Effects of a Self–micro-emulsifying Delivery System Formulation Versus a Standard ω-3 Acid Ethyl Ester Product on the Bioavailability of Eicosapentaenoic Acid and Docosahexaenoic Acid: A Study in Healthy Men and Women in a Fasted State

Kevin C. Maki, PhD[1,2]; Orsolya M. Palacios, RD, PhD[1]; Mary A. Buggia, MD[1]; Rupal Trivedi, MD[2]; Mary R. Dicklin, PhD[1]; and Cathleen E. Maki, RN, MSN[1,2]

[1]*Midwest Biomedical Research/MB Clinical Research, Glen Ellyn, IL, United States; and* [2]*Great Lakes Clinical Trials, Chicago, IL, United States*

ABSTRACT

Purpose: Intakes of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are associated with several potential health benefits, but standard ethyl ester (EE) formulations of these ω-3 fatty acids require the co-ingestion of fat for adequate absorption. The objective of this research was to assess the relative bioavailability of EPA and DHA administered in a proprietary self–micro-emulsifying delivery system (SMEDS) formulation compared with EPA and DHA in a standard ω-3 acid EE product in healthy men and women in a fasted state.

Methods: This randomized crossover study investigated the bioavailability of 2 encapsulated formulations of EPA and DHA, a capsule containing 500 mg EPA + DHA administered in a SMEDS formulation (SMEDS treatment), and a capsule containing 840 mg EPA + DHA in a standard ω-3 acid EE formulation (EE treatment). Subjects consumed a single dose of their assigned capsule in a fasting state, and plasma was collected before and for 24 h after dosing. Subjects underwent a ≥14-day washout and were crossed over to the other treatment condition. Plasma concentrations of EPA, DHA, and EPA + DHA were assessed.

Findings: Twenty-three subjects (11 women, 12 men; mean [SEM] age, 33.8 [2.1] years; and body mass index, 24.9 [0.7] kg/m^2) completed the trial. The baseline-adjusted, dose-normalized, arithmetic means (SD) of the incremental (i)-AUC_{0-24h} for EPA + DHA were 543 (266) and 102 (88.2) h · μg/mL/g for the SMEDS and EE formulations, respectively ($P < 0.001$). The $iAUC_{0-24h}$ least-squares geometric mean ratio (90% CI) for SMEDS:standard EE was 475/58 = 8.2 (4.8–13.9), indicating markedly higher bioavailability of EPA + DHA with the SMEDS formulation compared to the standard EE formulation. This finding was also true for EPA (geometric mean ratio [90% CI], 18.2 [11.3–29.3]) and DHA (geometric mean ratio [90% CI], 4.5 [2.9–7.0]).

Implications: The SMEDS delivery system markedly enhanced appearance in plasma of EPA and DHA, compared to a standard EE formulation, when ingested in the fasting state. ClinicalTrials.gov identifier: NCT03443076. (*Clin Ther.* 2018;40:2065–2076)

Key words: bioavailability, docosahexaenoic acid, eicosapentaenoic acid, fish oils, ω-3 self–micro-emulsifying delivery system.

INTRODUCTION

The ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) play important roles in a number of physiologic functions.[1–3] A wide range of dietary supplement and prescription products are available for those wanting to increase their intakes

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of EPA and DHA. Often, the ω-3 fatty acids in these products are provided in ethyl ester (EE) forms, but EPA and DHA from EE products are poorly absorbed when consumed without a meal containing fat.[4–8] Optimal absorption of EPA and DHA occurs with the consumption of a high-fat meal, which triggers the release of bile, facilitates the formation of mixed micelles in the gastrointestinal tract, and aids in the digestion of the EE bonds, thus making the EPA and DHA liberated through digestion available for absorption.[9,10] However, because it is not always convenient or recommended to consume a fat-containing meal, new technologies are being developed that enhance ω-3 fatty acid absorption.[6–8]

One of the technologies to enhance ω-3 fatty acid absorption is a self–micro-emulsifying delivery system (SMEDS), which enables rapid emulsification and microdroplet formation in situ after ingestion[11] and on entering the aqueous environment of the gut, thereby enhancing digestion and absorption of EPA and DHA EE in the absence of bile.[8] The relative bioavailability of a SMEDS formulation of ω-3 acid EE was examined previously in 2 single-dose crossover studies comparing the SMEDS formulation of EPA + DHA EE at 630- and 1680-mg doses versus a control product providing EPA + DHA EE at 840 and 3360 mg, respectively, under fasting conditions.[8] EPA + DHA appearance in plasma from the SMEDS formulation was 6.2- and 9.6-fold higher than the standard EE control in the low- and high-dose studies, respectively, as indicated by the baseline-adjusted and dose-normalized geometric mean ratios of the incremental (i)-AUC_{0-24} values of EPA + DHA.

The objective of this study was to assess the relative bioavailability of EPA and DHA administered in a proprietary SMEDS formulation, compared with EPA and DHA in a standard ω-3 acid EE product, in healthy men and women at a lower dose (500 mg EPA + DHA) than was studied in the previous trials. The primary outcome variable was the least-squares geometric mean ratio (LS GMR) of the $iAUC_{0-24h}$ values of EPA + DHA with the SMEDS formulation relative to that with the standard EE product.

SUBJECTS AND METHODS

Study Design

This randomized crossover study was conducted in accordance with the Good Clinical Practice guidelines, the Declaration of Helsinki,[12] and the US 21 Code of Federal Regulations. An independent institutional review board (Hummingbird IRB, Cambridge, Massachusetts) approved the protocol before initiation of the study, and subjects provided written informed consent before any study procedures were performed. The study consisted of 2 test periods, each of which included 2 overnight stays at the investigational site, separated by a washout period of at least 14 days. The study was conducted at 2 clinical research sites: Great Lakes Clinical Trials (Chicago, Illinois) and MB Clinical Research (Boca Raton, Florida).

Study Population

Men and women 18 to 55 years of age, inclusive, each with a body mass index of 18.50 to 29.99 kg/m^2 and considered to be in good health on the basis of medical history and routine laboratory tests were eligible for the study. Eligible subjects were willing to abstain from taking fish oil or ω-3 fatty acid supplements throughout the study period and to abstain from alcohol use within 24 h of each test period. Eligible current smokers were willing to not change their smoking habits or other nicotine use during the study period and were required to abstain from smoking on the mornings of test days until after lunch.

Potential subjects were excluded if they had fasting laboratory test results of clinical significance or if they had a positive urine drug-screening result. Individuals were also excluded if they had a clinically significant endocrine, cardiovascular, renal, hepatic, pulmonary, pancreatic, neurologic, gastrointestinal, or biliary disorder that, in the opinion of the Investigator, may have interfered with the interpretation of the study results, or if they had a recent history (prior 5 years) or presence of cancer other than nonmelanoma skin cancer. Those with uncontrolled hypertension (systolic blood pressure $\geq$160 mm Hg and/or diastolic blood pressure $\geq$100 mm Hg) or a history of difficulty swallowing capsules or predicted inability to swallow the study products were also excluded. Individuals who had made a blood donation in excess of 500 mL or who had excess blood loss within the 3 months before the day prior to the first test visit were excluded. Eligible individuals were not permitted to have used prescribed medication or over-the-counter medicinal products, including herbal and dietary supplements

(except for a daily ω-3 fatty acid–free multivitamin/mineral supplement or occasional use of acetaminophen or an NSAID, eg, ibuprofen or naproxen) within 7 days prior to any test visit.

Eligible individuals were also not permitted to consume more than 1 meal per week containing fish, nor were they permitted to take fish oil or an ω-3 fatty acid supplement within the 14 days prior to the first dose and throughout the testing period. Individuals who had a recent history or strong potential for drug or alcohol abuse; a known allergy to any of the ingredients in the study products; or, if female, were pregnant, planning to become pregnant during the study period, breastfeeding, or of childbearing potential and unwilling to commit to the use of a medically approved form of contraception throughout the study were excluded. Lastly, individuals who had a condition that the investigator believed may have interfered with his or her ability to provide informed consent, comply with the study protocol, or put the person at undue risk were excluded.

Testing Procedures

Eligible subjects reported to the site where clinic visit procedures (weight, heart rate, and blood pressure) were completed and a standardized EPA- and DHA-free dinner and snack were provided. The subjects remained at the site overnight and the next morning on the first test day (after fasting for at least 10 h), subjects received a single dose of the first treatment, according to their sequence, which was assigned based on randomly permuted blocks. Two encapsulated formulations of EPA and DHA EE were investigated. One treatment consisted of a capsule containing 500 mg of EPA + DHA (285 mg of EPA, 215 mg of DHA) EE administered in a proprietary SMEDS formulation.* The other treatment consisted of a capsule containing 840 mg EPA + DHA (465 mg EPA, 375 mg DHA) in a standard ω-3 acid EE formulation.† Because the products had a different appearance, subjects and clinic staff were not blinded to the treatment received at each test visit. However, treatment codes were used so that personnel involved with data management and statistical analyses were blinded to treatment condition.

Subjects ingested their assigned treatment capsule with 240 mL water and were not allowed any other fluid intake from 1 h prior to until 2 h after dosing. A mouth check was performed by site staff to ensure study product ingestion. Blood samples were collected by venipuncture immediately before dosing and for the next 24 h, at $t = 0.25$, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16 and 24 h, where $t = 0$ was the time of dosing. Plasma concentrations of EPA and DHA were determined for pharmacokinetic analyses, which included AUC_{0-24h} and C_{max} determinations. After dosing, subjects remained upright for 4 h and did not eat for 4.5 h, at which time a standardized low-fat (<15 g total fat) EPA- and DHA-free lunch was administered. A standardized EPA- and DHA-free dinner and snack were also provided at 6:30 PM and at 8:30 PM, respectively. Subjects remained at the site overnight until they provided the hour-24 blood sample. After a washout period of at least 14 days, subjects returned to the clinic for the second test period.

Laboratory Measurements and Study Procedures

The chemistry panel, hematology, and urinalysis measurements collected at the screening visit were assessed by 1 of 2 local independent clinical laboratories, LabCorp (Hollywood, Florida) or Swedish Covenant Hospital (Chicago, Illinois). Analyses of ω-3 fatty acids were performed by OmegaQuant LLC (Sioux Falls, South Dakota) under the supervision of William S. Harris, PhD.

Chemistry Panel

The fasting comprehensive chemistry panel collected at the screening visit included assessments of sodium, potassium, carbon dioxide, glucose, blood urea nitrogen, creatinine, blood urea nitrogen/creatinine, calcium, total protein, albumin, globulin, albumin/globulin, total bilirubin, aspartate aminotransferase, and alanine aminotransferase.

Hematology

The fasting comprehensive complete blood count collected at the screening visit included white and red blood cell counts and assessments of hemoglobin, hematocrit, mean corpuscular volume, mean

* Trademark: Nature Made® Omega-3 with Xtra Absorb™ Technology (Pharmavite, Northridge, California).

† Trademark: Lovaza® (GlaxoSmithKline Pharmaceuticals, Research Triangle Park, North Carolina).

corpuscular hemoglobin concentration, and a platelet count with reflex differential.

Urinalysis

Urinalysis was performed at the screening visit and included assessments of appearance, glucose, ketones (qualitative), hemoglobin (qualitative), protein, nitrite, bilirubin, specific gravity, pH, and urobilinogen, and microscopic examination. An in-clinic urine pregnancy test using the OneStep+ hCG Urine Dipstick Test (Henry Schein, Melville, New York) was conducted at the screening visit and on the first day of each of the test periods.

Urine Drug Screen

An in-clinic urine drug screening test using the EZ Split Key Cup 12 Panel Test (Alere Inc, Waltham, Massachusetts) was conducted at the screening visit and on the first day of each of the test periods. The urine drug screening included assessments of the presence of amphetamines, cocaine, marijuana, opiates, and phencyclidine.

EPA and DHA Analyses

Plasma samples were used for measurements of total (unesterified and esterified) EPA and DHA, according to validated methods of the bioanalytical laboratory, as described previously.[13]

Adverse Events

An assessment of adverse events (AEs) occurred at the clinic daily during each test period. Inquiring about AEs occurred with an open-ended question. On sampling days, AE assessment occurred after the last blood draw that day.

Statistical Analysis

Statistical analysis, including analyses of pharmacokinetic parameters, was conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina). Descriptive summaries of baseline demographic and clinical characteristics, collected at the screening visit, included age, sex, race, ethnicity, body weight, height, and body mass index. Continuous variables were summarized by subject count, mean and SD. Categorical variables were summarized by the number and percentage of subjects in the corresponding categories.

Concentrations of EPA and DHA for each time point were summarized using descriptive statistics, and plots of mean concentrations over time were generated for each treatment condition. C_{max} and AUC_{0-24h} were calculated for unadjusted; baseline-adjusted; and baseline-adjusted, dose-normalized EPA, DHA, and EPA + DHA, using a noncompartmental approach.[6,7,14]

AUC calculations were completed using the linear trapezoidal rule.[15] For baseline-adjusted AUC calculations, iAUC was calculated, so values below the baseline level did not contribute to the area, as described by Brouns et al.[15] Dose normalization was completed by dividing the relevant parameter by the number of grams of EPA, DHA, or EPA + DHA administered. T_{max} values for EPA, DHA, and EPA + DHA were also determined. Actual collection times were used in the pharmacokinetic parameter calculations. The baseline values used for calculations were from the sample collected immediately prior to dosing. If a negative concentration value resulted after baseline correction, it was set to an increment of zero and the time point at which the baseline value was crossed was interpolated for calculation of the positive area.

The relative bioavailability values for SMEDS and EE were determined based on the LS GMRs of the baseline-adjusted, dose-normalized $iAUC_{0-24h}$ values of EPA, DHA, and EPA + DHA.[6,7] The term *absorption multiplier* was used to refer to this ratio, although the authors recognize that incremental plasma levels of EPA and DHA can be influenced by factors other than absorption, including appearance/reappearance in plasma from pools such as those in the liver and adipose tissue.

Natural logarithm–transformed values were analyzed using a mixed-model ANOVA, including terms for sequence, treatment condition, and period as fixed effects, and subject nested within sequence as a random effect. Values were back-transformed in order to express LS GM values in the original units. Results by site and treatment sequence were inspected for evidence of material differences, and none were found, so results from the 2 research sites and treatment sequences were pooled. Sensitivity modeling that evaluated treatment by site and treatment by sequence interaction terms was also completed and did not show statistical evidence of interaction ($P > 0.10$ for all interaction terms; data not shown).

P values and 90% CIs for the LS GMRs of dose-adjusted C_{max} and AUC_{0-24h} values were calculated

to test the null hypothesis that the LS GMR was 1.0, with an α level of 0.05, 2-sided. Because a single primary outcome variable was prespecified (the LS GMR of the baseline-adjusted and dose-normalized EPA + DHA $iAUC_{0-24h}$ for SMEDS:standard EE), it was tested without correction for multiple comparisons. All other statistical tests were considered exploratory outcomes. Therefore, while no correction was made to the *P* values reported for exploratory variables, *P* values of <0.05 and >0.005 should be viewed as marginally significant.

One subject did not complete both treatment conditions, so was excluded from all pharmacokinetic analyses. None of the values for EPA or DHA were below the limits of quantitation, and none of the samples could not be obtained from subjects who completed both conditions. Since no substantial delays occurred in blood collection procedures, graphical illustrations use the scheduled time after dosing for the calculation of descriptive statistics.

RESULTS

A total of 37 volunteers were screened, and 24 eligible subjects were randomized to a treatment sequence. Twenty-three subjects (11 women, 12 men) completed both test periods and provided data for analysis. The primary reason for screening failure was a positive drug screen (n = 2); other reasons included excessive habitual alcohol intake (n = 1); withdrawal of consent, loss to follow-up or unable to commit to the visit schedule (n = 1 each); use of excluded medications (n = 1); and inaccessible veins (n = 1). In addition, 5 subjects were screened as backup subjects and qualified for participation but were not randomized (n = 5). One subject was randomized but did not complete the trial due to withdrawal of consent (n = 1). Baseline characteristics of the analysis sample, including race, ethnicity, age, weight, and body mass index, are summarized in Table I.

Table I. Characteristics of the study subjects at baseline (N = 23).

Characteristic	Value
Sex, no. (%)	
Male	12 (52)
Female	11 (48)
Race, no. (%)	
White	17 (74)
Black/African American	5 (22)
Asian/Pacific Islander	1 (4)
Ethnicity, no. (%)	
Non-Hispanic/other	16 (70)
Hispanic/Latino	7 (30)
Smoking status, no. (%)	
Nonsmoker	22 (96)
Current smoker	1 (4)
Age, mean (SEM), y	33.8 (2.1)
Weight, mean (SEM), kg	73.2 (2.8)
Height, mean (SEM), cm	171 (1.9)
Body mass index, mean (SEM), kg/m^2	24.9 (0.7)

EPA, DHA, and EPA + DHA Responses

Table II shows the mean predose plasma concentrations of EPA, DHA, and EPA + DHA, by treatment. No statistically significant differences in predose concentrations were found. The mean plasma concentrations of EPA + DHA, as well as EPA and DHA individually, rose after the intake of both the SMEDS and standard EE treatments and remained above baseline over the 24 h following a single oral dose. Unadjusted mean values by time point are shown in Figure 1 (EPA + DHA) and Figure 2 (EPA and DHA individually), and baseline-adjusted mean values by time point are shown in Figure 3 (EPA + DHA) and Figure 4 (EPA and DHA individually).

Table II. Plasma concentrations of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and sum of EPA + DHA at baseline (N = 23).* Data are given as mean (SD).

ω-3 Fatty Acid	SMEDS	EE
EPA, μg/mL	11.7 (4.9)	12.6 (6.4)
DHA, μg/mL	37.5 (14.1)	37.2 (13.4)
EPA + DHA, μg/mL	49.3 (17.2)	49.8 (18.4)

EE = ethyl ester; SMEDS = self–micro-emulsifying delivery system.
* *Baseline* is defined as the predose blood collection time point in each test period.

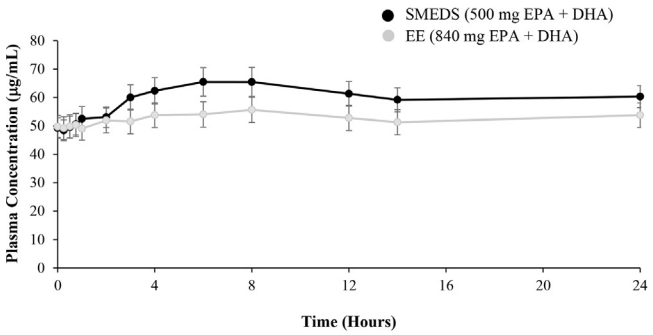

Figure 1. Mean (SD) sum of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) plasma concentrations over 24 h after a single oral dose of ω-3 formulated self–micro-emulsifying delivery system (SMEDS) or a standard ω-3 formulated ethyl ester (EE). N = 23.

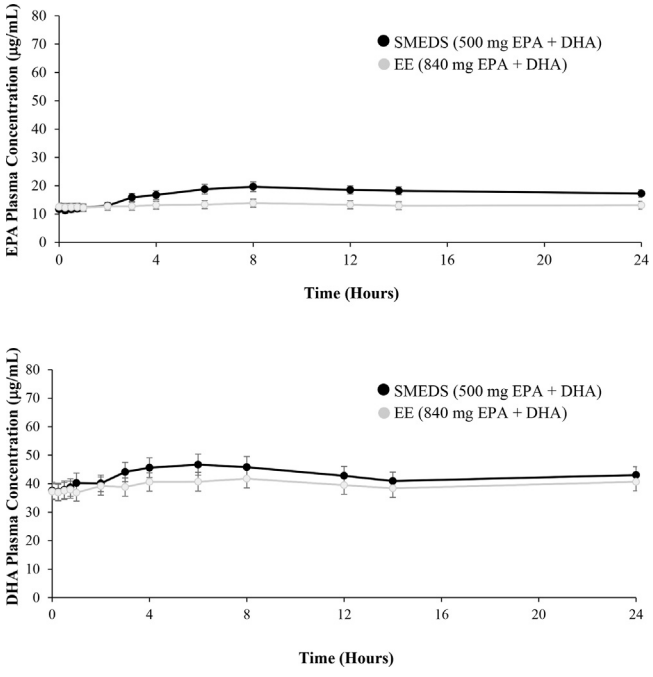

Figure 2. Mean (SD) eicosapentaenoic acid (EPA; top panel) and docosahexaenoic acid (DHA; bottom panel) plasma concentrations over 24 h after a single oral dose of ω-3 formulated self–micro-emulsifying delivery system (SMEDS) or a standard ω-3 formulated ethyl ester (EE). N = 23.

Baseline-adjusted Pharmacokinetic Parameters

Table III shows the baseline-adjusted $iAUC_{0-24h}$ and C_{max} values for EPA, DHA, and EPA + DHA, including the arithmetic mean (SD), LS GM, and LS GMR with 90% CI. The LS GMR of the baseline-adjusted EPA + DHA $iAUC_{0-24h\ values}$ of SMEDS:standard EE (the absorption multiplier) was 4.9 (90% CI, 2.9–8.3; $P < 0.0001$). As observed in previous studies,[8] the absorption multiplier was higher for EPA (11.2; 90% CI, 6.9–17.9; $P < 0.0001$) than for DHA (2.6; 90%

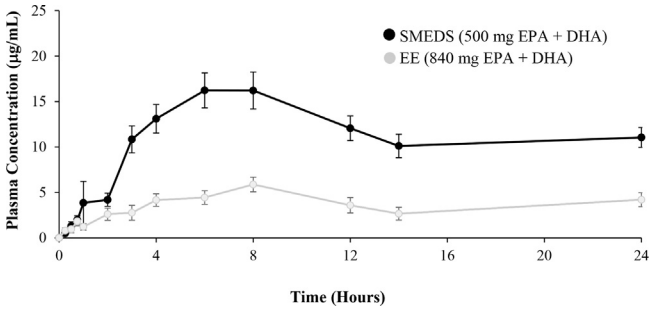

Figure 3. Baseline-adjusted mean (SD) sum of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) plasma concentrations over 24 h after a single oral dose of ω-3 formulated self–micro-emulsifying delivery system (SMEDS) or a standard ω-3 formulated ethyl ester (EE). N = 23.

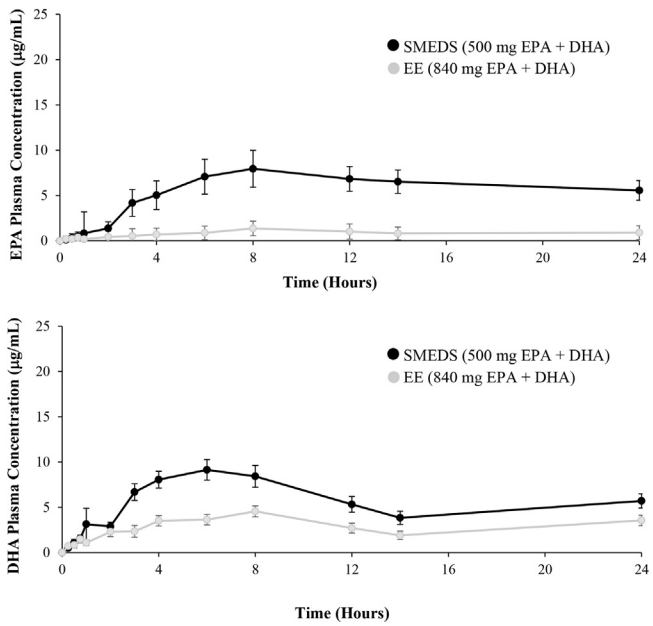

Figure 4. Baseline-adjusted mean (SD) eicosapentaenoic acid (EPA; top panel) and docosahexaenoic acid (DHA; bottom panel) plasma concentrations over 24 h after a single oral dose of ω-3 formulated self–micro-emulsifying delivery system (SMEDS) or a standard ω-3 formulated ethyl ester (EE). N = 23.

CI, 1.6–4.0; $P = 0.0014$). C_{max} LS GMRs were all significantly ($P < 0.0001$) above 1.0 with the SMEDS formulation compared with the standard EE formulation. Mean EPA, DHA, and EPA + DHA T_{max} values ranged from 6.9 to 8.8 h and did not differ between conditions (data not shown).

Baseline-adjusted and Dose-normalized Pharmacokinetic Parameters

Table IV shows the baseline-adjusted and dose-normalized $iAUC_{0-24h}$ and C_{max} values for EPA, DHA, and EPA + DHA. The LS GMR of the baseline-adjusted and dose-normalized EPA + DHA

$iAUC_{0-24h}$ of SMEDS:standard EE (the absorption multiplier) was 8.2 (90% CI, 4.8−13.9; $P < 0.0001$). The absorption multipliers were 18.2 for EPA (90% CI, 11.3−29.3; $P < 0.0001$) and 4.5 for DHA (90% CI, 2.9−7.0; $P < 0.0001$). The C_{max} LS GMRs were all significantly ($P < 0.0001$) above 1.0 with SMEDS compared with the standard EE.

A sensitivity analysis was completed to confirm the results for the primary outcome variable using the raw median values as an alternative to the GM values. The median EPA + DHA $iAUC_{0-24h}$ values were 258.3 and 50.6 μg·h/mL with the SMEDS and standard EE conditions, respectively, and the ratio of these values was 5.1. The dose-normalized median EPA + DHA $iAUC_{0-24h}$ values were 516.6 and 60.2 μg·h/mL with the SMEDS and standard EE conditions, respectively, which yielded a median ratio of 8.6.

Since both male and female subjects were included in the trial, a subgroup analysis was conducted to assess whether results differed by sex. Results indicate no statistically significant (treatment by sex interaction) or clinically relevant between-sex differences in the degree to which the baseline-adjusted, dose-normalized $iAUC_{0-24h}$ and C_{max} values differed between the SMEDS and standard EE conditions (data not shown).

Adverse Events

No AEs of the gastrointestinal system were recorded, and none of the AEs reported, such as pain or discoloration at venipuncture sites, were considered by the study physicians to be related to the products administered. All AEs were mild in severity, and there were no serious AEs.

DISCUSSION

Fatty fish such as salmon or tuna are among the main sources of EPA and DHA in the conventional US diet, but the average usual intake is just 0.07 oz/d.[16] The American Heart Association has set a goal for Americans to consume at least 7 oz/wk (average of 1 oz/d) of long-chain ω-3 fatty acid−rich fish, and the 2015 Dietary Guidelines for Americans currently recommend 8−12 oz/wk (averages of 1.1−1.7 oz/d) of a variety of seafood.[16,17] Given the low intakes of dietary sources of long-chain ω-3 fatty acids, it is not surprising that the average usual intakes of EPA and DHA are only 23 and 63 mg/d, respectively, in the US diet.[16] The sum (86 mg/d) is substantially below the recommended intake of EPA + DHA of ~250 mg/d.[16]

In addition to playing roles in physiologic mechanisms, such as maintaining cell membrane integrity and acting as substrate for compounds such as prostaglandins, leukotrienes, protectins and resolvins that mediate inflammatory responses, higher intakes of EPA and DHA have been associated with several health benefits, including a reduced risk for cardiac death.[18−21] Higher intakes of EPA and DHA have also been shown to lower the circulating triglyceride level in a dose-dependent manner and to be associated with a number of other potentially favorable changes in cardiometabolic risk markers, including reductions in blood pressure, heart rate, the interleukin-1 receptor-like 1 marker for cardiac stress, lipoprotein-associated phospholipase-A_2, and the concentration of small, dense low-density lipoprotein particles.[21−29] Given low dietary intakes of EPA and DHA in the United States, EPA and DHA dietary supplements are one option to help fill the gap between typical and recommended intakes.

Since fish oil in the triglyceride form contains only ~300 mg of EPA + DHA per gram, concentrates have been developed to reduce the number of capsules required to attain target levels of EPA + DHA intake. These concentrates are available in dietary supplement and pharmaceutical formulations. EE forms of EPA and DHA are used in many such products. However, previous studies have shown that the EPA and DHA from EE is poorly absorbed unless consumed with a meal containing enough fat.[4,5,8]

One technology to enhance lipophilic agent absorption without the requirement for fat co-ingestion is the SMEDS evaluated in the present study, which enables rapid emulsification and microdroplet formation on entering the aqueous environment of the gut.[14] Two prior studies have demonstrated that the SMEDS formulation enhanced the absorption of EPA + DHA from EE at single doses of 630 and 1680 mg, both compared with the same standard EE control product used in the present trial.[8] The absorption multipliers in those studies were 6.2 and 9.6, respectively, as indicated by the LS GMR of the $iAUC_{0-24h}$ for EPA + DHA for SMEDS:standard EE.[8] In a recent trial that compared repeated daily dosing of the SMEDS formulation and the standard EE formulation of EPA + DHA (1.2−1.3 g of EPA + DHA), 12-week intake of the SMEDS formulation led to significantly higher concentrations of EPA and DHA in plasma,

mononuclear cells, and red blood cells and substantially increased the ω-3 index, a marker for tissue EPA and DHA status, compared to intake of the standard EE formulation.[30] A higher ω-3 index (>8% of erythrocyte membrane phospholipid fatty acids) versus a lower value (<4%) has been associated with a reduced risk for ischemic heart disease–related death.[31,32] Based on these data, the ~2% mean increase observed by West et al.[30,32] in the ω-3 index after 12-week intake of SMEDS-formulated EPA + DHA would be predicted to reduce fatal ischemic heart disease by 22%.

Both products evaluated in the present study were well tolerated, and the analysis yielded an absorption multiplier of 8.2 for the SMEDS formulation compared to the standard EE formulation. This result is at roughly the midpoint between the absorption multipliers from the 2 prior studies of 6.2 and 9.6, respectively. Because the same standard EE formulation comparator was used, these results support the view that the difference in multipliers between the 2 prior studies was more likely to be attributable to random variation than to any systematic difference related to the dose administered.

In the present trial, the baseline-adjusted and dose-normalized LS GM EPA + DHA $iAUC_{0-24h}$ with the SMEDS formulation was 475 h·μg/mL/g, which is 44% greater than the value of 331 h·μg/mL/g reported in each of the prior 2 studies. The baseline-adjusted and dose-normalized LS GM EPA + DHA $iAUC_{0-24h}$ with the standard EE formulation was 58.0 h·μg/mL/g, which is also higher than the values of 53.2 and 35.7 h·μg/mL/g reported in the prior 2 studies, by 9% and 62%, respectively (mean, 36%). Accordingly, both the numerator and denominator of the absorption multiplier were higher by 36%–44% in the present trial. Whether this difference was due to differences in the assay methods employed, the subjects studied, or other factors is uncertain. Nonetheless, since all 3 studies, which used the same standard EE formulation comparator, showed markedly higher EPA + DHA $iAUC_{0-24h}$ values with the SMEDS formulation, the results from the 3 trials are concordant in demonstrating greater EPA + DHA bioavailability with the SMEDS formulation. A potential limitation of this study was that it was conducted in fasting subjects, and therefore the results cannot necessarily be extrapolated to conditions in which the subjects consume a low-fat or high-fat meal.

CONCLUSIONS

The SMEDS formulation employed in this study providing 500 mg EPA + DHA as EE produced 8.2-fold higher baseline-adjusted and dose-normalized iAUC0-24h for EPA + DHA compared to that from a standard EE formulation capsule. Thus, the bioavailability of EPA + DHA was markedly

Table III. Summary of baseline*-adjusted incremental (i)-AUC_{0-24h} and C_{max} for eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and sum of EPA + DHA, by treatment (N = 23).

Parameter	SMEDS, Mean (SD)	Standard EE, Mean (SD)	SMEDS, LS GM	EE, LS GM	LS GMR (90% CI)	*P*
EPA						
$iAUC_{0-24h}$, h·μg/mL	140 (62.6)	20.2 (22.2)	132	11.9	11.2 (6.9–17.9)	<0.0001
C_{max}, μg/mL	9.1 (4.2)	2.0 (1.2)	8.5	1.7	4.9 (3.8–6.4)	<0.0001
DHA						
$iAUC_{0-24h}$, h·μg/mL	135 (80.7)	68.7 (53.7)	119	46.5	2.6 (1.6–4.0)	0.0014
C_{max}, μg/mL	12.2 (7.8)	5.8 (2.8)	10.6	5.1	2.1 (1.7–2.6)	<0.0001
EPA + DHA						
$iAUC_{0-24h}$, h·μg/mL	271 (133)	86.0 (74.1)	237	48.8	4.9 (2.9–8.3)	<0.0001
C_{max}, μg/mL	20.9 (11.1)	7.5 (3.9)	18.8	6.3	3.0 (2.3–3.8)	<0.0001

EE = ethyl ester; LS GM = least-squares geometric mean; LS GMR = least-squares geometric mean ratio; SMEDS = self–micro-emulsifying delivery system.

* *Baseline* is defined as the predose blood collection time point in each test period.

Table IV. Summary of baseline*-adjusted, dose-normalized incremental (i)-AUC_{0-24h} and C_{max} for eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and sum of EPA + DHA, by treatment (N = 23).

Parameter	SMEDS, Mean (SD)	Standard EE, Mean (SD)	SMEDS, LS GM	EE, LS GM	LS GMR (90% CI)	*P*
EPA						
$iAUC_{0-24h}$, h·μg/mL/g	491 (220)	43.4 (47.8)	464	25.5	18.2 (11.3–29.3)	<0.0001
C_{max}, μg/mL/g	31.8 (14.7)	4.3 (2.7)	29.8	3.7	8.0 (6.2–10.4)	<0.0001
DHA						
$iAUC_{0-24h}$, h·μg/mL/g	626 (376)	183 (143)	552	124	4.5 (2.9–7.0)	<0.0001
C_{max}, μg/mL/g	56.7 (36.2)	15.4 (7.4)	49.1	13.7	3.6 (2.9–4.5)	<0.0001
EPA + DHA						
$iAUC_{0-24h}$, h·μg/mL/g	543 (266)	102 (88.2)	475	58.0	8.2 (4.8–13.9)	<0.0001
C_{max}, μg/mL/g	41.8 (22.1)	8.9 (4.6)	37.6	7.5	5.0 (3.9–6.4)	<0.0001

EE = ethyl ester; LS GM = least-squares geometric mean; LS GMR = least-squares geometric mean ratio; SMEDS = self–micro-emulsifying delivery system.
* *Baseline* is defined as the predose blood collection time point in each test period.

enhanced with the SMEDS formulation when consumed in a fasting state.

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K.C. Maki and M.R. Dicklin designed the research; M.A. Buggia, R. Trivedi, and C.E. Maki conducted the research and acquired the data; K.C. Maki, O.M. Palacios, and M. Dicklin analyzed and interpreted the data; K.C. Maki and O.M. Palacios drafted the manuscript; and K.C. Maki, O.M. Palacios, and M.R. Dicklin provided critical manuscript editing. All of the authors read and gave final approval of the final version of the manuscript.

CONFLICTS OF INTEREST

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Address correspondence to: Kevin C. Maki, PhD, Midwest Biomedical Research—Center for Metabolic and Cardiovascular Health, 489 Taft Avenue, Suite 202, Glen Ellyn, IL 60137. E-mail: kmaki@mbclinicalresearch.com