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ORIGINAL RESEARCH ARTICLE

# Ibuprofen Sodium Is Absorbed Faster than Standard Ibuprofen Tablets: Results of Two Open-Label, Randomized, Crossover Pharmacokinetic Studies

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**Abstract**

*Background* A novel ibuprofen (IBU) formulation, Advil® Film-Coated Tablets ($IBU_{Na}$), was developed.

*Objective* Pharmacokinetic comparison of $IBU_{Na}$ versus other IBU formulations.

*Study Design* Two randomized, single-dose, open-label, five-way crossover pharmacokinetic studies.

*Setting* Inpatient research clinic.

*Subjects* Seventy-one healthy adult volunteers.

*Intervention* Study 1: In three periods, fasted subjects received 400-mg IBU dose equivalents as $IBU_{Na}$ 2 × 256 mg, Advil® Liqui-Gels® ($IBU_{LG}$) 2 × 200 mg, and Motrin® IB ($IBU_{Mot}$) 2 × 200 mg tablets. In two periods following a high-fat breakfast, subjects received 400-mg IBU dose equivalents as $IBU_{Na}$ 2 × 256 mg and $IBU_{LG}$ 2 × 200 mg. Study 2: In five study periods, fasted subjects received 400-mg IBU dose equivalents as $IBU_{Na}$ 2 × 256 mg, Advil® FastGel® ($IBU_{FG}$) 2 × 200 mg, Nurofen® ($IBU_{Nur}$) 2 × 200 mg, Advil® ($IBU_{Adv}$) 2 × 200 mg, and Nurofen® Express containing IBU lysinate ($IBU_{Lys}$) 2 × 342 mg.

*Main Outcome Measure* Log-transformed area under the plasma concentration versus time curve to last observable concentration ($AUC_L$) and maximum plasma concentration ($C_{max}$) were the primary pharmacokinetic parameters; time to maximum measured plasma concentration ($T_{max}$) was analyzed post hoc.

*Results* $IBU_{Na}$ was bioequivalent to $IBU_{LG}$ (fasted and fed) and $IBU_{FG}$ and $IBU_{Lys}$ (fasted) for rate ($C_{max}$) and extent ($AUC_L$) of IBU absorption. After fasting, $AUC_L$ was bioequivalent for $IBU_{Na}$ and $IBU_{Mot}$, $IBU_{Adv}$, and $IBU_{Nur}$, but $C_{max}$ occurred significantly earlier with $IBU_{Na}$. After fasting, median $IBU_{Na}$ $T_{max}$ was comparable to that for $IBU_{LG}$, $IBU_{FG}$, and $IBU_{Lys}$, but was much shorter than that for $IBU_{Mot}$, $IBU_{Nur}$, and $IBU_{Adv}$. Food slowed absorption of $IBU_{Na}$ and $IBU_{LG}$ similarly. All treatments were tolerated similarly.

*Conclusion* $IBU_{Na}$ is absorbed faster but to a similar extent as standard IBU formulations.

**Key Points**

A novel formulation of ibuprofen sodium ($IBU_{Na}$) is absorbed faster than (but to a similar extent to) standard ibuprofen (IBU) in healthy subjects; a clinical study found it to provide faster pain relief than standard IBU formulations in subjects with dental pain.

$IBU_{Na}$ has a pharmacokinetic profile similar to that of other faster-absorbed formulations of IBU.

All IBU formulations were well tolerated, most adverse events were mild in nature, and no significant safety findings were noted.

**Trial Registration** As these are pharmacokinetic studies, trial registration was not done.

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## 1 Introduction

When treating acute pain, rapid onset of relief is desirable. With ibuprofen (IBU), one of the most widely used non-prescription analgesics available, pain relief is directly related to IBU plasma levels [1]. Although IBU is almost completely absorbed, allowing for nearly 100 % bioavailability, the rate of absorption depends on dissolution of the given formulation [2]. IBU, which is a carboxylic acid, shows low solubility in aqueous acidic media such as that which is found in the stomach [3]. As a result, meaningful pain relief typically takes approximately 45 min after ingestion of an over-the-counter (OTC) dose (400 mg) of standard IBU [4, 5]. Patients experiencing acute painful conditions such as headache, musculoskeletal pain, menstrual cramps, or dental pain would benefit from a faster onset of pain relief.

In an effort to provide more rapid pain relief, newer IBU formulations have been designed to dissolve more readily in the acidic environment of the stomach. Such formulations include IBU salt conjugates [e.g., IBU lysinate ($IBU_{Lys}$), arginine ($IBU_{Arg}$), or sodium ($IBU_{Na}$)] and gelatin capsules containing solubilized IBU that achieve maximum plasma concentrations ($C_{max}$) that are higher and are reached earlier (time to maximum measured plasma concentration; $T_{max}$) than those found with standard IBU tablets [2, 4, 6]. Clinically, $IBU_{Arg}$ has been found to provide a faster onset of pain relief versus standard IBU [4, 5, 7], while both $IBU_{Lys}$ [8] and solubilized IBU [9–11] have demonstrated more rapid pain relief compared with acetaminophen. Recently, a novel tablet formulation of IBU sodium dihydrate has been developed that has a thin-film coating and is manufactured using a patent-pending process. This report details two studies evaluating the pharmacokinetic profile of this new formulation in comparison with both standard IBU tablets and rapidly absorbed IBU formulations.

## 2 Methods

### 2.1 Study Design and Procedures

Two single-dose, randomized, open-label, inpatient, five-way crossover bioequivalence studies (Study 1, Study 2) were conducted to evaluate the pharmacokinetics of 400-mg dose equivalents of IBU administered in various different formulations. In both studies, subjects received all interventions according to a computer-generated random sequence provided by Pfizer Consumer Healthcare's Biostatistics Department; treatment periods were separated by a washout period of at least 48 h. Subjects remained on site for the duration of each respective study.

In Study 1, conducted from July 29 to August 7, 2009, at PPD Development, LP (Austin, TX, USA), subjects received ibuprofen sodium dihydrate tablets [Advil® Film-Coated Tablets ($IBU_{Na}$), Pfizer Consumer Healthcare, Madison, NJ, USA] 2 × 256 mg, solubilized IBU liquid capsules [Advil® Liqui-Gels® ($IBU_{LG}$), Pfizer Consumer Healthcare] 2 × 200 mg, and standard IBU tablets [Motrin® IB ($IBU_{Mot}$), McNeil Consumer Healthcare, Fort Washington, PA, USA] 2 × 200 mg in each of three study periods following an overnight fast. For the remaining two study periods, subjects received $IBU_{Na}$ tablets 2 × 256 mg or $IBU_{LG}$ 2 × 200 mg within 20 min of a standardized high-fat breakfast. In Study 2, conducted from June 9 to 18, 2010, at Bio-Kinetic Clinical Applications, LLC (Springfield, MO, USA), subjects received $IBU_{Na}$ tablets 2 × 256 mg, solubilized IBU liquid capsules [Advil® FastGel® ($IBU_{FG}$), Pfizer Consumer Healthcare] 2 × 200 mg, two formulations of standard IBU tablets [Nurofen® ($IBU_{Nur}$), Reckitt Benckiser, Slough, Berkshire, UK; and Advil® ($IBU_{Adv}$), Pfizer Consumer Healthcare] 2 × 200 mg, and caplets of Nurofen® Express containing IBU lysinate ($IBU_{Lys}$) (Reckitt Benckiser) 2 × 342 mg following an overnight fast.

Both protocols were approved by the appropriate institutional review board prior to study initiation, and both trials were conducted in compliance with International Conference on Harmonisation (ICH) standards for Good Clinical Practice and the Declaration of Helsinki and its amendments. All subjects provided written informed consent prior to the conduct of any study-related procedures.

### 2.2 Subjects

Subjects for Studies 1 and 2 were adult male and female (non-pregnant and non-lactating) volunteers in normal physical health, as determined by physical examination and laboratory evaluation, between 18 and 45 years of age and with a body mass index (BMI) of 18–29 $kg/m^2$. Females of childbearing potential were required to be using reliable contraception. Excluded were individuals with a presence or history of any significant systemic medical disorder or condition felt to increase subject risk. Other exclusion criteria included hypersensitivity to aspirin, IBU, or other nonsteroidal anti-inflammatory drugs; alcohol or substance abuse within 2 years of enrollment; tobacco use within 6 weeks of enrollment; use of an investigational drug or participation in an investigational trial within 30 days of study initiation; and participation in another pharmacokinetic study or donation of blood/plasma within 4 weeks of the first treatment period, within 6 weeks of first treatment if >300 mL of blood was contributed, within 8 weeks of first treatment if >400 mL of blood was contributed, or within 10 weeks of first treatment if hemoglobin or hematocrit was noted to be abnormal.

Eligible subjects agreed not to take any medications (except oral contraceptives), nutritional supplements (except vitamin and mineral supplements), weight loss or energy products, herbal teas, or herbal supplements for 14 days prior to and during each study period. They also agreed not to ingest caffeine for 24 h or alcohol for 3 days prior to and during the study.

It was estimated that 30 subjects were needed for each study to provide at least 80 % power to establish bioequivalence, assuming that the bioavailability of $IBU_{Na}$ was within 7.5–9.0 % of that for the reference, and the within-subject variability for Log $C_{max}$ was 0.178–0.187 or less based on previous studies; additional subjects were enrolled assuming an $\sim$15 % dropout rate to ensure at least 30 subjects completed each study.

### 2.3 Bioanalysis

For IBU pharmacokinetic analyses, blood samples (3 mL each, collected into sodium heparin tubes) were drawn prior to dosing (hour 0) and at 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, and 90 min and at 2, 3, 4, 6, 8, 10, 12, and 16 h postdose. Once obtained, blood samples were mixed thoroughly, put on ice, and centrifuged within 30 min of collection. Following centrifugation, plasma was removed and stored at −20 °C until analyzed. Plasma was analyzed for racemic IBU using a validated method of high-performance liquid chromatography with tandem mass spectrometry detection. This method allowed for a lower limit of IBU quantitation of 0.2 μg/mL. Expressed as a percent coefficient of variation, the intra-assay precision was 0.542–3.36 %; the inter-assay precision was 1.11–2.79 %.

### 2.4 Pharmacokinetic Parameters and Analysis

Only those subjects providing evaluable data from at least two study treatment periods were included in the pharmacokinetic analyses of each study. Data were considered inevaluable if two consecutive plasma concentrations were missing for that period, predose plasma IBU concentration was >5 % of $C_{max}$ for that period, or if the subject experienced emesis at or before two times the median $T_{max}$ for that period. Concentrations below the limit of quantitation (0.2 μg/mL) were set to zero.

Untransformed pharmacokinetic parameters were derived using WinNonlin® version 5.1 (Pharsight, Inc., Mountain View, CA, USA). The following parameters were calculated based on actual sampling times: area under the plasma concentration versus time curve to last observable concentration ($AUC_L$) and from time zero to infinity ($AUC_I$), $C_{max}$, $T_{max}$, half-life, elimination rate constant, volume of distribution, and clearance.

Data for $AUC_L$, $AUC_I$, and $C_{max}$ (log transformed) were analyzed via analysis of variance (ANOVA) with effects for sequence, subject (sequence), period, and treatment terms in the model. For Study 1, fasting-state paired comparisons were conducted between $IBU_{Na}$ versus $IBU_{LG}$ and $IBU_{Na}$ versus $IBU_{Mot}$; fed-state comparisons were made between $IBU_{Na}$ versus $IBU_{LG}$. For Study 2, $IBU_{Na}$ was compared with $IBU_{FG}$, $IBU_{Nur}$, $IBU_{Adv}$, and $IBU_{Lys}$ all in the fasting state. Additionally, $IBU_{FG}$ was also compared with $IBU_{Adv}$. Bioequivalence was considered established if the two-sided 90 % confidence interval (CI) for the least squares means ratio of study drug to reference formulation was between 80 and 125 %. Post hoc analyses of $T_{max}$ were performed using the Wilcoxon rank-sum test; Hodges-Lehmann estimates were used to evaluate treatment differences. No other changes were made to the planned protocols following initiation of the studies. Statistical analyses were performed using SAS® version 9.2 (SAS Institute, Cary, NC, USA).

### 2.5 Safety Analysis

Safety was evaluated among all subjects who took at least one dose of study medication. Adverse events (AEs) were coded using the *Medical Dictionary for Regulatory Activities* (Study 1, version 9.0; Study 2, version 13.0) and classified by severity and relationship to study medication. Prestudy and poststudy physical examinations and laboratory findings of clinical relevance were recorded.

## 3 Results

### 3.1 Subject Disposition and Baseline Demographics

Seventy-one healthy adults ($N = 36$ in Study 1 and $N = 35$ in Study 2) were randomized to receive study medication. Seven subjects discontinued prematurely, including four subjects in Study 1 (two voluntary withdrawals due to painful blood collections and two due to AEs) and three subjects in Study 2 (two due to AEs and one due to uncooperativeness). In Study 1, all four subjects who discontinued early (during treatment period 1) were excluded from all pharmacokinetic analyses; three additional subjects had data excluded for specific periods. In Study 2, one subject discontinued early (treatment period 1) and was excluded from all pharmacokinetic analyses; four additional subjects had data excluded from specific periods.

The demographic characteristics (Table 1) of subjects enrolled in Studies 1 and 2 were generally similar in terms of age, weight, height, and BMI; approximately equal proportions of male and female subjects participated. Most subjects in both studies were white.

### 3.2 IBU Pharmacokinetic Results

Mean IBU plasma concentration versus time curves and pharmacokinetic results for Study 1 are presented in Fig. 1 and Table 2, respectively. Using log-transformed data, $IBU_{Na}$ demonstrated an equivalent extent of absorption relative to $IBU_{Mot}$ in the fasted state on the basis of $AUC_L$; the 90 % CI for $AUC_I$ was also contained within the limits of bioequivalence. However, $IBU_{Na}$ reached a $C_{max}$ that was higher (90 % CI 125.2–145.5) than that for $IBU_{Mot}$. Additionally, the $T_{max}$ for $IBU_{Na}$ was 82.0 min faster (95 % CI 62.1–108.0, $P < 0.001$) (Table 3) than that for $IBU_{Mot}$.

Comparisons of $IBU_{Na}$ and $IBU_{LG}$ indicated bioequivalence under both fasted and fed conditions for both the rate and extent of IBU absorption. The 90 % CIs for the $AUC_I$ were in line with $AUC_L$ findings. As expected, the rate of IBU absorption with $IBU_{Na}$ and $IBU_{LG}$ was slower in the fed state than in the fasted state (Fig. 1 and Table 2).

Mean IBU plasma concentration versus time curves and pharmacokinetic results for Study 2 are presented in Fig. 2 and Table 4. Compared with standard IBU formulations ($IBU_{Adv}$ and $IBU_{Nur}$), $IBU_{Na}$ had an equivalent extent of absorption ($AUC_L$); the 90 % CIs for $AUC_I$ were also within the limits of bioequivalence. $IBU_{Na}$ was absorbed significantly faster compared with $IBU_{Adv}$ and $IBU_{Nur}$; $C_{max}$ was higher (90 % CI 117.5–136.4) for $IBU_{Na}$ versus $IBU_{Adv}$ and was also greater (90 % CI 121.3–140.5) for $IBU_{Na}$ versus $IBU_{Nur}$. As summarized in Table 3, the $T_{max}$ for $IBU_{Na}$ was faster than that for $IBU_{Adv}$ and $IBU_{Nur}$, ($P < 0.001$ for both comparisons).

$IBU_{Na}$ was bioequivalent to both $IBU_{FG}$ and $IBU_{Lys}$ on the basis of $C_{max}$ and $AUC_L$. There were no significant differences in $T_{max}$ between $IBU_{Na}$ and either $IBU_{FG}$ or $IBU_{Lys}$.

**Table 1** Baseline demographics

| | Study 1 ($N = 36$) | Study 2 ($N = 35$) |
|---|---|---|
| Age, mean (range), years | 27.4 (18–45) | 25.6 (18–45) |
| Weight, mean (range), kg | 68.4 (50.8–94.3) | 71.9 (50.6–95.8) |
| Height, mean (range), cm | 169.1 (155–190) | 173.1 (157.0–197.0) |
| BMI, mean (range), kg/m$^2$ | 23.9 (19–28) | 23.9 (18.8–28.9) |
| Race, *N* (%) | | |
| White | 31 (86.1) | 33 (94.3) |
| Black | 4 (11.1) | 0 |
| Asian | 1 (2.8) | 1 (2.9) |
| Other | 0 | 1 (2.9) |
| Ethnicity, *N* (%) | | |
| Non-Hispanic | 19 (52.8) | 32 (91.4) |
| Hispanic | 17 (47.2) | 3 (8.6) |
| Sex, *N* (%) | | |
| Male | 18 (50) | 18 (51.4) |
| Female | 18 (50) | 17 (48.6) |

*BMI* body mass index (height in meters/mass in kg$^2$), *N* number

### 3.3 Safety and Tolerability

Four subjects prematurely discontinued from these studies due to an AE (Study 1: one each for emesis and headache; Study 2: one each for hemorrhoids and contact dermatitis). Fifteen subjects from Study 1 reported 31 AEs; 14/31 (45.2 %) were considered treatment related, and all were rated as mild except for one report each of nausea,

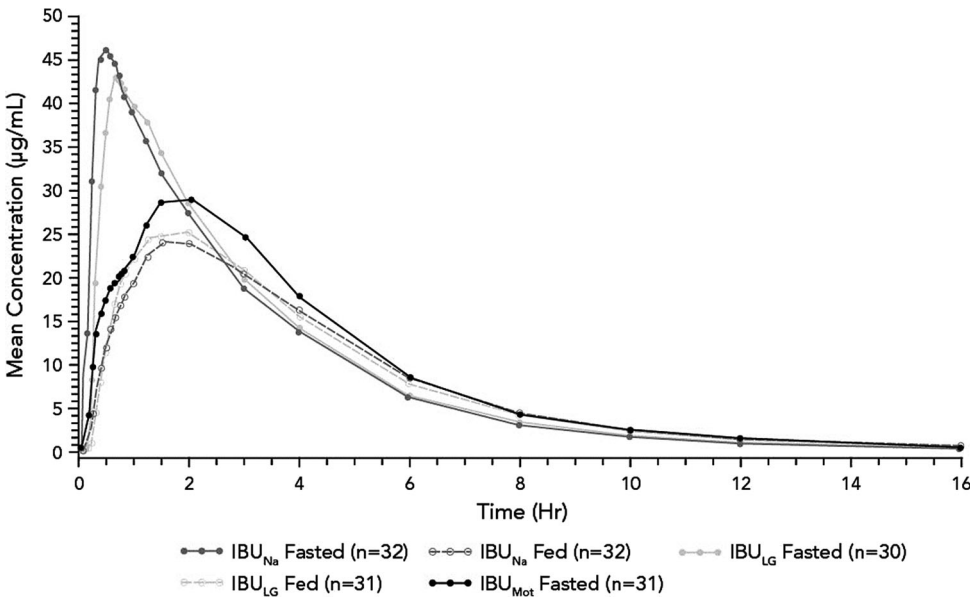


**Fig. 1** Study 1: Mean ibuprofen (IBU) plasma concentrations from time 0 (predose) to hour 16 postdose in subjects administered 400-mg dose equivalents of IBU via a novel IBU sodium dihydrate tablet (Advil® Film-Coated Tablets; $IBU_{Na}$) and Advil® Liqui-Gels® liquid capsules ($IBU_{LG}$) under fed and fasted conditions and Motrin® IB tablets ($IBU_{Mot}$) under fasted conditions

**Table 2** Study 1 pharmacokinetic parameters and bioequivalence

| Treatment (*N*) | $AUC_L$ (μg·h/mL) | $AUC_I$ (μg·h/mL) | $C_{max}$ (μg/mL) | $t_{½}$ (h) | Kel (1/h) | CL (L/h) | $V_d$ (L) |
|---|---|---|---|---|---|---|---|
| Mean (SD) | | | | | | | |
| $IBU_{Na}$ fasted ($N = 32$) | 145.7 (29.6) | 147.2 (30.1) | 50.6 (10.3) | 2.21 (0.38) | 0.32 (0.06) | 2.82 (0.55) | 8.87 (1.62) |
| $IBU_{Na}$ fed ($N = 32$) | 127.2 (28.6) | 130.6 (29.2) | 31.5 (8.8) | 2.65 (1.01) | 0.28 (0.07) | 3.19 (0.59) | 12.03 (4.85) |
| $IBU_{LG}$ fasted ($N = 30$) | 143.8 (32.6) | 145.5 (33.2) | 48.6 (11.2) | 2.35 (0.36) | 0.30 (0.05) | 2.87 (0.56) | 9.54 (1.42) |
| $IBU_{LG}$ fed ($N = 31$) | 125.9 (29.7) | 128.9 (30.6) | 34.2 (9.7) | 2.56 (0.75) | 0.29 (0.07) | 3.24 (0.62) | 11.68 (3.36) |
| $IBU_{Mot}$ fasted ($N = 31$) | 143.4 (32.2) | 145.6 (32.4) | 37.4 (7.8) | 2.38 (0.50) | 0.30 (0.06) | 2.85 (0.51) | 9.67 (2.57) |
| LSM ratios, % (90 % CI)[a] | | | | | | | |
| $IBU_{Na}/IBU_{LG}$ fasted[b] | 102.0 (99.1–105.0) | 102.0 (99.1–105.0) | 104.2 (96.6–112.4) | – | – | – | – |
| $IBU_{Na}/IBU_{Mot}$ fasted[b] | 102.4 (99.5–105.4) | 101.8 (98.9–104.8) | 135.0 (125.2–145.5) | – | – | – | – |
| $IBU_{Na}/IBU_{LG}$ fed[b] | 101.7 (98.8–104.7) | 102.1 (99.2–105.1) | 91.2 (84.6–98.3) | – | – | – | – |

[a] Based on fitted log-transformed data

[b] Reference formulation

*$AUC_I$* area under the plasma concentration vs. time curve from time 0 to infinity, *$AUC_L$* area under the plasma concentration vs. time curve from time 0 to last measurable concentration, *CI* confidence interval, *CL* clearance, *$C_{max}$* maximum measured plasma concentration, *IBU* ibuprofen, *$IBU_{LG}$* Advil® Liqui-Gels® liquid capsules, *$IBU_{Mot}$* Motrin® IB tablets, *$IBU_{Na}$* Advil® Film-Coated Tablets, *Kel* elimination rate constant, *LSM* least squares mean, *N* number, *SD* standard deviation, *$t_{½}$* half-life, *$V_d$* volume of distribution

vomiting, headache, and blurred vision of moderate severity. The most common AE among all treatments in Study 1 was headache (six reports). In Study 2, 17 subjects reported 35 AEs; 9/35 (25.7 %) were considered treatment related, and all were rated as mild. The most common AE across all treatments in Study 2 was dizziness (12 reports). No severe or serious AEs occurred during either study. With the exception of the development of a mild ear infection that resolved spontaneously without any treatment in one subject in Study 2, there were no clinically significant laboratory, vital sign, or physical examination findings noted during either study. No new or unexpected safety concerns emerged in the $IBU_{Na}$ arms versus those of comparator IBU formulations; AE rates were similar across all treatments (data not shown).

## 4 Discussion

Results of the two pharmacokinetic studies presented here demonstrate that this novel formulation of $IBU_{Na}$ was absorbed at a rate faster than standard IBU tablets and was comparable with rates of other fast-absorbed IBU formulations. $IBU_{Na}$ was bioequivalent to $IBU_{LG}$, $IBU_{FG}$, and $IBU_{Lys}$ in terms of both the rate and extent of absorption in the fasted state. $T_{max}$ was approximately 5–10 min faster with $IBU_{Na}$ than $IBU_{LG}$ in the fasted state. Feeding had a similar effect on the rate of absorption of both $IBU_{Na}$ and $IBU_{LG}$, as both $C_{max}$ and $T_{max}$ were similar between the two formulations in both the fasted and fed states. $IBU_{Na}$ was absorbed to the same extent as standard IBU when administered as $IBU_{Mot}$, $IBU_{Adv}$, and $IBU_{Nur}$, but was absorbed more rapidly, with $T_{max}$ values of 30–35 min versus 120, 82.5, and 120 min, respectively. All IBU treatments were well tolerated.

IBU formulations that employ IBU dissolved in a gelatin capsule or conjugated to a salt allow healthy subjects to more rapidly absorb the product and in this way improve upon the relatively low solubility of standard tablets that are composed of IBU free acid. Since IBU is almost entirely absorbed, faster absorption does not increase the extent of absorption; hence, overall IBU exposure is similar to that of standard IBU, as shown in previous studies [2, 6]. Pharmacodynamic investigations have demonstrated that faster absorption of IBU arginate is associated with a faster onset of analgesia compared with standard IBU tablets [4, 5]. Furthermore, in a study modeling the pharmacokinetics and pharmacodynamics of an effervescent formulation of IBU, faster absorption of that formulation was also associated with faster onset of analgesia in patients with dental pain compared with standard IBU [12].

Similarly, $IBU_{Na}$ tablets have been designed with this same goal in mind. IBU is a carboxylic acid that does not rapidly dissolve in an acidic aqueous environment such as that of the stomach [3]. In vitro investigations have shown a significantly faster rate of dissolution for $IBU_{Na}$ compared with standard IBU tablets at acidic pH levels [13]. The current findings demonstrate that these novel $IBU_{Na}$

**Table 3** Study 1 and Study 2 post hoc analysis of median $T_{max}$ differences

| Study 1 | |
|---|---|
| Treatment (*N*) | Median $T_{max}$ (min) |
| $IBU_{Na}$ fasted ($N = 32$) | 30.4 |
| $IBU_{Na}$ fed ($N = 32$) | 90.0 |
| $IBU_{LG}$ fasted ($N = 30$) | 40.5 |
| $IBU_{LG}$ fed ($N = 31$) | 90.0 |
| $IBU_{Mot}$ fasted ($N = 31$) | 120.0 |
| **Study 1** | |
| Comparison | Median difference (95 % CI) in minutes and *P* values[a] |
| $IBU_{Na}$ vs. $IBU_{LG}$ fasted | 12.4 (7.1–18.3), $P = 0.003$[b] |
| $IBU_{Na}$ vs. $IBU_{Mot}$ fasted | 82.0 (62.1–108.0), $P < 0.001$[b] |
| $IBU_{Na}$ vs. $IBU_{LG}$ fed | 0.0 (−30.0 to 14.5), $P = 0.809$ |
| **Study 2** | |
| Treatment (*N*) | Median $T_{max}$ (min) |
| $IBU_{Na}$ ($N = 33$)[c] | 35.2 |
| $IBU_{FG}$ ($N = 31$)[c] | 40.0 |
| $IBU_{Nur}$ ($N = 33$)[c] | 120.0 |
| $IBU_{Adv}$ ($N = 32$)[c] | 82.5 |
| $IBU_{Lys}$ ($N = 32$)[c] | 35.1 |
| **Study 2** | |
| Comparison | Median difference (95 % CI) in minutes and *P* values[a] |
| $IBU_{Na}$ vs. $IBU_{FG}$ | 1.5 (−6.2 to 13.1), $P = 0.527$ |
| $IBU_{Na}$ vs. $IBU_{Nur}$ | 75.2 (50.6–99.8), $P < 0.001$[b] |
| $IBU_{Na}$ vs. $IBU_{Adv}$ | 63.8 (39.8–92.5), $P < 0.001$[b] |
| $IBU_{Na}$ vs. $IBU_{Lys}$ | −2.3 (−9.8 to 5.1), $P = 0.649$ |

[a] Hodges–Lehmann estimator (median of the pairwise differences), the 95 % CI and *P* values are from the Wilcoxon rank-sum test

[b] Statistically significant at the 0.05 level

[c] A total dose of two tablets/capsules/caplets was administered to each subject with a total dose equivalent to 400 mg of IBU

*CI* confidence interval, *IBU* ibuprofen, $IBU_{Adv}$ Advil® tablets, $IBU_{FG}$ Advil® FastGel® liquid capsules, $IBU_{LG}$ Advil® Liqui-Gels® liquid capsules, $IBU_{Lys}$ Nurofen Express® caplets containing IBU lysinate, $IBU_{Mot}$ Motrin® IB tablets, $IBU_{Na}$ Advil® Film-Coated Tablets, $IBU_{Nur}$ Nurofen® tablets, *N* number, $T_{max}$ time to maximum measured (i.e., peak) plasma concentration

tablets, which have a thin-film coating and are manufactured using a patent-pending process, provide faster absorption with a more rapid attainment of peak IBU plasma concentrations compared with standard IBU tablets. Under fasted conditions, $C_{max}$ for $IBU_{Na}$ was approximately 30 % greater and $T_{max}$ occurred roughly 1–1.5 h sooner than for standard IBU tablets. Importantly, $AUC_L$ values for $IBU_{Na}$ and each of the standard IBU tablets tested were similar, indicating that conjugation of IBU with sodium salt does not alter the extent of IBU absorption and yields overall IBU exposure similar to conventional IBU tablets.

Our results are consistent with those of previous pharmacokinetic evaluations of older formulations of $IBU_{Na}$. In a pair of open-label, randomized, single-dose, crossover studies conducted in healthy volunteers, Sorgel et al. [13] compared the pharmacokinetics of $IBU_{Na}$ with those of standard IBU tablets, $IBU_{Lys}$, and $IBU_{LG}$ (first study), as well as with $IBU_{Arg}$ and $IBU_{Lys}$ (second study). These studies have shown that $IBU_{Na}$ had a significantly higher $C_{max}$ (47.6 vs. 36.8 μg/mL, $P < 0.01$) and shorter $T_{max}$ (0.6 vs. 1.4 h, $P = 0.018$) compared with standard IBU tablets and had no significant differences in absorption rate compared with $IBU_{Lys}$, $IBU_{Arg}$, or $IBU_{LG}$ [13]. Similarly, Dewland et al. [14] compared the single-dose pharmacokinetics (400-mg equivalents) of $IBU_{Na}$ with those of a novel IBU/poloxamer formulation and standard IBU tablets in healthy volunteers. While the overall extent of absorption was similar for all of the formulations, $T_{max}$ averaged 55 min shorter with $IBU_{Na}$ compared with standard IBU tablets (median of 35 vs. 90 min, respectively; $P < 0.0002$), and $C_{max}$ was approximately 30 % higher (41.47 vs. 31.88 μg/mL, respectively). It is worth noting that the $T_{max}$ values for $IBU_{Na}$ across both the current and previous pharmacokinetic studies are comparable—between 30 and 36 min.

Patients suffering from acute pain desire pain relief as quickly as possible. Previous studies have shown that the rate and extent of IBU absorption may be impaired during pain episodes when IBU is taken in its standard oral formulation, but that fast-dissolving IBU formulations fare much better in this regard [15, 16]. The current investigation did not characterize the pharmacokinetic/pharmacodynamic profile of analgesia following $IBU_{Na}$ administration. However, a clinical efficacy study using this same $IBU_{Na}$ formulation found it to provide a faster onset of analgesia compared with standard IBU in subjects with dental pain [17]. In that 8-h inpatient study examining the effect of the current $IBU_{Na}$ formulation on postsurgical dental pain using the third molar dental extraction model, $IBU_{Na}$ was associated with a significantly earlier time to meaningful pain relief (median 42.4 min) in comparison with placebo (>8 h, $P < 0.001$), pooled $IBU_{Adv}$/$IBU_{Mot}$ (median 55.3 min, $P < 0.001$), and $IBU_{Mot}$ (median 60.7 min, $P < 0.001$) and was marginally faster than $IBU_{Adv}$ (median 52.0 min, $P = 0.075$) [17].

Two other randomized studies using previous $IBU_{Na}$ formulations in the third molar extraction model of dental pain showed similar findings [18, 19]. In the QUIKK trial, first perceptible pain relief occurred 6 min earlier ($P = 0.004$) with a previous $IBU_{Na}$ formulation than with

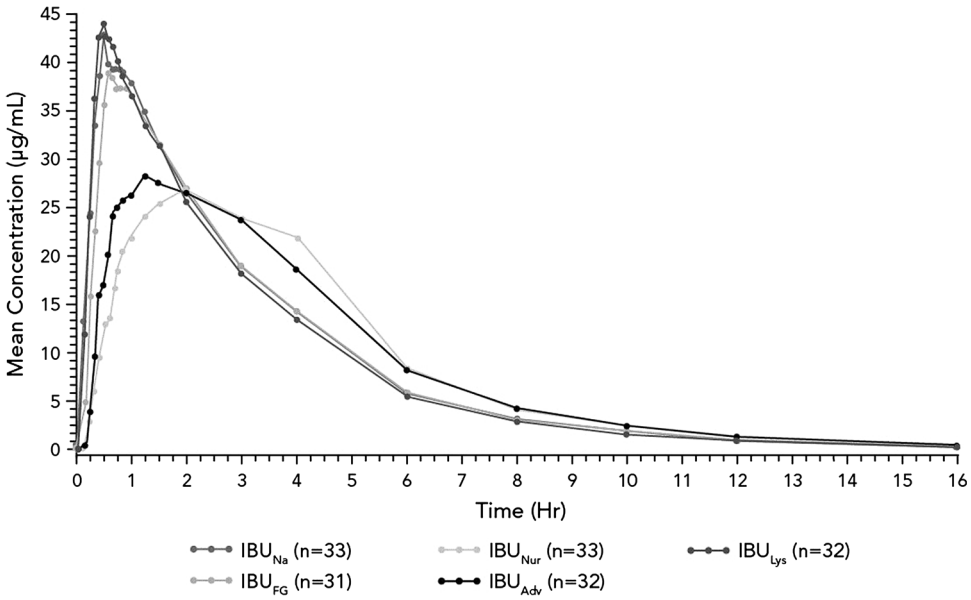


**Fig. 2** Study 2: Mean ibuprofen (IBU) plasma concentrations from time 0 (predose) to hour 16 postdose in subjects administered 400-mg dose equivalents of IBU under fasted conditions via a novel IBU sodium dihydrate tablet (Advil® Film-Coated Tablets; $IBU_{Na}$), Advil® FastGel® liquid capsules ($IBU_{FG}$), Nurofen® Express caplets containing IBU lysinate ($IBU_{Lys}$), standard Advil® tablets ($IBU_{Adv}$), and Nurofen® tablets ($IBU_{Nur}$)

**Table 4** Study 2 pharmacokinetic parameters and bioequivalence

| Treatment (*N*) | $AUC_L$ (µg·h/mL) | $AUC_I$ (µg·h/mL) | $C_{max}$ (µg/mL) | $t_{½}$ (h) | Kel (1/h) | CL (L/h) | $V_d$ (L) |
|---|---|---|---|---|---|---|---|
| Mean (SD) | | | | | | | |
| $IBU_{Na}$ ($N = 33$) | 140.8 (34.3) | 142.1 (35.0) | 47.0 (10.7) | 2.12 (0.27) | 0.33 (0.04) | 2.96 (0.63) | 8.84 (1.30) |
| $IBU_{FG}$ ($N = 31$) | 133.8 (33.2) | 135.2 (33.8) | 46.8 (12.0) | 2.17 (0.34) | 0.33 (0.05) | 3.11 (0.64) | 9.59 (2.21) |
| $IBU_{Nur}$ ($N = 33$) | 140.5 (33.2) | 141.9 (33.9) | 36.1 (7.3) | 2.17 (0.27) | 0.32 (0.04) | 2.95 (0.60) | 9.10 (1.52) |
| $IBU_{Adv}$ ($N = 32$) | 140.3 (30.3) | 141.8 (31.1) | 37.7 (8.4) | 2.16 (0.28) | 0.33 (0.04) | 2.93 (0.56) | 9.03 (1.49) |
| $IBU_{Lys}$ ($N = 32$) | 136.4 (29.9) | 137.7 (30.7) | 49.9 (12.6) | 2.16 (0.35) | 0.33 (0.05) | 3.03 (0.58) | 9.20 (1.26) |
| LSM ratios, % (90 % CI)[a] | | | | | | | |
| $IBU_{Na}/IBU_{FG}$[b] | 105.2 (102.1–108.3) | 105.1 (102.1–108.1) | 101.3 (94.0–109.2) | – | – | – | – |
| $IBU_{Na}/IBU_{Nur}$[b] | 101.0 (98.1–103.9) | 100.9 (98.1–103.8) | 130.6 (121.3–140.5) | – | – | – | – |
| $IBU_{Na}/IBU_{Adv}$[b] | 100.3 (97.4–103.2) | 100.2 (97.4–103.1) | 126.6 (117.5–136.4) | – | – | – | – |
| $IBU_{Na}/IBU_{Lys}$[b] | 102.2 (99.3–105.2) | 102.2 (99.4–105.2) | 95.4 (88.6–102.8) | – | – | – | – |
| $IBU_{FG}/IBU_{Adv}$[b] | 95.4 (92.6–98.2) | 95.4 (92.7–98.1) | 125.0 (115.9–134.8) | – | – | – | – |

[a] Based on fitted log-transformed parameters

[b] Reference formulation

*$AUC_I$* area under the plasma concentration vs. time curve from time 0 to infinity, *$AUC_L$* area under the plasma concentration vs. time curve from time 0 to last measurable concentration, *CI* confidence interval, *CL* clearance, *$C_{max}$* maximum measured plasma concentration, *IBU* ibuprofen, *$IBU_{Adv}$* Advil® tablets, *$IBU_{FG}$* Advil® FastGel® liquid capsules, *$IBU_{Lys}$* Nurofen Express® caplets containing IBU lysinate, *$IBU_{Na}$* Advil® Film-Coated Tablets, *$IBU_{Nur}$* Nurofen® tablets, *Kel* elimination rate constant, *LSM* least squares mean, *N* number, *SD* standard deviation, *$t_{½}$* half-life, *$V_d$* volume of distribution

standard IBU tablets according to stopwatch assessments, although the time to substantial pain relief was not significantly different between the formulations [18]. Patient diary assessments indicated that significantly more patients treated with $IBU_{Na}$ reported "some" to "complete" pain relief at 15 min (43 vs. 29 % for standard IBU tablets, $P < 0.001$) and at 30 min (82 vs. 63 %, $P < 0.001$) [18].

In a study by Schleier et al. [19], the first sign of perceptible pain relief occurred within 15 min for 52.5 % of patients treated with a previous $IBU_{Na}$ formulation vs. 35.9 % of those treated with standard IBU tablets ($P < 0.001$). Substantial pain relief was attained after a median of 42 versus 56 min with $IBU_{Na}$ versus standard IBU [19]. In addition, reduction in pain intensity occurred to a greater degree and was faster with $IBU_{Na}$, such that pain intensity was reduced by 50 % after an average of 30 min with $IBU_{Na}$ versus 57 min with standard IBU tablets ($P < 0.02$) [19]. Taken together, these data indicate that the faster absorption achieved with various formulations of $IBU_{Na}$ translates into more rapid pain relief.

The current studies are limited in that they were performed in healthy volunteers, and therefore, the results obtained may not be generalizable to those with underlying comorbidities or to those with active pain. A previous study found that pain was associated with an inhibition of absorption of IBU and a decrease in the conversion of racemic IBU to the active *S*-(+) enantiomer [15]. Nonetheless, data from clinical studies utilizing the dental pain model have shown a more rapid onset of analgesia with this novel $IBU_{Na}$ formulation [17] as well as previous formulations [18, 19] of $IBU_{Na}$ versus standard IBU formulations, suggesting that although the absorption and conversion of racemic IBU to the active *S*-(+) enantiomer with this formulation may be delayed by pain, the faster-absorbed formulation still provides faster onset of analgesia than standard formulations in the presence of pain. Lastly, because subjects were not allowed to take concomitant medications while participating in these studies, the potential for drug–drug interactions could not be assessed. However, these would be expected to be the same as those known for standard IBU.

## 5 Conclusions

A newly developed, novel tablet formulation of $IBU_{Na}$ was absorbed more rapidly but achieved similar exposure in comparison with standard IBU tablets in healthy volunteers. In addition, $IBU_{Na}$ was absorbed at the same rate as other rapidly absorbed IBU formulations.

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