteers were imaged in a standing position every 30 min to 4 h and then hourly to 10 h.

Blood samples (5 ml) were withdrawn from an indwelling cannula situated in the forearm vein into 9 ml serum monovettes. They were taken at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 min, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10 h postdose. The samples were allowed to stand at room temperature for 30 min and then centrifuged at 2500*g* for 15 min. The serum fraction was removed and placed in a 5-ml polypropylene screw-top tube labeled with the study number, subject number, and time point of sample. Samples were stored at –20°C.

Scintigraphic Data Analysis

Images were analyzed using the WebLink® image analysis program. For each subject, an image was selected that presented a full, clearly defined stomach shape, and regions of interest (ROIs) were drawn around the stomach shape and the anatomic marker. A further ROI was drawn in the field of view in order to account for background radiation levels. The counts per cell within each ROI were then determined. The same ROIs were used to analyze each image in the data set—the marker was used to align the ROIs in each image. All data were then corrected for radioactive decay and background and expressed in terms of corrected counts per cell within each ROI. Two independent trained operators separately assessed each scintigraphic image. Three parameters were used to assess gastric emptying rate: onset of emptying, time to 50% emptying (t_{50}), and time to 90% emptying (t_{90}).

Serum Paracetamol Analysis

HPLC analysis of serum paracetamol concentrations was performed using a validated HPLC-UV detection method. Serum samples (100 μl), internal standard solution (100 μl; 5 μg/ml 3-acetamidophenol), Tris(hydroxymethyl)methylamine (100 μl; 2 M), and ethyl acetate (1.6 ml) were mixed in a polypropylene tube and then centrifuged at 4000*g* for 5 min. The solvent layer was then separated and evaporated to dryness under nitrogen at 60°C. The residue was reconstituted in 0.5 ml 5% acetonitrile in water. Chromatography was carried out using a HP1050 HPLC-UV system (Hewlett Packard, Waldbronn, Germany) with a Spherisorb ODS2 150 × 4.6 mm i.d. column and UV detection at 245 nm. Chromatograms were acquired and processed using HP ChemStation software. Concentration of paracetamol was reported as μg/ml.

Pharmacokinetic Analysis

Partial areas under the concentration–time curves from 0 to 30 min ($AUC_{0\text{-}30}$) and from 0 to 600 min ($AUC_{0\text{-}600}$) were calculated using the model-independent trapezoidal method. The elimination rate constant (k_{el}) and elimination half-life ($t_{½}$) were calculated by regression of the linear terminal section of the semilogarithmic concentration vs. time plot. Area under the concentration–time curves from 600 min to infinity were calculated by dividing the concentration at 600 min by k_{el}; this was then used to calculate area under the concentration–time curves from dosing to infinity ($AUC_{0\text{-}\infty}$).

Statistical Analysis

Disintegration times, gastric emptying times, and logarithmically transformed AUC values were compared using a linear ANOVA model with a Tukey-Kramer Multiple Comparisons Post Test, using Minitab® software. The model incorporated factors for subject, session (i.e., sequence of administration), and study arm. Linear correlations between areas under the curve and gastric emptying and disintegration times were determined using GraphPad InStat® software.

RESULTS AND DISCUSSION

In Vitro Studies

Validation of Tablet Manufacture and Radiolabeling Procedures

Dissolution profiles for the tablets produced in house (both unlabeled and radiolabeled) were shown to be similar to those for the commercially produced tablets at both 30 and 50 rpm ($f_2 > 61$ in all cases). In all cases, the percentage coefficient of variation between replicates was <20% at the first time point and <10% at all other time points. They also complied with the tablet hardness standards laid down in the marketing authorizations for P and PA. Therefore, tablets produced using the small-scale batch procedure give a valid reflection of the *in vivo* behavior of these marketed products.

Comparison of the Effect of Carbonated and Noncarbonated Dissolution Medium on Dissolution Rate

The dissolution rate of P tablets was faster in carbonated soda water than in degassed soda water and 0.05 M HCl. The f_2 values for the comparisons were 28.4 and 24.6, respectively, indicating significant differences. When compared to the dissolution profile of PA tablets in 0.05 M HCl, the f_2 value was 50.1, indicating similarity. When the dissolution profile of P tablets in degassed soda water was compared with that of P tablets in 0.05 M HCl, the f_2 value was 50.6, again indicating similarity. These profiles are illustrated in Fig. 1. As with

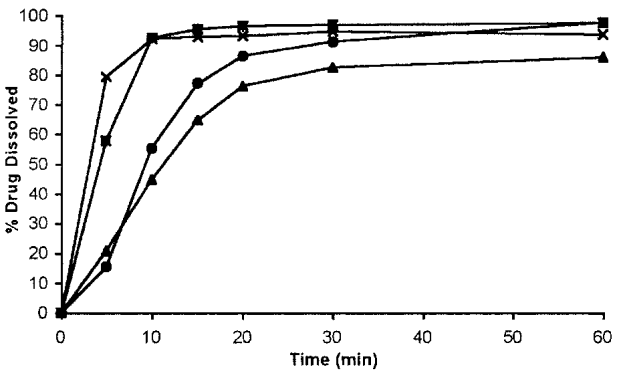


Fig. 1. *In vitro* dissolution profiles in various dissolution media at 30 rpm (n = 12).

Table I. Summary Statistics for *In Vivo* Disintegration Times, Gastric Emptying Times, and Areas Under the Concentration–Time Curves

	PA fasted	PA fed	P fasted	P fed
Dis. time (min)	10.2 (9.3)	14.3 (11.0)	22.5 (12.8)	46.4 (38.0)
Onset (min)	8.2 (15.7)	15.2 (11.5)	23.4 (22.2)	50.2 (48.6)
t_{50} (min)	22.4 (33.5)	76.9 (30.5)	47.5 (33.5)	106.4 (52.5)
t_{90} (min)	30.9 (35.6)	152.7 (39.4)	64.1 (37.6)	155.5 (55.1)
AUC_{0-30} ($\mu g \cdot min/ml$)	171.7 (111.1)	28.7 (27.1)	60.6 (87.3)	11.3 (14.5)
AUC_{0-600} ($\mu g \cdot min/ml$)	2403.7 (349.3)	2208.6 (364.7)	2264.3 (428.8)	2259.0 (406.9)
$AUC_{0-\infty}$ ($\mu g \cdot min/ml$)	2568.0 (400.8)	2418.6 (425.3)	2441.8 (443.4)	2475.2 (465.0)

Values displayed as mean (standard deviation). Dis. time, time to complete tablet disintegration; onset, onset of gastric emptying.

dissolution in 0.05 M HCl, the percentage coefficient of variation between replicates was <20% at the first time point and <10% at all other time points.

The pH of carbonated soda water and degassed soda water was determined to be 5.40 and 5.88, respectively. Changes in pH have little effect on paracetamol solubility at values below its pK_a of 9.5 (12), so it is reasonable to assume that the increased dissolution rate in carbonated soda water when compared to degassed soda water and 0.05 M HCl is not related to a change in pH. Carbonation increases the drug dissolution rate from P tablets to the extent that the dissolution profile is similar to that for PA tablets in 0.05 M HCl. The increase in dissolution rate is probably a result of turbulence caused by the release of gaseous carbon dioxide at the tablet/dissolution fluid interface, leading to a disruption of the boundary diffusion layer. This is consistent with the hypothesis that carbon dioxide generation, resulting from the reaction of sodium bicarbonate with HCl in the stomach, increases the rate of paracetamol dissolution from PA tablets compared to P tablets.

Clinical Study

Eleven subjects completed all four study arms. One subject reported flu symptoms on study day 2 and was excluded from participation on that day. These symptoms were considered to be unrelated to the study treatments. Data from this subject were excluded from subsequent analysis. No other adverse events were volunteered or elicited during the study. The remaining 11 volunteers had a mean age of 27.0 years (range 21–36) and a mean body mass index (BMI) of 23.3 (range 20.0–27.0).

Table I shows summary statistics for tablet disintegration and gastric emptying (GE) times and AUC values. Ninety percent emptying time is presented instead of 100% emptying time because a very small amount of activity can persist in the stomach ROI for a prolonged period in some cases. Results of the Tukey-Kramer tests are shown in Table II.

The results of the ANOVA indicated significant effects for study arm on disintegration time ($p = 0.001$), onset of emptying ($p = 0.014$), t_{50} ($p < 0.001$), t_{90} ($p < 0.001$), and AUC_{0-30} ($p = 0.001$). Subject significantly affected AUC_{0-inf} ($p < 0.001$) but not any other parameters. There were no significant effects for session. Although the mean disintegration times are suggestive of faster disintegration for PA than for P in both the fed and fasted states (Table I), the difference is significant in the fed state only (Table II). For both formulations mean disintegration times are suggestive of faster disintegration in the fasted state than in the fed state (Table I), but the differences are not significant (Table II).

Fig. 2 shows mean gastric emptying curves for the four study arms. Posterior images were not taken for practical reasons, so it was necessary to apply a correction factor to the observed counts to allow for movement within the stomach. The gastric emptying curve for PA in the fasted state is approximately exponential, suggesting a nonnutrient liquid emptying curve, whereas that for P in the fasted state approximates a sigmoidal solid emptying curve. PA tablets emptied from the stomach faster than P in the fasted state (Table I), but the differences were not significant (Table II).

A dramatically retarded gastric emptying time for PA in the fasted state was observed in two cases (Subjects 9 and 12: t_{50} values of 104.6 and 70.3 min, respectively, vs. mean t_{50} of 22.4 min). Both subjects were female, which raises the possibility that the atypical values may be linked to the menstrual cycle. It has been observed that the menstrual cycle has been associated with changes in gastric emptying patterns and that women exhibit slower gastric emptying than men (13–16). Periods of apparent stasis, where no gastric emptying occurs,

Table II. Statistical Comparison of Parameters Using Tukey-Kramer Multiple-Comparisons Test (n = 11)

	p Values			
	PA fasted vs. PA fed	PA fasted vs. P fasted	PA fed vs. P fed	P fasted vs. P fed
Dis. time	0.9738	0.4632	0.0053*	0.0629
Onset	0.9553	0.6783	0.0426*	0.1491
t_{50}	0.0084*	0.4115	0.2144	0.0029*
t_{90}	0.0001*	0.2531	0.9972	0.0001*
AUC_{0-30}	0.0484*	0.0416*	0.9999	0.2725

* Significant at 5% level.

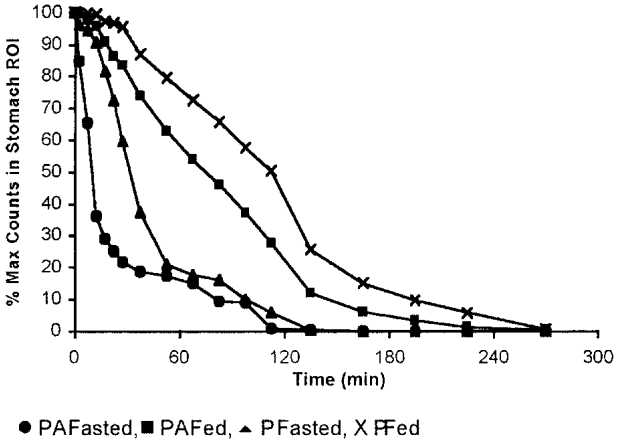


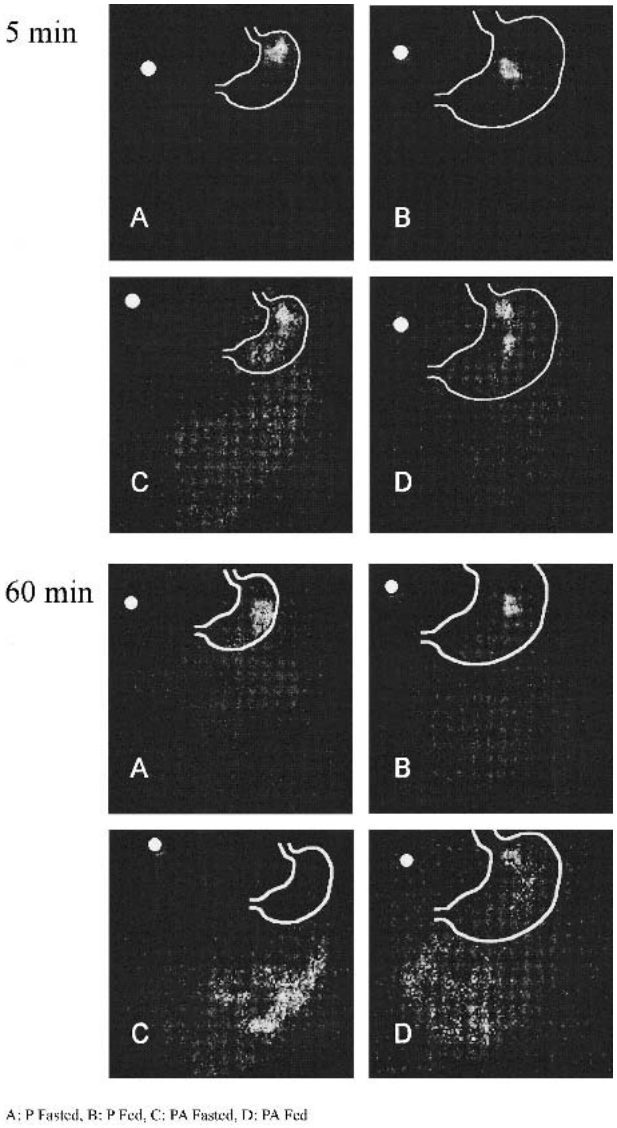
Fig. 2. Mean gastric emptying curves (n = 11).

are also observed infrequently when subjects have been dosed with tablets after an overnight fast (17). Because the gastric emptying data for PA in the fasted state are skewed significantly by the atypical results from two subjects, it is possible that a significant difference in gastric emptying rates of the two formulations may have been shown with a larger cohort of subjects. If data from these two subjects are excluded, then the exponential shape of the GE curve for PA in the fasted state becomes more pronounced (data not shown), and t_{50} and t_{90} are significantly faster for PA than for P in the fasted state ($p = 0.0110$ and 0.0035, respectively).

PA also emptied faster than P in the fed state (Table I), but, with the exception of onset of emptying, the differences were not significant (Table II). The GE curves in both cases were approximately linear, indicating that the formulation emptied with the meal as expected (Fig. 2). This was consistent with the findings of the recent pharmacokinetic study (6). For both formulations, the rate of gastric emptying was significantly more rapid in the fasted state than in the fed state (Table I and Table II).

Representative scintigraphic images are shown in Fig. 3. It can be seen that the stomach is noticeably larger in the fed arms (B, D). At 5 min, P tablets are still largely intact and remain in the stomach in both fed and fasted conditions. In the same volunteer, significant disintegration of PA tablets can be seen in both states at this time point, and some gastric emptying has occurred in the fasted state. After 60 min, the P formulation has disintegrated in the fasted state but still remains almost entirely in the stomach, whereas in the fed state disintegration is incomplete. Meanwhile, PA has completely emptied from the fasted stomach at this stage and is approximately 50% emptied in the fed state.

Fig. 4 shows the early part of the serum concentration–time profile, which illustrates the absorption rate of the two formulations. A significant correlation was shown between $AUC_{0\text{-}30}$ and t_{50} for all treatment arms ($p < 0.05$ in all cases). This indicates that the extent of early absorption increased with increasing rate of gastric emptying. The mean $AUC_{0\text{-}30}$ values for PA are more than twice those for P in both the fed and fasted states (Table I), although the difference between formulations is significant in the fasted state only (Table II). Food is again shown to reduce the rate of absorption of both formulations (Table I), but in this case the difference is significant for PA only (Table II). As expected, the $AUC_{0\text{-}600}$ and $AUC_{0\text{-}\infty}$ were similar for all four study arms (Table I and Table II).



A: P Fasted, B: P Fed, C: PA Fasted, D: PA Fed

Fig. 3. Representative scintigraphic images from a single volunteer (subject 7).

The results confirm faster disintegration and gastric emptying of PA tablets compared to conventional P tablets. Al-

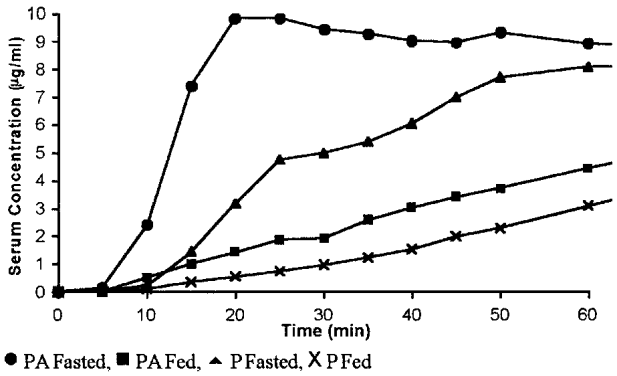


Fig. 4. Mean serum concentration–time profiles (n = 11).

though 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 seems that a combination of these factors is responsible for the faster rate of absorption of paracetamol from PA compared to P observed in both this study and in previous studies.

REFERENCES

1. L. F. Prescott. Paracetamol: past, present, and future. *Am. J. Ther.* **7**:143–147 (2000).
2. L. Prescott. *Paracetamol (Acetaminophen): A Critical Bibliographic Review*, Taylor & Francis, London, 1996.
3. R. Heading, J. Nimmo, L. Prescott, and P. Tothill. The dependence of paracetamol absorption on the rate of gastric emptying. *Br. J. Pharmacol.* **47**:415–421 (1973).
4. J. A. Clements, R. C. Heading, W. S. Nimmo, and L. F. Prescott. Kinetics of acetaminophen absorption and gastric emptying in man. *Clin. Pharmacol. Ther.* **24**:420–431 (1978).
5. G. Paintaud, P. Thibault, P. E. Queneau, J. Magnette, M. Berard, L. Rumbach, P. R. Bechtel, and P. Carayon. Intraindividual variability of paracetamol absorption kinetics after a semi-solid meal in healthy volunteers. *Br. J. Clin. Pharmacol.* **53**:355–359 (1998).
6. A. Rostami-Hodjegan, M. R. Shiran, R. Ayesh, T. J. Grattan, I. Burnett, A. Darby-Dowman, and G. T. Tucker. A new rapidly absorbed paracetamol tablet containing sodium bicarbonate. I. A four way crossover study to compare the concentration–time profile of paracetamol from the new paracetamol/sodium bicarbonate tablet and a conventional paracetamol tablet in fed and fasted volunteers. *Drug Dev. Ind. Pharm.* **28**:523–531 (2002).
7. T. Grattan, R. Hickman, A. Darby-Dowman, M. Hayward, M. Boyce, and S. Warrington. A five way crossover human volunteer study to compare the pharmacokinetics of paracetamol following oral administration of two commercially available paracetamol tablets and three development tablets containing paracetamol in combination with sodium bicarbonate or calcium carbonate. *Eur. J. Pharm. Biopharm.* **49**:225–229 (2000).
8. A. Rostami-Hodjegan, M. R. Shiran, G. T. Tucker, B. R. Conway, W. J. Irwin, L. R. Shaw, and T. J. Grattan. A new rapidly absorbed paracetamol tablet containing sodium bicarbonate. II. Dissolution studies and *in vitro/in vivo* correlation. *Drug Dev. Ind. Pharm.* **28**:533–543 (2002).
9. J. N. Hunt and J. D. Pathak. The osmotic effects of some simple molecules and ions on gastric emptying. *J. Physiol.* **154**:254–269 (1960).
10. L. R. Shaw, W. J. Irwin, T. J. Grattan, and B. R. Conway. Discriminatory dissolution testing for paracetamol formulations, *British Pharmaceutical Conference*, Pharmaceutical Press, Glasgow, 2001, p. 196.
11. J. W. Moore and H. H. Flanner. Mathematical comparison of curves with an emphasis on *in-vitro* dissolution profiles. *Pharm. Tech.* **20**:64–74 (1996).
12. L. R. Shaw. *The development of a novel* in vitro *model suitable for the prediction of bioavailability*, School of Pharmaceutical and Biological Sciences, Aston University, Birmingham, 2001.
13. A. Wald, D. H. V. Thiel, L. Hoechstetter, J. S. Gavaler, K. M. Egler, R. Verm, L. Scott, and R. Lester. Gastrointestinal transit: the effect of the menstrual cycle. *Gastroenterology* **80**:1497–1500 (1981).
14. L. P. Degen and S. F. Phillips. Variability of gastrointestinal transit in healthy women and men. *Gut* **39**:299–305 (1996).
15. W. R. Hutson, R. L. Roehrkasse, and A. Wald. Influence of gender and menopause on gastric emptying and motility. *Gastroenterology* **96**:11–17 (1989).
16. L. C. Knight, H. P. Parkman, K. L. Brown, M. A. Miller, D. M. Trate, A. H. Maurer, and R. S. Fisher. Delayed gastric emptying and decreased antral contractility in normal pre-menopausal women compared with men. *Am. J. Gastroenterol.* **92**:968–975 (1997).
17. R. Khosla and S. S. Davis. Gastric emptying and small and large bowel transit of non-disintegrating tablets in fasted subjects. *Int. J. Pharm.* **52**:1–10 (1989).