A Study Investigating the Absorption and Pharmacokinetics of a Newly Developed Paracetamol/Caffeine Formulation Containing Sodium Bicarbonate in Healthy Volunteers

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ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

ABSTRACT:

Aims: To assess pharmacokinetic (PK) bioequivalence between a newly developed formulation, rapid-relese paracetamol plus sodium bicarbonate and caffeine (RAPC), containing 500 mg paracetamol + 65 mg caffeine + 325 mg sodium bicarbonate), and the currently marketed Panadol® Extra product in both the fasted and semi-fed states.
Study design: A single center, randomized, open label, four-way crossover, PK study
Place and Duration of Study: MDS Pharma Services (Now Celerion), 2420, W. Baseline Road, Tempe, AZ 85283, between July 17, 2009 to August 10, 2009
Methodology: We included 30 healthy volunteers (20 men, 10 women; age range 18-55 years). The characterized PK parameters included total and partial area under the concentration time curve ($AUC_{0\text{-}30min}$, $AUC_{0\text{-}60min}$, $AUC_{0\text{-}t}/AUC_{0\text{-}inf}$), time to reach peak drug plasma concentration/therapeutic level ($T_{max}/T_{c\geq4ug/ml}$), and maximum measured plasma concentration (C_{max}). The safety of the study treatments was also assessed.
Results: In both fasted and semi-fed states, the exposure to paracetamol and caffeine for new RAPC formulation was bioequivalent to Panadol® Extra for $AUC_{0\text{-}10\ hrs}$, $AUC_{0\text{-}\infty}$ and C_{max} with 90% confidence intervals (CIs), all being within the range 0.80 to 1.25, except for a higher paracetamol C_{max} for RAPC in fasted state. RAPC exhibited significantly greater early absorption for both paracetamol (≥1.8-fold greater) and caffeine (≥1.3-fold greater) as determined by $AUC_{0\text{-}30min}$ and $AUC_{0\text{-}60min}$, as well as significantly faster T_{max} for both paracetamol (about 30 minutes faster) and caffeine (≥15 minutes faster) compared to currently marketed Panadol® Extra. The time to reach the therapeutic paracetamol plasma concentration ($Tc_{\geq4\mu g/ml}$) was about 12 and 33 minutes faster in fasted and semi-fed states respectively. The new formulation was safe and well tolerated.
Conclusion: The newly developed RAPC formulation was found to be bioequivalent to Panadol® Extra caplets, and showed significantly faster absorption in both fasted and semi-fed states.

Keywords: Paracetamol/Acetaminophen, Caffeine, Sodium Bicarbonate, Bioequivalence, Pharmacokinetics, Rapid-release formulation, Drug Absorption.

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1. INTRODUCTION

Episodic tension-type headache (ETTH) is the most common form of headache disorder and accounts up to 78% of all headache disorders [1]. ETTH typically causes mild to moderate dull pain that radiates in a band-like fashion bilaterally and occurs usually less than 15 days per month for at least 3 months. Prevalence rate of ETTH varies widely ranging from 29 to 71 percent among studies, and is most commonly seen in young adults over 20 years of age [2]. ETTH is caused by muscle contractions in the head, face, neck and shoulders, which are usually related to stress, fatigue, emotional conflicts, depression or repressed hostility. Tension headaches are usually self-treated with over-the-counter (OTC) analgesics, of which paracetamol is one of those most frequently used. Caffeine has also demonstrated to have an analgesic adjuvant effect in combination with paracetamol to provide significantly superior headache relief [3].

Fast relief of pain, within ≤30 minutes of dosing, is an essential requirement for ETTH sufferers [4-8]. Several approaches have previously been utilized in an attempt to achieve a rapidly absorbed paracetamol solid dose formulation [9-10]. Inclusion of sodium bicarbonate in the caplets, which has a prokinetic effect on gastric emptying rate, offers an effective approach for increasing the rate of absorption of paracetamol from oral dosage forms [11-12].

To enhance the speed of absorption of paracetamol and caffeine to help pain relief more rapidly, a combination of paracetamol and caffeine (RAPC) in a sodium bicarbonate caplet formulation has been developed. No data has been previously published on the effect of sodium bicarbonate for the absorption of both paracetamol and caffeine. The present pivotal pharmacokinetic (PK) study was conducted to assess bioequivalence and rate of absorption for both paracetamol and caffeine between the new RAPC formulation (total dose of two tablets containing 1000 mg paracetamol + 130 mg caffeine + 650 mg sodium bicarbonate) and currently marketed Panadol® Extra tablets (total dose of two tablets containing 1000 mg paracetamol + 130 mg caffeine).

2. MATERIAL AND METHODS

Subjects

Potential subjects willing to participate in the study were recruited from the site's database of potential volunteers, referrals and Institutional Review Board (IRB) approved advertising. To be eligible of participation in the study, the subjects were required to be of 18-55 years of age, with a body mass index (BMI) of 18-30 kg/m^2 (both inclusive), in good general health, who could understand and were willing, able and likely to comply with all the study procedures and restrictions. The females of child-bearing potential were required to practice a reliable method of contraception during the study.

The subjects were excluded if they were intolerant or hypersensitive to the study drug, were taking any prescription/ herbal/ OTC medication 7 days prior to dosing, or using any enzyme inducing drug 30 days prior to screening. Subjects were also excluded if they smoked more than 5 cigarettes a day, had donated blood within 3 months of the screening visit, or had donated more than 1500ml of blood within 12 months of prior to dosing. Vegetarian subjects were also excluded from the study. Additionally, subjects who consumed beverages containing grapefruit/seville oranges or marmalade/ or had caffeine containing drinks or food 24 hours prior to dosing, and who had undertaken any unusually strenuous physical activity 24 hours prior to the screening and admission, were also excluded.

All subjects were informed with objectives, drugs, potential risks, dates and activities prior to their participation. A written consent form was signed by each subject.

The study was conducted in accordance with the ethical principles of Declaration of Helsinki [13-14], and other applicable regulations. The study was initiated after approval by MDS Pharma (now Celerion) Services Institutional Review Board.

Study Drugs

The test product was RAPC caplets (single dose comprising of two caplets totaling 1000 mg paracetamol + 130 mg caffeine + 650 mg sodium bicarbonate) and the reference product was Panadol® Extra caplets (single dose comprising of two caplets totaling 1000 mg paracetamol + 130 mg caffeine). Each treatment was taken with 150 ml of water.

Methodology

This was an open label, randomized, single-dose (two RAPC caplets and two Panadol® Extra caplets), four way crossover pharmacokinetic (PK) study in 30 healthy volunteers. The treatments were given both in fasted and semi-fed states. Subjects received each study treatment in randomized order based on a William Square design, during the 10 day confinement period. The treatments of this study were:

1. Treatment A – a single dose of two RAPC caplets (1000 mg paracetamol + 130 mg caffeine + 650 mg sodium bicarbonate) in fasted state.
2. Treatment B – a single dose of two RAPC caplets (1000 mg paracetamol + 130 mg caffeine + 650 mg sodium bicarbonate) in semi-fed state.
3. Treatment C – a single dose of two Panadol® Extra caplets (1000 mg paracetamol + 130 mg caffeine) in fasted state.
4. Treatment D – a single dose of two Panadol® Extra caplets (1000 mg paracetamol + 130 mg caffeine) in semi-fed state.

The study drugs were administered two hours after eating a standard meal, which is considered to be a realistic scenario in clinical practice. Subjects ate breakfast 2 hours before dosing for the semi-fed state and were restricted from having breakfast in the morning for the fasted state. In addition, no food or drink was allowed after midnight for fasted state. The content of all the meals were standardized with respect to protein, carbohydrate and fat content and the timings of meals and drinks were standardized.

Blood Sampling

The blood samples were withdrawn either from an indwelling cannula or venapuncture (situated in a forearm vein) and transferred into 4.9 lithium heparinized polypropylene monovettes. A 1 ml discard was taken from the cannula prior to sampling and the cannula was flushed after sampling with approximately 1 ml heparinized saline.

Blood samples were centrifuged at approximately 3000 revolutions per minute (rpm) at approximately 4 Celsius (°C) for approximately 15 minutes. Approximately 2.5 ml plasma was separated from each sample and transferred equally into two 5 ml polypropylene screw top tubes. Plasma samples were stored in tubes labelled with the study number, randomization number, study session and time point of the blood sample and frozen at approximately -20°C within 1 hour of sampling.

The samples were collected at pre-dose and at different time points through 10 hours post-dose (pre-dosing, 0.15, 0.30, 0.45, 1, 1.5, 2, 3, 4, 5, 6, 7 and 10 hours post dose). A wash-out period of 48 hours was chosen between adjacent doses to allow for elimination of any metabolites. Total of approximately 360 ml of blood was collected from each study

participants throughout the study, of which approximately 274 ml (14 x 4.9 ml x 4) was used for PK analysis.

Paracetamol and caffeine in plasma was analyzed by using a validated High Performance Liquid Chromatography (HPLC) method with ultra violet (UV) detection and a validated Liquid Chromatography Mass Spectrometry (LC-MS/MS) method.

Pharmacokinetic Calculations

The non-compartmental method of analysis was used for evaluating the primary and secondary PK parameters. The primary PK parameters included area under the concentration time curve (AUC) between 0 to 10 hours ($AUC_{0\text{-}10hrs}$), AUC between zero and infinity ($AUC_{0\text{-}\infty}$), and maximum measured plasma concentration (C_{max}) after single dose. To compare the ~~speed~~ rate of early drug absorption between the two formulations in both fasted and semi-fed states, the secondary PK parameters included AUC between zero and 30 minutes and 60 minutes ($AUC_{0\text{-}30min}$ and $AUC_{0\text{-}60min}$), time to reach maximum drug concentration (T_{max}), and time to reach the therapeutic paracetamol plasma concentration ($T_{c\geq4ug/ml}$).

$AUC_{0\text{-}10hrs}$ was calculated by trapezoidal rule method. The $AUC_{0\text{-}\infty}$ was calculated as $AUC_{0\text{-}10hrs} + C_t/k_e$, where C_t is the last quantifiable concentration, k_e is the terminal elimination rate constant and was determined by least squares regression analysis during the terminal log-linear phase of the concentration–time curve. All the other partial AUC values ($AUC_{0\text{-}30min}$ and $AUC_{0\text{-}60min}$) were calculated by the trapezoidal rule method.

Statistical Analyses

A linear mixed effects model was used to analyze the logarithmically transformed (natural log) primary PK variables ($AUC_{0\text{-}\infty}$, $AUC_{0\text{-}10\ hrs}$ and C_{max}) using PROC MIXED in SAS® (SAS v.8.2. 2006. SAS Institute, Carry, NC). The model included factors for subjects (as a random effect), period (as a fixed effect) and formulations (treatment, as a fixed effect). The analysis was performed separately for paracetamol and caffeine plasma concentration, for each fasted and semi-fed states. The residual variance from the model was used to construct 90% confidence intervals for the difference between two formulations. These were then back-transformed (antilogged) to obtain point estimates and 90% confidence intervals for the ratio of the treatment geometric means. Bioequivalence was concluded if the 90% confidence interval for the treatment mean ratio was completely contained within the range 0.80-1.25.

Secondary PK parameters including $AUC_{0\text{-}30min}$, $AUC_{0\text{-}60min,}$ and T_{max} were analyzed using non-parametric method Wilcoxon signed-rank test. The 95% confidence intervals for median of differences were calculated based on Hodges-Lehmann method. These tests were performed at 5% level of significance.

In addition, $AUC_{0\text{-}30min}$, $AUC_{0\text{-}60min}$ and $T_{c\geq4ug/ml}$ were analyzed using parametric methods as described for primary parameters above.

Safety evaluation

The safety and tolerability of the study treatments was based on adverse events (AEs) reported by all subjects following dosing with study formulations.

3. RESULTS

Demography

Of the 81 subjects screened for this study, 30 were randomized, and 28 of the randomized subjects completed all four periods of the study. All the randomized subjects completed at least one treatment period of the study.

A total of 20 (66.7%) males and 10 (33.3%) females participated in the study. All of these subjects were Caucasian. The mean age was 34 years (range 22 to 48 years). The mean weight was 67.89 kg (range 48.1 to 88.3 kg), and the mean height was 164.5 cm (range 146 to 182 cm). The average BMI was reported as 25 kg/m^2 (range 20.2 to 29.5 kg/m^2).

Pharmacokinetic Results

The mean plasma paracetamol and caffeine concentration versus time curves for both treatments in the fasted and semi-fed states are presented in Figure 1 – 4. ~~Mean plasma caffeine concentration versus time curves for both treatments in the fasted and semi-fed states are presented in Figure 2.~~

Figure 1: Mean plasma paracetamol concentration for RAPC and Panadol® ~~Extra®~~ Extra (in fasted state)

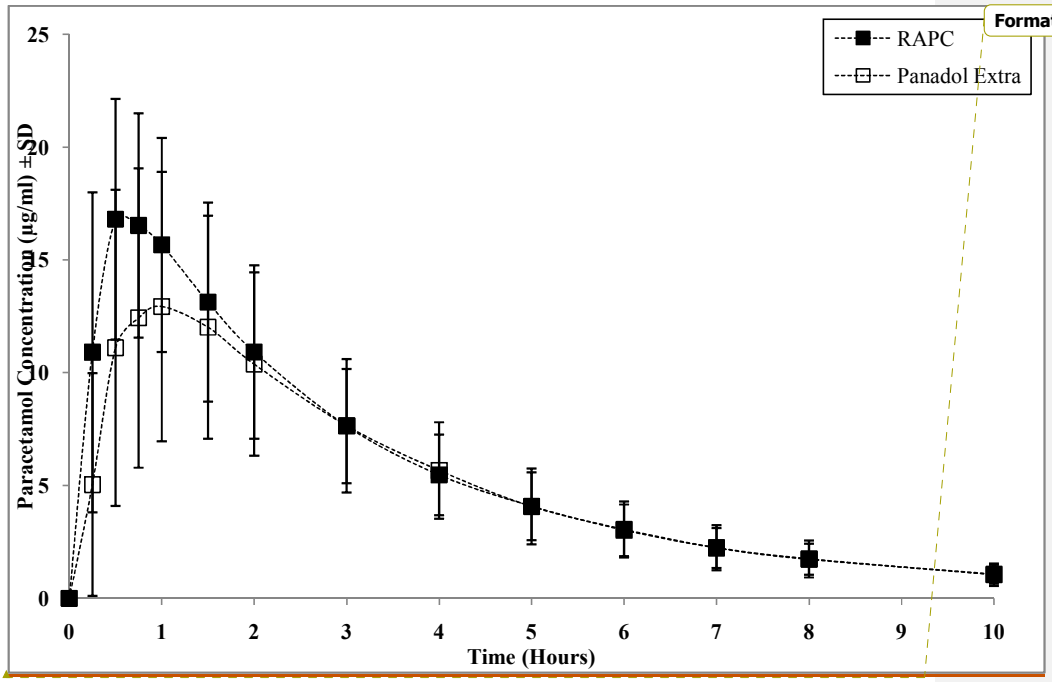

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Figure 2: Mean plasma paracetamol concentration for RAPC and Panadol® -Extra (in semi-fed state)

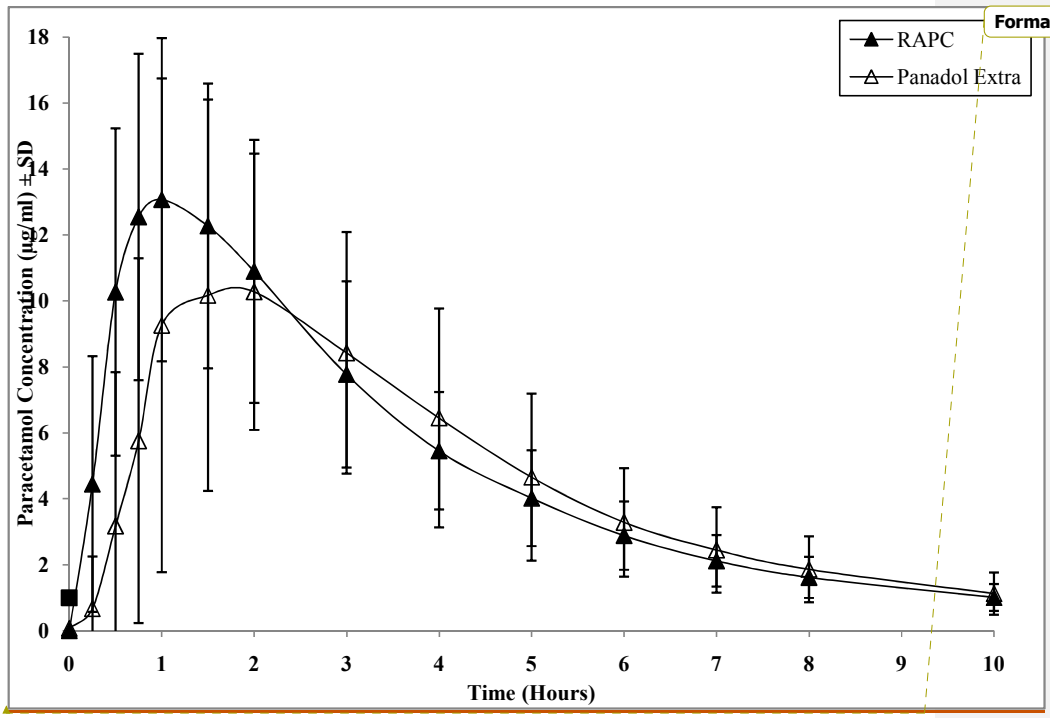

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Figure 3: Mean plasma caffeine concentration for RAPC and Panadol® ~~Extra~~® Extra (in fasted state)

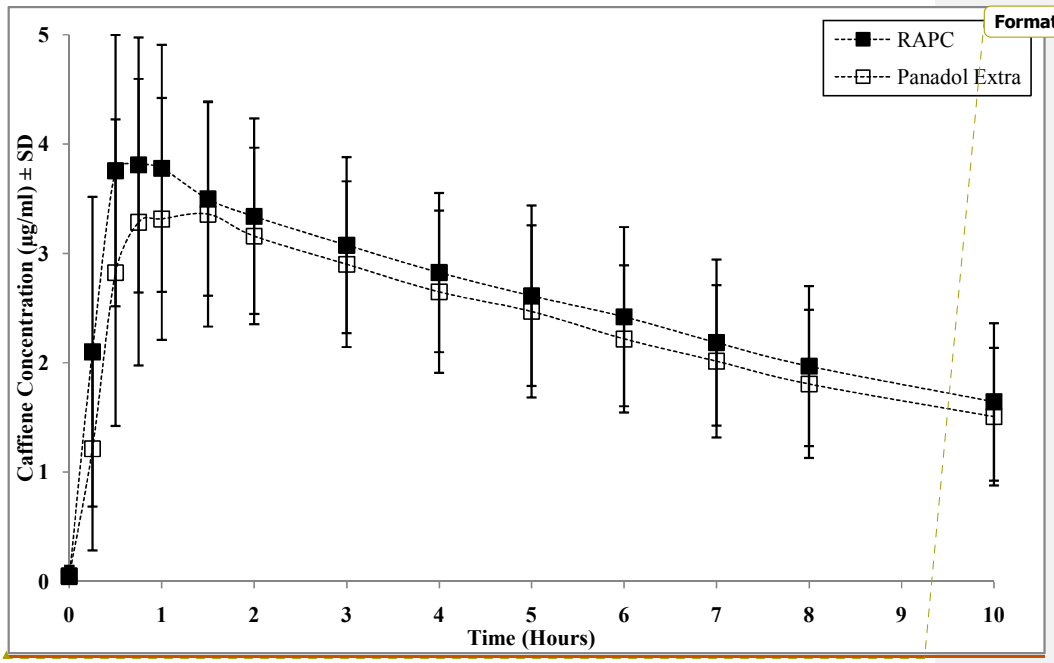

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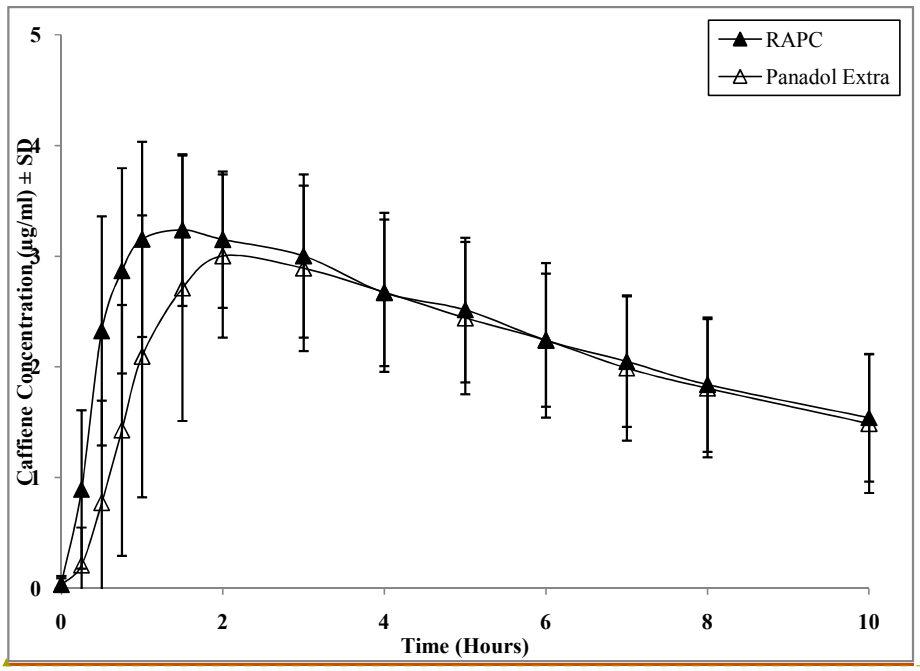
Figure 4: Mean plasma caffeine concentration for RAPC and Panadol® ~~Extra~~® Extra (in semi-fed state)



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Results for bioequivalence assessment by using PK parameters are summarized in Table 1 and Table 2 for paracetamol and caffeine, respectively. In the fasted state, the exposure to paracetamol for RAPC was bioequivalent to Panadol® Extra for $AUC_{0\text{-}10\ hrs}$ and $AUC_{0\text{-}\infty}$ with 90% confidence intervals (CIs), all being within the range 0.80 to 1.25 (Table 1). The two treatments were not bioequivalent for C_{max} in fasted state (Table 1). For exposure to caffeine, RAPC was bioequivalent to Panadol® Extra for $AUC_{0\text{-}10\ hrs,}$ $AUC_{0\text{-}\infty}$ and C_{max} in fasted state (Table 2).

In the semi-fed state, the exposure to paracetamol for RAPC was bioequivalent to Panadol® Extra for $AUC_{0\text{-}10\ hrs}$, $AUC_{0\text{-}\infty}$ and C_{max} with 90% confidence intervals (CIs), all contained within the range 0.80 to 1.25 (Table 1). RAPC was also bioequivalent to Panadol® Extra for $AUC_{0\text{-}10\ hrs}$, $AUC_{0\text{-}\infty}$ and C_{max} in reference to the exposure of caffeine (Table 2).

Table 1: Testing Bioequivalence between RAPC and Panadol® Extra in the Fasted and Semi-fed States for Paracetamol Plasma concentration

PK Parameters	Comparisons	Fasted			Semi-fed		
		Means[1]		Ratio[2]	Means[1]		Ratio[2]
		Panadol®			Panadol®		
		RAPC	Extra	(90% CI)[3]	RAPC	Extra	(90% CI)[3]
$AUC_{0-10hrs}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	55.4	49.8	1.11 [1.08, 1.15]	49.1	45.8	1.07 [1.04, 1.10]
$AUC_{0-\infty}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	59.2	53.4	1.11 [1.08, 1.14]	52.5	49.6	1.06 [1.03, 1.09]
C_{max} (µg/mL)	RAPC vs. Panadol® Extra	17.9	14.0	1.28 [1.18, 1.40]	13.8	13.9	1.00 [0.92, 1.08]

[1]Means are the exponentiated least squares means of log-transformed variables.

[2]Ratio is the exponentiated LS means for difference of the log-transformed data.

[3]Exponentiated 90% confidence intervals of LS means for difference of the log-transformed data.

Table 2: Testing Bioequivalence between RAPC and Panadol® Extra in the Fasted and Semi-fed States for Caffeine Plasma concentration

PK Parameters	Comparisons		Fasted			Semi-fed		
			Means[1]		Ratio[2]	Means[1]		Ratio[2]
			Panadol®			Panadol®		
			RAPC	Extra	(90% CI)[3]	RAPC	Extra	(90% CI)[3]
$AUC_{0-10hrs}$ (µg·hr/mL)	RAPC	vs. Panadol® Extra	24.8	23.0	1.08 [1.05, 1.11]	22.6	20.7	1.09 [1.07, 1.12]
$AUC_{0-\infty}$ (µg·hr/mL)	RAPC	vs. Panadol® Extra	42.3	38.4	1.10 [1.04, 1.16]	37.9	35.5	1.08 [1.02, 1.13]
C_{max} (µg/mL)	RAPC	vs. Panadol® Extra	3.9	3.6	1.28 [1.04, 1.13]	3.4	3.3	1.03 [0.99, 1.08]

[1]Means are the exponentiated least squares means of log-transformed variables.

[2]Ratio is the exponentiated LS means for difference of the log-transformed data.

[3]Exponentiated 90% confidence intervals of LS means for difference of the log-transformed data.

A summary of the results of the statistical analysis for partial AUC values ($AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$) and T_{max} in both fasted and semi-fed states by using non-parametric/parametric method (excluding T_{max}) are given in Table 3A/3B and Table 4A/4B for paracetamol and caffeine, respectively.

In fasted state for paracetamol, RAPC had a significantly greater exposure for $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$ ($p < 0.0001$) and T_{max} was significantly shorter (by ~29 minutes, ~~p~~P <0.~~00~~01) than Panadol® Extra(Table 3A). Similar results were found in the semi-fed state for exposure to paracetamol, $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$ were significantly greater and T_{max} was significantly shorter for RAPC (by ~30 minutes, P<0.05~~p=0.0198~~) than Panadol® Extra (Table 3A).

In the fasted state for caffeine, RAPC showed a significantly higher exposure for $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$ (~~p =0.0009~~P<0.01 and P<0.01~~0.0003~~, respectively) and T_{max} was significantly shorter (by ~15 minutes, P<0.01~~p=0.0013~~) than Panadol® Extra (Table 4A). Similarly, in the semi-fed state for exposure to caffeine, $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$ were significantly greater and T_{max} was significantly shorter for RAPC (by ~30 minutes, P<0.05~~p=0.0403~~) than Panadol® Extra (Table 4A).

Similar results were obtained based on the extra analysis for the secondary parameters, $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$. In both fasted and semi-fed states, for exposure to paracetamol and caffiene, RAPC was superior to the Panadol Extra (Table 3B & Table 4B).

Table 3A: Results of Analyses for $AUC_{0\text{-}30\ min}$, $AUC_{0\text{-}60\ min}$ and T_{max} for paracetamol in fasted and semi-fed state using non-parametric method.

PK Parameters	Comparison	Fasted		Semi-fed	
		Median Diff.[1] 95% CI[3]	P-value[2]	Median Diff.[1] 95% CI[3]	P-value[2]
$AUC_{0\text{-}30\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	2.31 (1.41, 3.19)	<.0001	1.90 (1.15, 2.34)	<.0001
$AUC_{0\text{-}60\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	4.72 (2.63, 6.54)	<.0001	5.2 (3.48, 6.77)	<.0001
T_{max} (hr)	RAPC vs. Panadol® Extra	-0.48 (-0.52, -0.25)	<.0001	-0.50 (-0.51, -0.00)	0.0198

1) Hodge-Lehmann estimate of median difference between two treatments.
2) Probability associated with Wilcoxon signed rank test.
3) 95% Confidence Intervals for median of differences is based on Hodges-Lehmann method.

Table 3B: Results of Analyses for $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$ for paracetamol in fasted and semi-fed state using parametric method.

PK Parameters	Comparisons	Fasted			Semi-fed		
		Means[1]		Ratio[2]	Means[1]		Ratio[2]
		RAPC	Panadol® Extra	(90% CI)[3]	RAPC	Panadol® Extra	(90% CI)[3]
$AUC_{0\text{-}30\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	4.4	1.7	2.52 [1.80, 3.53]	1.8	0.1	17.11 [8.66, 33.82]
$AUC_{0\text{-}60\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	12.6	7.0	1.79 [1.44, 2.23]	7.4	1.8	4.25 [2.64, 6.86]

1) Means are the exponentiated least squares means of log-transformed variables.
2) Ratio is the exponentiated LS means for difference of the log-transformed data.
3)Exponentiated 90% confidence intervals of LS means for difference of the log-transformed data.

Table 4A: Results of Analyses for $AUC_{0\text{-}30\ min}$, $AUC_{0\text{-}60\ min}$ and T_{max} for caffeine in fasted and semi-fed state using non-parametric method.

PK Parameters	Comparison	Fasted		Semi-fed	
		Median Diff.[1] 95% CI[3]	P-value[2]	Median Diff.[1] 95% CI[3]	P-value[2]
$AUC_{0\text{-}30\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	0.34 (0.16, 0.54)	0.0009	0.37 (0.26, 0.47)	<.0001
$AUC_{0\text{-}60\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	0.72 (0.37, 1.00)	0.0003	1.13 (0.75, 1.44)	<.0001
T_{max} (hr)	RAPC vs. Panadol® Extra	-0.25 (-0.50, -0.22)	0.0013	-0.50 (-0.50, -0.00)	0.0403

1) Hodge-Lehmann estimate of median difference between two treatments.
2) Probability associated with Wilcoxon signed rank test.
3) 95% Confidence Intervals for median of differences is based on Hodges-Lehmann method.

Table 4B: Results of Analyses for $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$ for caffeine in fasted and semi-fed state using parametric method.

PK Parameters	Comparisons	Fasted			Semi-fed		
		Means[1]		Ratio[2]	Means[1]		Ratio[2]
		RAPC	Panadol® Extra	(90% CI)[3]	RAPC	Panadol® Extra	(90% CI)[3]
$AUC_{0\text{-}30\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	0.9	0.6	1.62 [1.35, 1.95]	0.4	0.1	5.11 [3.60, 7.23]
$AUC_{0\text{-}60\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	2.8	2.1	1.35 [1.21, 1.50]	1.8	0.6	2.91 [2.16, 3.94]

1) Means are the exponentiated least squares means of log-transformed variables.
2) Ratio is the exponentiated LS means for difference of the log-transformed data.
3) Exponentiated 90% confidence intervals of the LS means for difference of the log-transformed data.

In fasted state for exposure to paracetamol, RAPC was significantly 60% faster in reaching therapeutic level (4µg/ml) (Nielsen, 1991; Liu, 2012) (by 12 minutes, P<0.01) as compared with Panadol® Extra. Similar results were observed in semi-fed state, RAPC was 65% quicker in reaching 4 µg/ml (by 33 minutes, P<0.01) as compared with Panadol® Extra (Table 5).

Table 5: Time to reach plasma paracetamol concentration at therapeutic level (4ug/ml) for RAPC and Panadol Extra in fasted and semi-fed state

Term	Time (hours) Fasted State				Time (hours) Semi-Fed State			
	RAPC[1]	Panadol® Extra[1]	Diff.[2] (%)	P-value[3]	RAPC[1]	Panadol® Extra[1]	Diff.[2] (%)	P-value[3]
$T_{C\geq 4\mu g/ml}$[4]	0.14	0.34	-0.20 (59.5)	0.0009	0.30	0.85	-0.55 (64.3)	<.0001

1 Least square (LS) means from Proc mixed of SAS for time to reach 4 µg/ml for RAPC and Panadol Extra.
2Difference between LS mean of RAPC with Panadol Extra in hours and as a percentage of LS mean time of Current Product.
3 P-value from Proc mixed of SAS.
4 $T_{C\geq 4\mu g/ml}$ is time to reach plasma paracetamol concentration equal or greater than 4µg/ml.

In the fasted state for caffeine, RAPC showed a higher exposure for $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$ and T_{max} was significantly shorter (by ~15 minutes, p = 0.001) than Panadol® Extra (Table 4). Similarly, in the semi-fed state for exposure to caffeine, $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$ were greater and T_{max} was significantly shorter for RAPC (by ~30 minutes, *P* = 0.04) than Panadol® Extra (Table 4).

Similar results were obtained based on the extra analysis for the secondary parameters, $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$. In both fasted and semi-fed states, for exposure to paracetamol and caffiene, RAPC was superior to the Panadol Extra (Table 3B & Table 4B).

Table 4: Results of Analyses for $AUC_{0\text{-}30\ min}$, $AUC_{0\text{-}60\ min}$ and T_{max} for Caffiene in fasted and semi-fed state

PK Parameters		Fasted			Semi-fed		
		Means[1]		Ratio[2]/Difference[4]	Means[1]		Ratio[2]/Di
		RAPC	Panadol® Extra	CI[3]	RAPC	Panadol® Extra	CI[3]
$AUC_{0\text{-}30\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	0.9	0.6	1.62 [1.35, 1.95]	0.4	0.1	5.11 [3.60, 7.23]
$AUC_{0\text{-}60\ min}$ (µg·hr/mL)	RAPC vs. Panadol® Extra	2.8	2.1	1.35 [1.21, 1.50]	1.8	0.6	2.91 [2.16, 3.94]
T_{max} (hr)	RAPC vs. Panadol® Extra	P-value[5]	0.0013	-0.25 [-0.50, -0.22]	P-value[5]	0.0403	-0.50 [-0.50, -0.00]

[1]Means are the exponentiated least squares means of log-transformed variables. Hodge-Lehmann estimate of median difference between two treatments for T_{max}.

[2]Ratio is the exponentiated LS means for difference of the log-transformed data.

[3]Exponentiated 90% confidence intervals of LS means for difference of the log-transformed data. 95% Confidence Intervals for median of differences is based on Hodges-Lehmann method for T_{max}.

[4]Difference for T_{max}.

[5]Probability associated with Wilcoxon signed rank test.

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Safety Results

A total of 18 treatment-emergent AEs were reported in the study by 11 subjects. All were mild in intensity and 9 of them were treatment-related.

Following RAPC in the fasted state, a total of 5 treatment emergent AEs were reported by four (13.3%) of the 30 subjects ~~(Table 6)~~. These included dizziness, abdominal pain, upper abdominal pain and diarrhea. Following RAPC in the semi-fed state, a total of six treatment emergent AEs were reported by 5 (17.9%) of the 28 subjects ~~(Table 6)~~. The treatment emergent AEs included dizziness, headache, burning sensation, parasthesia and palpitations.

Following Panadol® Extra, in the fasted state, a total of six treatment emergent AEs were reported by three (10.3%) of the 29 subjects ~~(Table 6)~~. These included headache, nausea, myalgia, dysacusis, menorrhagia and dry throat. Following Panadol® Extra in the semi-fed state, only one treatment emergent AE, back pain, was reported by one (3.4%) of the 29 subjects ~~(Table 6)~~.

3. DISCUSSION

The present study was conducted to determine the bioequivalence ($AUC_{0\text{-}10\ hrs}$, $AUC_{0\text{-}\infty}$ and C_{max}) between two RAPC caplets (containing a total of 1000 mg paracetamol + 130 mg caffeine + 650 mg sodium bicarbonate) and two Panadol® Extra caplets (containing a total of 1000 mg paracetamol + 130 mg caffeine) for both paracetamol and caffeine absorption in fasted and semi-fed states.

Results from this PK study indicated that both the formulations were bioequivalent when dosed in both fasted and semi-fed states as measured by $AUC_{0\text{-}\infty}$ and $AUC_{0\text{-}10\ hrs.}$

The absorption of paracetamol from RAPC caplets was significantly faster than that from Panadol® Extra in both fasted and semi-fed states, i.e., RAPC demonstrated shorter T_{max}, greater values of $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$. In addition, the time to reach therapeutic plasma level of paracetamol ($T_{c\geq\ 4\mu g/ml}$) was statistically significantly shorter for RAPC caplets. Furthermore, the addition of sodium bicarbonate in RAPC caplets also resulted in a significantly increased rate of absorption (shorter T_{max}, greater $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$) for adjuvant caffeine. Based on the literature data [17], the faster rate of absorption obtained for both the ingredients of RAPC caplets was probably due to the faster gastric emptying rate due to addition of sodium bicarbonate in the formulation, which resulted in the faster delivery of paracetamol and caffeine to the absorption site in the small intestine. Other factors like increased dissolution, faster disintegration and alteration in permeability of gastrointestinal tract epithelium or gastrointestinal mucus may have the contribution for faster rate of absorption [18].

Although the C_{max} for paracetamol was higher following RAPC caplets ingestion in fasted state, the higher C_{max} is still in the range we observed in other clinical studies. One possible explanation for the observed difference is gastric emptying due to addition of sodium bicarbonate are more pronounced in the fasted state [19]. The lower C_{max} values of both RAPC and Panadol® Extra caplets in the fed state rather than the fasted state are in line with the observation, considerable dilution and retardation of absorption due to food solutes may be responsible for lower C_{max} in fed state [20]. However, RAPC caplets still have faster absorption for paracetamol and caffeine in fed state.

5. CONCLUSION

The current study found that RAPC caplets were bioequivalent to Panadol® Extra caplets when dosed in both fasted and semi-fed states with respect to paracetamol and caffeine $AUC_{0\text{-}10\ hrs}$ and $AUC_{0\text{-}\infty.}$ However, with respect to paracetamol C_{max}, although RAPC caplets were bioequivalent to Panadol® Extra caplets when dosed in semi-fed state; the treatments were not bioequivalent when dosed in fasted state where C_{max} was higher following RAPC caplets.

With respect to caffeine C_{max}, RAPC caplets were bioequivalent to Panadol® Extra caplets when dosed in both fasted and semi-fed states.

RAPC demonstrated improved PK parameters (such as shorter $T_{max,}$ $T_{c\geq4ug/ml}$, greater values of $AUC_{0\text{-}30\ min}$ and $AUC_{0\text{-}60\ min}$) to Panadol® Extra in regard to early absorption of paracetamol and caffeine in both fasted and semi-fed states.

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COMPETING INTERESTS

The authors of the article declare no competing interests existing.

AUTHORS' CONTRIBUTIONS

Jeffery D Liu designed the study wrote the protocol, and the first draft of the manuscript and Ashok Gupta performed the statistical analysis. Mark J Allison conducted this clinical trial at the clinical site. All authors read and approved the final manuscript.

CONSENT (WHERE EVER APPLICABLE)

All authors declare that 'written informed consent was obtained from the participants of this study (or other approved parties) for publication of this study. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL (WHERE EVER APPLICABLE)

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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~~APPENDIX~~