Bioavailability of Aspirin in Fasted and Fed States of a Novel Pharmaceutical Lipid Aspirin Complex Formulation*

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OBJECTIVES

NSAIDS cause gastrointestinal mucosal injury in part through disruption of its protective phospholipid bilayer. Especially with aspirin (acetylsalicylic acid), dyspeptic symptoms are common, leading clinicians to frequently recommend that aspirin be taken with food to reduce these side effects.

However, food can interfere with absorption and lead to lower bioavailability, particularly with enteric-coated formulations.

A liquid formulation using a novel pharmaceutical lipid aspirin complex (PL-ASA) has been specifically designed to prevent the disruption of the protective mucosal bilayer without impacting absorption.

The objective of this study was to evaluate if food interferes with the bioavailability of PL-ASA liquid-filled capsules.

METHODS

Study Design:

Randomized, open label, crossover study to assess bioavailability of PL-ASA administered orally.

A total of 20 healthy volunteers fasted for ≥10 hours and then were randomized as either

- **Fasted,** receiving 650 mg of PL-ASA, or as
- **Fed,** with a standard high-fat meal and 650 mg of PL-ASA 30 minutes later.

After a washout of 7 days, participants crossed over to the other regimen (Fig 1).

Blood samples for PK evaluation: <1 hour prior to administration; then at 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, and 90 minutes and at 2, 3, 4, 6, 8, 10, 12 and 24 hours post administration.

PK primary endpoints:

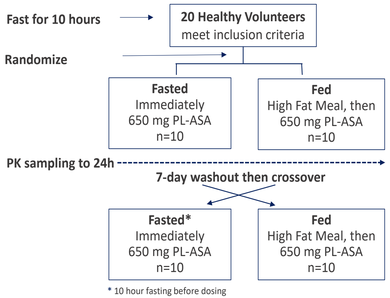
Primary PK assessments were made on $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, λz, $t_{½}$, V_D/F, CL/F and ratios of the least square means (LSM) of the log-transformed PK parameters of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max} of salicylic acid (SA) in the presence or absence of food.

PK secondary endpoints:

Parameters as above, for acetylsalicylic acid.

RESULTS

Figure 1: Study Design and Study Population



A total of 20 subjects were randomized and completed the study without protocol deviation. Baseline characteristics are shown in Table 1.

Table 1: Demographics of Study Population

	Overall (n = 20)
Age (years)	
Mean (SD)	36.8 (8.55)
Median (min-max)	35.0 (22—56)
Sex	
Female	9 (45.0)
Male	11 (55.0)
Race	
White, n (%)	15 (75.0)
Black / African American, n (%)	3 (15.0)
Hispanic/Latino	1 (5.0)
Asian	1 (5.0)
Height (inches)	
Mean (SD)	68.4 (4.77)
Median (min-max)	70.0 (61.0--77.0)
Weight (pounds)	
Mean (SD)	178.8 (40.84)
Median (min-max)	180.5 (112.6 – 256.0)
Body Mass Index (kg/m²)	
Mean (SD)	26.6 (4.13)
Median (min-max)	27.9 (20.0 – 31.3)

Figure 2: Mean Plasma Salicylic Acid Concentration Versus Time

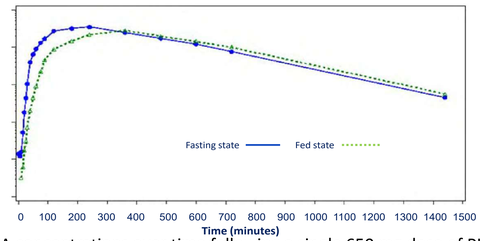
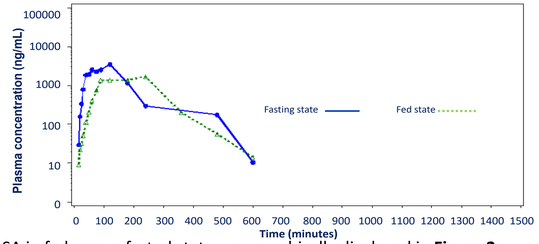


Figure 3: Mean Plasma Acetylsalicylic Acid Concentration Versus Time



Mean SA concentrations over time following a single 650 mg dose of PL-ASA in fed versus fasted states are graphically displayed in **Figure 2**. Overall, the curves in the fasted and fed states were very similar, however, mean peak SA concentration was 28.1% higher in the fasted state and mean time to maximum SA concentration occurred about 1.5 hours later in the fed state. Detailed listings of all SA parameters in both fed and fasted states are shown in **Table 2**. Most PK parameters in fed and fasted states were similar except for median C_{max} that was significantly higher in the fasted state (p=0.01), and median t_{max} that was significantly higher in the fed state (p=0.002). Mean acetylsalicylic acid concentrations over time following a single 650 mg dose of PL-ASA in fed versus fasted states are graphically displayed in **Figure 3**.

Table 2: Summary of Fed and Fasted Salicylic Acid PK Parameters after a Single Dose of 650 mg PL-ASA

PK Parameter*	Fed N=20			Fasted N=20			P-Value†
	Mean (SD)	CV (%)	Median (range)	Mean (SD)	CV (%)	Median (range)	
$AUC_{0\text{-}t}$ (µg x min] /mL)	14945.7 (6436.2)	43.1	14929.1 (7844.8 – 33463.9)	16521.8 (5958.7)	36.1	16582.0 (7915.6 – 32414.2)	0.3
$AUC_{0\text{-}\infty}$ (µg x min] /mL)	15202.9 (6723.0)	44.2	14952.5 (8175.7 – 35576.8)	16791.0 (6167.9)	36.7	17036.1 (8224.8 – 34102.3)	0.3
C_{max} (µg/mL)	29.9 (8.6)	28.9	29.7 (17.9 – 55.3)	38.3 (9.9)	25.8	38.9 (22.2 – 57.8)	0.01
t_{max} (min)	283.5 (96.1)	33.9	360.0 (90.0 – 360.0)	180.0 (50.6)	28.1	180.0 (90.0 – 240.0)	0.002
λ_z (1/min)	0.0048 (0.0009)	19.2	0.0050 (0.0023 – 0.0061)	0.0048 (0.0009)	18.9	0.0050 (0.0024 – 0.0060)	0.8
$t_{½}$ (min)	152.9 (43.1)	28.4	137.5 (113.0 – 296.8)	152.9 (43.1)	28.2	139.2 (115.9 – 292.8)	0.8
CL/F (mL/min)	50.1 (19.2)	38.4	43.5 (18.3 – 79.5)	44.0 (16.7)	37.9	38.2 (19.1 – 79.0)	0.3
VD/F (mL)	10400 (3128)	30.1	9880 (6086 – 15433)	9148 (2498)	27.3	8093 (5644 – 13824.0)	0.3

* N=20 for all PK parameters, †P-value based on the Wilcoxon Rank-Sum test$AUC_{0\text{-}t}$ =area-under-the-curve, $AUC_{0\text{-}\infty}$ =$AUC_{0\text{-}t}$ extrapolated to infinity, C_{max} =maximum plasma concentration, CL/F =apparent clearance, CV=coefficient of variation, λ_z =terminal elimination rate constant, µg=micrograms, mg=milligrams, min=minutes, mL=milliliters, n=number of patients, PK=pharmacokinetic, PL-ASA=pharmaceutical lipid-aspirin complex, SD= standard deviation. t_{max} =time of peak drug concentration, $t_{½}$ =first-order elimination half-life, V_D/F=apparent volume of distribution

Per FDA guidelines, log-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max} were used to calculate ratios of fed to fasted states as summarized in **Table 3.**

Table 3: Summary of Ratios between Fed and Fasted States for Log- Transformed PK Parameters of Salicylic Acid

PK Parameters	Least-square Mean		Geometric Mean		Ratio* (%)	90% CI†	ANOVA p-value‡
	Fed	Fasted	Fed	Fasted			
$AUC_{0\text{-}t}$ (ng×min/mL)	9.53	9.65	13772.6	15521.3	88.7	(82.27, 95.8)	0.01
$AUC_{0\text{-}\infty}$ (ng×min/mL)	9.55	9.66	14000.7	15767	88.8	(82.2, 96)	0.02
C_{max} (ng/mL)	3.36	3.61	28.9	37.1	77.8	(72.3, 83.6)	<0.0001

* Ratio = Geometric Mean (Fed) / Geometric Mean (Fasted) X 100%, †90% Confidence Interval on the Ratio of Fed and Fasted, ‡p-value for the difference in the treatment estimates. Significant difference was defined as p-value < 0.05. ANOVA=analysis of variance; $AUC_{0\text{-}t}$ =area-under-the-curve, $AUC_{0\text{-}\infty}$ =$AUC_{0\text{-}t}$ extrapolated to infinity; C_{max} =maximum plasma concentration; CI-confidence interval; mL=millilliters; min=minutes; N=number of patients; ng=nanograms; PK=pharmacokinetic

CONCLUSIONS/DISCUSSION

- Food had an effect on peak SA levels (C_{max}) and the time required to reach them (T_{max}) after PL-ASA but did not impact the extent of exposure (AUC) which remained well within the FDA proposed boundaries for bioavailability compared with intake in a fasted state.
- The efficacy of aspirin is believed to be related to overall exposure rather than peak dose, therefore, food effects on C_{max} and T_{max} are not considered clinically significant.
- The current study demonstrates that PL-ASA can be taken with food with only minimal impact on overall drug exposure and bioavailability.

DISCUSSION:

- Patients are worried about taking aspirin on an empty stomach and frequently take it with food.
- Coated aspirin formulations suffer from erratic absorption and bioavailability that are further exacerbated when taken with food.
- PL-ASA liquid-filled capsules maintain predictable absorption and bioavailability when taken with food.
- PL-ASA is a new, reliable aspirin option designed to overcome limitations of existing formulations. Further studies are warranted to evaluate PL-ASA versus coated aspirin, currently the most popular aspirin formulation.

Declaration of Interest

PLx Pharma Inc. was the sponsor. The content is solely the responsibility of the authors.

Drs. Angiolillo, Bhatt, and Prats received consulting fees from PLx Pharma Inc. Dr Marathi was employed by PLx at the time of the study and is an investor, option holder, and a co-inventor of the PL-ASA delivery technology; Dr. Deliargyris and Ms. Fan are employees of PLx. All other authors had no conflicts.

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