Drug Development and Industrial Pharmacy, 2011; 37(7): 747–753

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI: 10.3109/03639045.2010.538058

informa
healthcare

ORIGINAL ARTICLE

Comparison of a novel fast-dissolving acetaminophen tablet formulation (FD-APAP) and standard acetaminophen tablets using gamma scintigraphy and pharmacokinetic studies

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Abstract

Context: Acetaminophen (paracetamol, APAP) is widely used to relieve mild-to-moderate pain and reduce fever. Absorption of the drug can be impacted by dosage form; this may have implications for pain relief in some individuals, potentially accounting for suboptimal efficacy in analgesia.

Objective: To assess the disintegration and dissolution of a new fast-dissolving acetaminophen tablet formulation (FD-APAP) and the impact on pharmacokinetic and pharmacodynamic parameters.

Materials and methods: Two randomized, single-center, open-label, single-dose, two-way crossover studies in healthy subjects to compare FD-APAP (2×500 mg tablets) with standard acetaminophen (2×500 mg tablets). Gamma scintigraphy was used to assess tablet disintegration (Study 1, $N=24$), and plasma profiles were evaluated in the fasted state (Study 2, $N=40$).

Results: In Study 1, the mean time to complete disintegration (12.9 vs. 69.6 min, $P<0.0001$) and onset of disintegration were both significantly faster with FD-APAP than with standard acetaminophen ($P<0.0001$). For Study 2, median T_{max} was significantly faster for FD-APAP (0.50 vs. 0.67 h, $P<0.01$) and $AUC_{0-30\ min}$ was significantly greater (4.51 vs. 2.74, $P<0.05$). AUC_{0-t} and AUC_{0-inf} were comparable between the two study treatments.

Discussion: Despite the absence of comparative clinical data, the FD-APAP formulation may be expected to overcome some of the issues associated with the slow and variable absorption of standard acetaminophen tablet formulations, improving therapeutic outcome and avoiding the need to switch to alternative therapeutic options.

Conclusion: Compared with standard acetaminophen, the FD-APAP formulation results in significantly faster onset of disintegration and more rapid absorption.

Keywords: Optizorb, disintegration, dissolution, analgesia, onset

Introduction

Acetaminophen (paracetamol, APAP) is available in many countries for non-prescription, over-the-counter (OTC) sale in conventional liquid, suppository, capsule, tablet, and caplet dosage forms. Acetaminophen is often recommended as the first-line drug treatment in the management of osteoarthritis[1–3], acute low back pain[4], and other mild-to-moderate pain states[5]. It is effective and well-tolerated when taken at the recommended dose (up to 4000 mg/day), and within a therapeutic dose range carries little risk of serious adverse events[6]. In prospective clinical studies involving over 30,000 patients, there have been no reports of hepatic failure or death[7].

Acetaminophen is primarily absorbed from the upper small intestine and gives a mean peak plasma concentrations of 15–20 µg/mL within 30 to 120 min after oral administration of a 1000 mg dose in adults[8]. For standard 500 mg solid dose acetaminophen tablet formulations, the rate of absorption is limited by the process of tablet disintegration and dissolution in the stomach and the

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(Received 15 June 2010; revised 21 October 2010; accepted 03 November 2010)

rate of gastric emptying into the upper small intestine[9]. Importantly, following oral administration, the rate of acetaminophen absorption from conventional formulations can be variable, which can result in a delayed or unpredictable therapeutic effect[9–11].

It has previously been shown that *in vivo–in vitro* correlation methods may be used successfully to relate the *in vitro* dissolution characteristics of different products to their *in vivo* release and therapeutic outcomes[12]. An acetaminophen tablet that contains 630 mg of sodium bicarbonate has been shown to be absorbed twice as fast as standard acetaminophen tablets[9–13]. This faster rate of absorption is attributed to an increase in the disintegration rate and also an accelerated gastric emptying rate that leads to a swifter transport of acetaminophen to the small intestine where absorption takes place[10]. However, the sodium content of this product (173 mg in each 500 mg tablet) precludes its use in patients on a sodium-restricted diet.

The same validated methodology as previously used to evaluate the *in vitro* dissolution of the rapidly absorbed acetaminophen tablet containing sodium bicarbonate[12] has also been applied to a new fast-dissolving acetaminophen tablet formulation (FD-APAP). The results indicate that at 3 min, 90% of the acetaminophen is dissolved from this new formulation compared with only 10–15% for >50 other marketed acetaminophen formulations (unpublished data). Subsequently, this formulation, FD-APAP (Panadol Advance®) with Optizorb® technology, was selected for further investigation. FD-APAP is a unique acetaminophen formulation that contains alginic acid and calcium carbonate and, unlike previously developed fast-acting acetaminophen formulations, it does not contain high sodium content. The reported *in vivo* studies were designed to examine and extend the *in vitro* results by assessing the disintegration and dissolution of FD-APAP and subsequent impact on downstream pharmacokinetic and pharmacodynamic parameters.

Materials and methods

Gamma scintigraphy study

This randomized, single-center, open-label, single-dose, two-way crossover study assessed disintegration following administration of FD-APAP (2 × 500 mg tablets) and standard acetaminophen (2 × 500 mg tablets; Panadol original tablets, GlaxoSmithKline Consumer Healthcare, Weybridge, UK [PL 00071/5074R]) in healthy male subjects. Eligible subjects were aged 18–55 years, nonvegetarian, and with a body mass index (BMI) of 18–30 kg/m^2. The study was conducted at Bio-Images Research Ltd., Glasgow, UK between September 15, 2005 and November 16, 2005. Ethics approval was provided by Tayside Committee on Medical Research Ethics in Dundee, UK. All subjects provided written consent according to the Declaration of Helsinki and the study was conducted under the guidance of Good Clinical Practice.

Both study products were supplied by the Clinical Supply Department, GlaxoSmithKline Consumer Healthcare. Each tablet was radiolabeled by the study site with 0.25 MBq indium [^{111}In]-labeled diethylenetriamine pentaacetic acid (DTPA) (two tablets = 0.5 MBq per assessment visit). Radiolabeling was performed in accordance with a documented methodology similar to that used in other scintigraphic studies[14,15] and validated using method development work completed prior to the start of the present study (unpublished data). *In vitro* dissolution testing was not conducted in this study; however, the results of a prior study utilizing the same radiolabeling techniques showed good correlation between release of acetaminophen and [^{111}In]-DTPA-labeled acetaminophen and that the radiolabeling procedure did not affect tablet dissolution properties[9]. From this, we concluded that there was no reason to suggest that this procedure would have an adverse impact on the results of the present study.

Subjects attended four study visits: a screening visit within 21 days of their first assessment visit, two assessment visits separated by a washout period of at least 7 days and a maximum of 21 days, and a follow-up visit on the same day as their second assessment visit or within 14 days thereafter. During the assessment visits, subjects received a radiolabeled breakfast ~2 h prior to dosing with one of the study products in accordance with a randomization schedule. The radiolabeled breakfast comprised one scrambled egg radiolabeled with 2 MBq technetium-99m [^{99m}Tc] tin colloid, one slice of bacon, one slice of toast with 15 g butter and jam, 100 g hash brown potatoes, and 200 mL whole milk. Prior to the two assessment visits, subjects were asked to follow a low-fat diet (for 48 h), were abstained from consuming alcohol or caffeine (24 h), and were fasted overnight (12 h prior to dosing).

Scintigraphy images of the abdominal area were taken at specified time points from 2 h pre-dose until 5 h post-dose or until disintegration and gastric emptying were complete, whichever was sooner. Anterior and posterior anatomical markers containing a maximum of 0.1 MBq [^{99m}Tc] tin colloid were taped to the skin at a position where the midclavicular line meets with the right costal margin orientated in approximately the same transverse plane as the pylorus. The subject was positioned so that the whole of the stomach was in the field of view. This was performed with the volunteer in a semi-recumbent posture from 15 min pre-dose until 2 h post-dose. At other times, subjects were imaged in a standing position. Anterior static scintigraphy images, each of 30 second duration, were recorded using a gamma camera (Siemens E-cam) with a 53.3 cm field of view and fitted with a low-energy, high-resolution collimator. The images were recorded using a Siemens E-cam acquisition unit and were stored on compact disc for subsequent analysis. Completion of gastric emptying was confirmed by two consecutive images with negligible activity in the gastric region of interest. Completion of disintegration was determined visually by

two consecutive images with no visible core remaining. Scintigraphy images were analyzed using the WebLink® image analysis program, as previously described[9].

The primary endpoint was the site and time of complete tablet disintegration; the time to onset of disintegration was a secondary endpoint. The time to complete disintegration of the tablets was compared using an analysis of variance (ANOVA) model. The model included factors for subject (a random effect), period, and treatment. The difference between the treatments was estimated with 95% confidence intervals (CIs). The location of complete disintegration of the tablets was summarized in a frequency table by treatment. The same method for analyzing the onset of disintegration of the tablets was applied and summarized in a frequency table by treatment.

Pharmacokinetic study

The randomized, single-center, open-label, single-dose, two-way crossover human pharmacology (Phase I) study in healthy subjects compared the plasma profile of acetaminophen following administration of FD-APAP (2 × 500 mg tablets) and standard acetaminophen (2 × 500 mg tablets; Panadol original tablets, GlaxoSmithKline Consumer Healthcare [PL 00071/5074R]) in the fasted state. Eligible subjects were healthy volunteers, aged 18–55 years with a BMI of 18–30 kg/m^2. Subjects who were pregnant, breast-feeding had a current or recurrent disease that may have affected the action, absorption, or disposition of the study treatment or who had taken any medication (prescription, OTC, or herbal) except the contraceptive pill within 7 days of dosing were excluded. The study was conducted at Icon Development Solutions Ltd. (previously known as Medeval Ltd.), Manchester, UK between April 20, 2005 and May 25, 2005. Ethics approval was provided by The Independent Ethics Review Committee (Manchester, UK). All subjects provided written consent according to the Declaration of Helsinki and the study was conducted under the guidance of Good Clinical Practice. Both study products (FD-APAP 2 × 500 mg tablets [batch number GSK5353B011] and standard acetaminophen 2 × 500 mg tablets [batch number 5ZH865 A]) were supplied by the Clinical Supply Department, GlaxoSmithKline Consumer Healthcare.

The study comprised a screening visit followed by two study sessions, with a washout period of at least 3 days in between. Subjects received both study treatments over the study duration according to a randomization schedule. Randomization was based on a Latin square design, which was balanced for carryover effect. On Day 1 of each study, session subjects received one of the study treatments, administered orally with 150 mL of chilled water. Pharmacokinetic blood samples were taken pre-dose and then at further specified times post-dose within 10 h of dosing. Subjects were resident in the Clinical Evaluation Unit at Icon Development Solutions Ltd. for ~24 h during each study session (from the evening prior to dosing until the last blood sample was taken at 10 h post-dose).

Plasma acetaminophen concentrations were determined by high-performance liquid chromatography (HPLC) with UV detection. Over the course of the study, 34 × 3 mL blood samples were taken from each subject. Blood samples were centrifuged (3000 rpm, 4°C) for 15 min yielding ~1.5 mL plasma, which was then placed in a polypropylene screw top tube, and stored at 20°C prior to analysis. Serum samples (200 µL) were added to 40 µL 3M perchloric acid (70% v/v) and centrifuged at 13,000 rpm for 6 min. The supernatant was then decanted into autosampler vials prior to analysis. Samples (20 µL) were analyzed by HPLC using a 150 m × 4.6 mm i.d. Spherisorb S3 ODS2 column maintained at 40°C. The mobile phase comprised methanol (10 mL) and distilled water (90 mL). The injection volume was 20 µL and the flow rate was set at 0.75 mL/min with detection wavelength 254 nm. The typical retention time for acetaminophen was 7.2 min. Quality control standards were prepared at four concentrations (0.25, 4.48, 12.45, and 24.33 µg/mL), which were run each day in order to check the calibration curves for accuracy and precision. The suitability of this methodology for monitoring acetaminophen concentrations in pharmacokinetic studies has been successfully validated over the concentration range 0.25–24.87 µg/mL (unpublished data).

The primary pharmacokinetic variables, AUC_{0-t}, AUC_{0-inf}, and C_{max}, were derived from the plasma acetaminophen concentration and elapsed time data using model independent methods in WinNonlin. The secondary variable, T_{max}, was similarly derived. $AUC_{0-30\ min}$ was calculated after all other variables were analyzed. Therapeutic threshold was defined as the minimum plasma acetaminophen level expected to product clinical effect; for the purposes of these analyses, the value used for the estimated minimum effective therapeutic concentration of acetaminophen was 4 µg/mL[16].

A linear mixed effects model was used to analyze the logarithmically transformed (natural log) AUC_{0-t}, AUC_{0-inf}, and C_{max} using PROC MIXED in SAS. The model included factors for subject (a random effect), period, and treatment. The residual variance from the model was used to construct 90% CIs for the difference between test treatment and the reference treatment. These were then back-transformed (antilogged) to give point estimates and CIs for the ratio of the treatment geometric means. Bioequivalence for AUC_{0-t}, AUC_{0-inf}, and C_{max} was determined if the 90% CI for the treatment mean ratio was completely within the range 0.80–1.25. T_{max} and $AUC_{0-30\ min}$ were analyzed nonparametrically by the use of a series of Wilcoxon rank sum tests as previously described[17]. Median differences between treatments were presented with 95% CI for the median difference based on a method by Hodges and Lehman[18]. Subjects with data from one treatment only were excluded.

Assessment of Safety

In both studies, the assessment of safety was based on adverse events reported by all subjects following dosing

with the study treatments, clinical laboratory evaluations (biochemistry, hematology, and urinalysis), and vital signs.

Results

Gamma scintigraphy study

Thirty subjects were screened, of whom 24 were randomized, successfully completed the study, and included in the intent-to-treat population. The 24 subjects had a mean age of 39.2 (±11.41) years (range 21–64 years), and the majority (21 subjects, 88%) were whites, one was black, and two were Asian.

The mean time to complete disintegration was five times faster for FD-APAP compared with standard acetaminophen (12.9 vs. 69.6 min, $P < 0.0001$; Figure 1). The mean time to onset of disintegration was significantly faster with FD-APAP than with standard acetaminophen ($P < 0.0001$). In 18 subjects (75%), onset of disintegration occurred within 5 min of taking FD-APAP. For FD-APAP, onset of disintegration occurred in the stomach for all 24 subjects and complete disintegration occurred in the stomach for 23/24 subjects. In contrast, onset of disintegration of standard acetaminophen tablets occurred in the stomach for 23/24 subjects but complete disintegration occurred in the stomach for only 16/24 subjects. The faster disintegration of FD-APAP is demonstrated in a representative scintigraphic image from one subject (Figure 2).

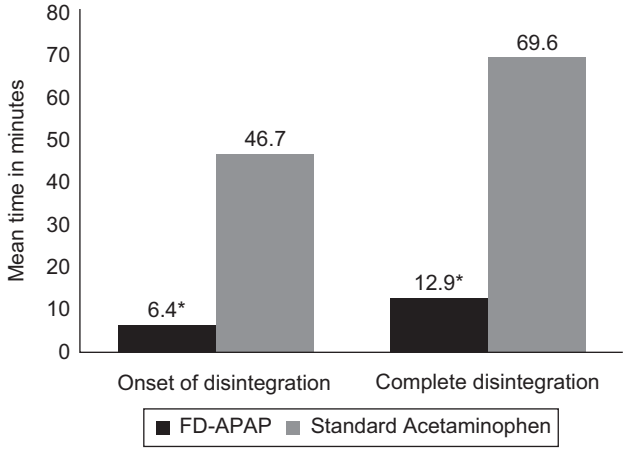

Figure 1. Mean *in vivo* disintegration time for fast-dissolving acetaminophen tablet formulation (FD-APAP) versus standard acetaminophen.

Pharmacokinetic study

Ninety-seven subjects were screened, of whom 40 were randomized and successfully completed both treatment periods and were included in the pharmacokinetic analysis. The 40 subjects (14 males and 26 females) had a mean age of 28.0 (±7.9) years (range 18–49 years) and a mean BMI of 23.11 (±2.63) kg/m^2. The majority of subjects (34 subjects, 85%) were whites, one was Afro-Caribbean, one was Asian, and four were of other mixed race.

The results from the statistical analysis of the pharmacokinetic study are shown in Table 1, with the plasma level profiles being shown graphically in Figure 3. AUC_{0-t} and AUC_{0-inf} were comparable between the two study treatments and both 90% CIs were within the range 0.8–1.25 indicating that the treatments were bioequivalent for extent of total acetaminophen absorption. In the fasted state, both study treatments were rapidly absorbed. However, compared with standard acetaminophen, C_{max} was reached faster and T_{max} was reached 15 min faster with FD-APAP (0.71 vs. 0.96 h, $P < 0.01$). In addition, FD-APAP had a somewhat higher C_{max} than

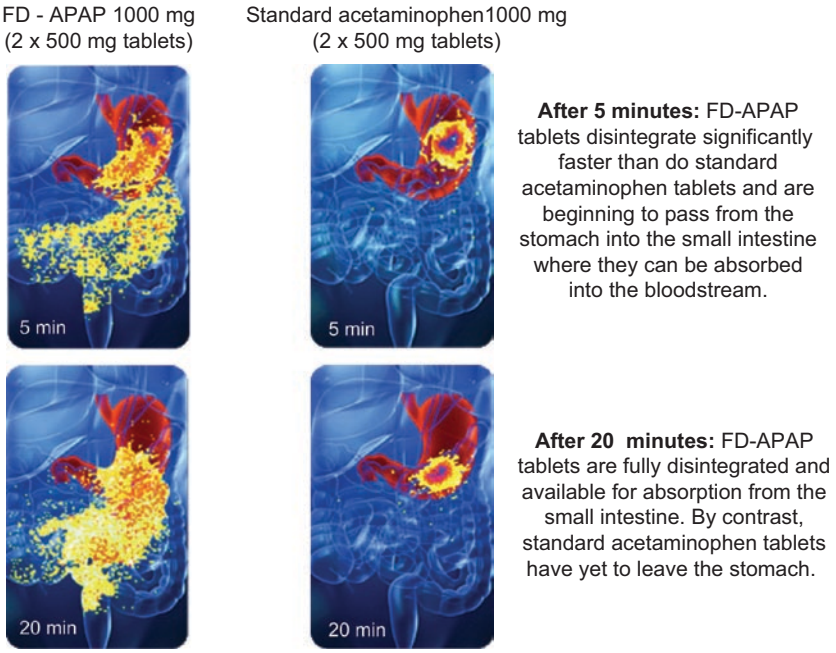

Figure 2. Representative scintigraphic images in one subject showing gastric emptying at 5 and 20 min after both study treatments.

Table 1. Bioequivalence and nonparametric pharmacokinetic variables.

Bioequivalence variables	FD-APAP[a]	Standard acetaminophen[a]	Point estimate[b]	90% CI for point estimate
AUC_{0-t} (μg·h/mL)	47.60	46.83	1.02	0.98, 1.05
AUC_{0-inf} (μg·h/mL)	51.45	50.61	1.02	0.98, 1.05
C_{max} (μg/mL)	18.96	16.86	1.12	0.99, 1.28
Rate of absorption variables	FD-APAP[c]	Standard acetaminophen[c]	Median difference[d]	95% CI for median difference (*P*-value)
T_{max} (h)	0.50	0.67	–0.2497	–0.459,–0.084 (0.0061)
$AUC_{0-30\ min}$ (μg·h/mL)	4.51	2.74	1.5200	0.175, 2.905 (0.0318)

[a]LS mean from ANOVA of logged data. Back-transformed values are presented (antilog).
[b]Treatment difference from ANOVA of log-transformed data. Back-transformed values are presented (antilog) This represents the treatment mean as a ratio of the reference mean.
[c]Median value.
[d]Hodges–Lehmann estimator for median treatment difference from nonparametric analysis.

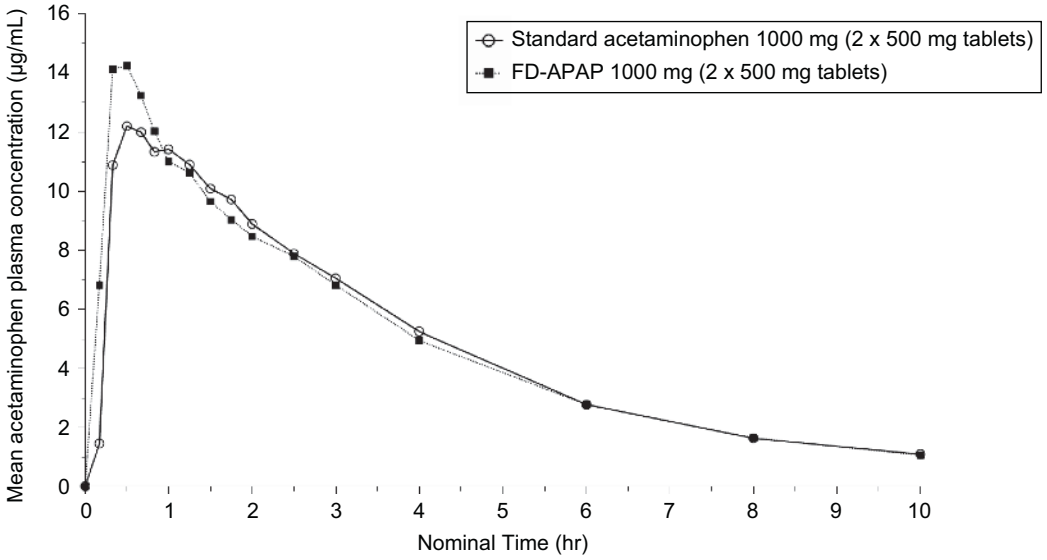

Figure 3. Mean plasma acetaminophen concentration–time profiles.

standard acetaminophen. Taken together, this resulted in a significantly greater early absorption of FD-APAP, as indicated by the $AUC_{0-30\ min}$ of 4.51 versus 2.74 μg·h/mL for FD-APAP and standard acetaminophen, respectively. The mean time taken to reach the plasma acetaminophen therapeutic threshold (4–7 μg/mL) was also determined, as an indication of the time to reach a therapeutic analgesic level[16]. In the fasted state, FD-APAP reached the therapeutic threshold 15 min faster than did standard acetaminophen (0.43 h vs. 0.68 h, $P < 0.05$).

Safety evaluations

In the bioequivalence investigation, both study treatments were well-tolerated with few adverse events and no significant safety issues with regards to vital signs, electrocardiograms (ECGs), or safety laboratory tests.

Discussion

The present studies were designed to assess the *in vivo* disintegration and dissolution of FD-APAP and subsequent impact on downstream pharmacokinetic and pharmacodynamic parameters. We have demonstrated that, compared with standard acetaminophen, FD-APAP results in faster onset of disintegration (5 min in 75% of patients), significantly greater early exposure (25% faster to reach T_{max} and 37% faster to reach therapeutic threshold), and it can be detected in the plasma within 10 min of dosing.

Gamma scintigraphy is an established method of tracking the behavior of radiolabeled formulations *in vivo*. A two-way crossover design was chosen to reduce variability and hence reduce the sample size. The crossover design also minimized the number of volunteers exposed to radioactivity. Although this was an open-label study, blinding was not considered to be necessary as the study measurements (scintigraphy) were entirely objective. The study was designed to mimic "actual use" of analgesia in the semi-fed (postprandial) state and involved administration of study drug 2 h after a standard meal, which is considered to be a realistic scenario in clinical practice, based on a typical adult feeding pattern of three meals per day plus intermittent snacks with administration of acetaminophen up to four times per day. The "actual use" design has high assay sensitivity for detecting differences in rate of absorption between acetaminophen tablet

formulations. Vegetarians were excluded from this study as there is evidence that the absorption of acetaminophen is impaired in this group of the population[19]. Female subjects were similarly excluded; it has been observed that the menstrual cycle has been associated with changes in gastric emptying patterns[20]. Any subjects with a BMI of 30 kg/m^2 or above were excluded as shielding caused by bone, muscle, other organs, and soft tissue would attenuate scintigraphy counts. To obviate other variables, none of the healthy male volunteers recruited suffered from any gastrointestinal disorders.

Bioequivalence between FD-APAP and standard acetaminophen was demonstrated for AUC_{0-t} and $AUC_{0\text{-inf}}$. The mean C_{max} was slightly higher with FD-APAP, but the range of individual C_{max} values for standard acetaminophen was below the maximum value (mean: 18 ± 10 μg/mL, range: 8–49 μg/mL) previously observed for standard acetaminophen in the fasted state[13]. Similar pharmacokinetic results have been found in an additional *in vivo* study involving 30 healthy volunteers that compared the same FD-APAP to a generic standard 500 mg acetaminophen tablet product available in Australia (Herron; unpublished data). Both products were bioequivalent (AUC_{0-t}, $AUC_{0\text{-inf}}$, and C_{max}); accelerated absorption of acetaminophen from FD-APAP was evident as measured by $AUC_{0-30\ min}$, $AUC_{0-60\ min}$, and plasma concentration at 30 min. Moreover, a therapeutic level (plasma concentration 4 μg/mL[16]) was reached 11 min faster than the Herron® product.

Many attempts have been made to improve the rate of onset of activity of acetaminophen. For example, soluble tablets have been shown to have a quicker rate of absorption[21] and a faster onset of analgesic action compared with conventional acetaminophen tablets[22]. However, soluble tablets are not always convenient as they have to be dissolved in water prior to administration, and moreover acetaminophen-containing solutions are unpalatable to some patients. Previous studies with a fast-acting acetaminophen formulation containing sodium bicarbonate have demonstrated that increased disintegration of acetaminophen correlates with faster drug absorption[9]. Clinical studies with this formulation have confirmed that these characteristics result in faster onset of pain relief[23]. However, this formulation, and many of the soluble tablets also contain high levels of sodium bicarbonate, and so are not appropriate for use in all patients, for example, in those on a restricted sodium diet.

Acetaminophen formulations containing calcium carbonate have been previously described in the literature but have been shown to have no significant effect on the variability or rate of acetaminophen absorption[10]. FD-APAP is a unique acetaminophen formulation, which incorporates alginic acid in addition to calcium carbonate. It is postulated that calcium alginate, formed by the reaction of calcium ions with alginic acid in the acidic environment of the stomach, in combination with carbon dioxide, generated from the calcium carbonate, facilitates the formation of a uniform suspension of fine particles with increased surface area leading to enhanced dissolution. Importantly, because FD-APAP does not contain the high levels of sodium found in many other fast-absorbed formulations, it is suitable for a much broader range of patients. It also has the additional advantage of being a physically smaller tablet than other fast-absorbed acetaminophen tablets taken orally, which should aid in ease of swallowing. We have shown that FD-APAP results in faster onset of disintegration and that it can be detected in the plasma within 10 min of dosing. The rapid absorption of FD-APAP may be expected to overcome some of the issues associated with the slow and variable absorption of standard acetaminophen tablet formulations, avoiding the need to switch to alternative therapeutic options. In the absence of directly comparative clinical data, the results from the current study and of those with other fast-acting acetaminophen formulations suggest that FD-APAP will have positive implications for pain relief, particularly amongst subjects in whom suboptimal pain relief is experienced with standard acetaminophen formulations.

Conclusion

Following ingestion of acetaminophen in solid form, rate of drug absorption, and onset of pharmacological activity, may vary from patient to patient. It has been shown that absorption of acetaminophen in tablet form is greatly affected by food and that minimum therapeutic concentrations of acetaminophen are not always reached, which could have implications for pain relief in some patients[24]. Such a perceived lack of effect may result in the subsequent use of alternative analgesic treatments with less favorable safety profiles. FD-APAP has been shown to result in significantly faster onset of disintegration and more rapid absorption than standard acetaminophen. Our results demonstrate that although stomach-emptying rates mask dissolution behavior, the scintigraphy provides an earlier indication of faster dissolution and is more sensitive than blood sampling. Despite the absence of comparative clinical data, FD-APAP is expected to overcome some of the issues associated with the slow and variable absorption of standard acetaminophen tablet formulations, thereby improving therapeutic outcome and avoiding the need to switch to alternative therapeutic options.

Acknowledgements

Both studies were funded by GlaxoSmithKline Consumer Healthcare, UK. The authors are grateful to Bridget O'Mahony, Blythe Lindsay, Sarah Connolly, and Janet Band for assistance with scintigraphy and to Tim Grattan and Ian Burnett for their assistance in both of the studies. The authors would also like to thank Hazel Palmer of Scius Solutions Pty Ltd. for assistance in the drafting and preparation of this manuscript; her contribution has been funded by GlaxoSmithKline Consumer Healthcare, USA.

Declaration of interest

This work has been carried out with financial support from GlaxoSmithKline Consumer Healthcare. GlaxoSmithKline Consumer Healthcare manufactures and markets OTC analgesics, including acetaminophen, ibuprofen, and fixed dose combination products.

Dr. Clive Wilson is the Chief Scientist of Bio-Images Research Ltd., UK. He was contracted and financially reimbursed by GlaxoSmithKline Consumer Healthcare in respect of the work undertaken in this research. Dr. Cyril Clarke is an employee of Icon Development Solutions Ltd., UK. He was contracted and financially reimbursed by GlaxoSmithKline Consumer Healthcare in respect of the work undertaken in this research. Dr. Yan Yan Starkey is an employee of GlaxoSmithKline Consumer Healthcare, USA. Her current position in the company is Medical Director. Dr. Geoffrey Clarke is an employee of GlaxoSmithKline Consumer Healthcare, USA. His current position in the company is Vice President, Analgesics R&D.

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