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A Novel Emulsion Gel Formulation Improves the Bioavailability of DHA in Healthy Adults: A Randomized Controlled Clinical Study

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Abstract Docosahexaenoic acid (DHA) is an omega-3 long-chain polyunsaturated fatty acid (LCPUFA), playing roles structurally and functionally from growth to health and the pathogenesis of diseases. Being a common nutrient supplement, the bioavailability of DHA is practically important. This study assessed the bioavailability of DHA after oral administration of emulsified DHA Gel Tablet, which was developed and manufactured by SIRIO and non-emulsified DHA algal oil in healthy individuals. The protocol was designed as a randomized, open, parallel clinical study. 19 healthy adults between 23 and 40 years old were randomly assigned into two groups receiving equal doses (300 mg) but different forms of DHA (DHA Gel Tablet, n = 10; DHA algal oil, n=9) in a fasting state. The blood was sampled at 0, 1, 2, 2.5, 3, 3.5, 4, 5, and 6 hours after ingestion. Free DHA in plasma was measured by liquid chromatography with LC-MS/MS. The maximum plasma concentration (C_{max}), the time to maximum concentration (T_{max}), and the area under the curve (AUC_{0-6}) were calculated from the measurements of free DHA. Compared with the DHA algal oil, the DHA Gel Tablet exhibited a higher C_{max} (0.772 ± 0.556 vs 0.308 ± 0.186 μg/ml, P= 0.0293) and greater AUC_{0-6} (1.611 ± 1.366 vs 0.550 ± 0.311 μg/ml*h, P =0.0491). The pharmacokinetic results showed that the C_{max} and AUC of the DHA Gel Tablet were 2.506 times higher and 2.929 times larger, indicating higher bioavailability of DHA treated with the emulsion technology. No side effects were observed in either group.

Keywords: *algal lipids, docosahexaenoic acid, lipid absorption, nutrition, n-3 fatty acid, physiology*

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1. Introduction

Docosahexaenoic acid (DHA) is an omega-3 long-chain polyunsaturated fatty acid (LCPUFA), which is indispensable to human nutrition and health. Structurally as a constituent, it integrates into cellular membranes within some tissues or organs; while functionally, it plays a vital role in biochemical and physiological processes throughout the body. Its functionalities span a wide spectrum, from providing developmental support in early life to contributing to metabolic, cardiovascular, immunological, neural, and mental health benefits in adults [1,2].

DHA can be obtained through two primary pathways. On the one hand, DHA can be synthesized endogenously by converting alpha-linolenic acid (ALA), found in oily seeds of terrestrial plants and nuts, through omega-3 elongation and desaturation reactions. However, the conversion rate from ALA to DHA is about 0-4% and 9% for healthy men and women [3,4], and is competitively affected by the presence of omega-6 fatty acids from dietary intake, which also utilize the same elongase and desaturase enzymes for elongation and desaturation [5]. On the other hand, DHA can come from consuming certain aquatic organisms or their extracts. Nevertheless, this approach may not be suitable for everyone due to bioaccessibility, taste and odor preferences, concerns about animal welfare, adherence to vegan diets, potential sea pollution, and gastrointestinal discomfort.

Several international commissions including the International Society for the Study of Fatty Acids and Lipids (ISSFAL) and the Chinese Nutrition Society have recommended 200 mg/day intake of DHA for pregnant and lactating women [6,7] However, this recommendation has been unmet worldwide. For instance, the median intake of DHA in the daily diet in 76 developing countries was only 48.9 mg/day [8]. Even in countries where marine

foods are available, DHA intakes have not been optimized [9]. Therefore, dietary supplements play an important role in meeting the optimal intake requirement of DHA. The efficacy of DHA supplements largely depends on the delivery technology used which may affect lipophilicity, oxidative sensitivity, bioavailability [10], taste and smell (which are particularly important for children's acceptance), and gastrointestinal comfort. To improve DHA bioavailability and consumer compliance (as well as other relevant characteristics) several delivery formulations have been developed including microemulsions, nanoemulsions, multilayer emulsions, pickering emulsions, liposomes, microcapsules, nanoparticles, and gels [11,12,13,14,15,16,17]. The DHA Gel Tablet was applied with a recently designed emulsion technology with a high oil-carrying capacity and bioaccessibility as shown in our previous *in vitro* study [18].

The present study aimed to determine whether the emulsion technology applied to the DHA Gel Tablet can improve the bioavailability of DHA *in vivo*.

2. Method

Study design and participants

This study was designed as a randomized, open, parallel clinical study in healthy volunteers. This trial was approved by the Independent Ethics Committee (IEC) obtained from The First Hospital of AUST, Ethics Committee (reference number 2023-KY-034-001). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. This study was carried out in adherence to the principles outlined in the Declaration of Helsinki. Individuals expressing interest were provided with comprehensive information regarding the associated risks before signing the informed consent document to start the trial.

This study included a total of 19 adults, consisting of 15 males and 4 females, ranging in age from 23 to 40 years. Exclusion criteria encompassed individuals with a medical background of chronic disease or any other physiological conditions that could potentially impact the research. Additionally, individuals with a daily smoking habit exceeding 5 cigarettes or used more than 14 units of alcohol (equivalent to 360 mL of beer, 45 mL of spirits with a 40% alcohol content, or 150 mL of wine) within the 3 months before the screening process were also excluded. Other exclusion criteria assessed include history of substance abuse within the past 6 months or drug use within the past 3 months; female subjects who are breastfeeding or have had a positive pregnancy test; any surgical procedures performed within a three-month; received vaccination within 1 month prior to screening or those who plan to receive vaccination during the study; donated blood ≥ 400mL within three months before screening or plan to do so during the study; special dietary requirements who are unable to comply with the diet provided and the corresponding regulations. Participants with needle sickness were also excluded. In addition, participants who had consumed large quantities (more than three times) of fish foods or other foods containing omega-3 in the week before screening were excluded. Before administration, participants were invited to the institution two days in advance for additional screening, collecting blood following a ten-hour overnight fast. The assessment of side effects includes clinical symptoms, physiological parameters (such as blood pressure, pulse rate, and ear temperature), physical examination, blood routine, blood biochemistry, urinalysis, and 12-lead electrocardiogram findings.

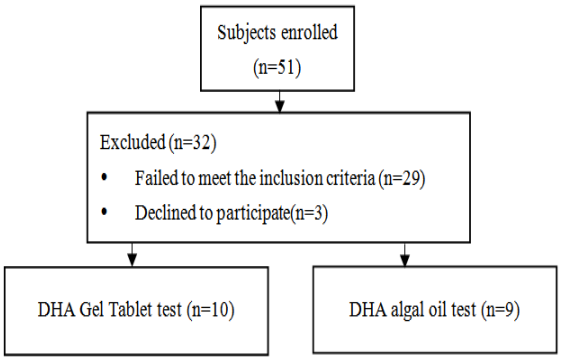

Figure 1. Flow diagram of the clinical study and participant distribution to DHA Gel Tablet and DHA algal oil supplementation groups. "n" represents the number of randomly assigned participants in that treatment order

Randomization and blinding

19 subjects were assigned to two groups randomly, the reference group received DHA algal oil (n=9, DHA 300 mg) while the test group received DHA Gel Tablet (n=10, DHA 300 mg) at once orally. This clinical study is an open study excluding statistical analysts. Allocation of screening numbers will be based on the sequential order in which participants sign the informed consent form, with each case being identified by a unique screening number. Randomized subjects who withdrew from the experiment for any reason, regardless of their adherence to the study medication, were assigned a unique randomization number and were prohibited from re-entering the trial.

Procedures

A typical pharmacokinetic day starts with the collection of fasting blood samples, followed by the oral administration of a single dose of DHA. Standardized meals were provided within the examination period. DHA Gel Tablet and DHA algal oil were supplied by SIRIO Pharma Co., Ltd. The gelled emulsion technology is a patent processed by SIRIO Pharma Co., Ltd. For baseline determination, blood samples were collected before the product was given at 24.0h, 16.0h, 12.0h, and 0h before oral administration. Participants were given test group (DHA Gel Tablet group) and reference group (DHA algal oil group) products and ingested with 250 mL water. The blood samples (4 ml) were then collected at 1.0 h, 2.0 h, 2.5 h, 3.0 h, 3.5 h, 4.0 h, 5.0 h and 6.0 h after ingestion. Blood samples were placed in pre-cooled and labeled vacuum blood vessels containing K_2EDTA anticoagulant before centrifuging at 2500 g for 10 min at 4℃. Samples were divided into two parts, in which about 1.0 ml of plasma was added to the detection tube, and the rest was put into the backup tube. The plasma samples were temporarily kept at -30℃~-15 ℃ within 2 hours after collection and transferred to the freezer of -90°C~-60°C within 12 hours till further analysis.

Blood sample analysis

Acetonitrile protein was used to precipitate free DHA in plasma in 50 μL samples, which was subsequently diluted. The LC-MS/MS technique was used to detect the amounts of free DHA. Blood samples were obtained using pre-cooled and labeled collection tubes that were filled with K_2EDTA anticoagulant and analyzed at Anhui Wanbang Pharmaceutical Technology Co., Ltd.

Pharmacokinetic parameters

The concentration data of free DHA were computed and analyzed using Phoenix WinNonlin software (version 8.1) to determine the pharmacokinetic parameters of the non-atrioventricular model. The primary pharmacokinetic parameters were computed to provide a thorough representation of the attributes observed in drug absorption, distribution, and elimination inside the human body. The baseline DHA levels were calculated as the average DHA concentration at -24h, -16h, -12h, and 0h. Data is presented as a change (∆) from baseline to assess the increase in free DHA following the single-dose ingestion. The AUC of the concentration of the free DHA over 6 h was calculated. C_{max} was defined as the maximum concentration of the free DHA observed for participants, while T_{max} was defined as the time taken to reach this maximum concentration. The linear trapezoidal rule was employed to compute the area under the curve (AUC) from the time of ingestion to the last detectable blood concentration.

Furthermore, while conducting pharmacokinetic analysis, samples with concentrations below the lower limit of quantification or are negative after adjustment for baseline should be treated as zero value.

Side effects assessment

In this clinical study, endpoints of side effects included clinical indicators (blood routine, urine routine, hepatorenal function), vital signs (blood pressure, pulse rate, and ear temperature), physical examination (including height and weight, skin, neck/thyroid, chest/lung, lymph gland, nerve system, abdominal/gastrointestinal system, mucous membrane), and 12-lead electrocardiogram examination.

Statistical analysis

Pharmacokinetic parameter calculations and statistical analyses were performed using individual blood concentration data from 19 participants. The area under the plasma concentration curve with incremental measurements (AUC_{0-6}), and the maximal incremental blood concentration (C_{max}) were corrected for baseline (time 0 hour) values. AUC_{0-6}, $C_{max,}$ and the time after administration for the maximal incremental plasma concentration to occur (T_{max}) were compared through an unpaired t-test. The data of AUC_{0-6} and T_{max} were log-transformed to adjust for skewness. All tests were two-sided (α=0.05) and were estimated using GraphPad Prism (version 8.0.2).

Characterization of the gelled emulsion

The cryogenic scanning electron microscopy (cryo-SEM) analysis was conducted utilizing the FEI Quanta 450 Environmental Scanning Electron Microscope. Firstly, apply conductive carbon adhesive on the sample stage, and stick the sample on the conductive carbon adhesive. Subsequently, the sample stage containing the adhered sample underwent a 30-second immersion in liquid nitrogen slush freezing, followed by its transfer to the sample preparation chamber under vacuum utilizing a cryogenic preparation and transmission system (PP3000T, Quorum, UK). Then, the sample was sublimated at - 90 ℃ for 10 min and was sputter plated with gold at a current of 10 mA for 60 seconds before being transferred to the SEM sample chamber for observation. The observation was conducted with a cold stage temperature of -140°C and an accelerating voltage of 10 kV.

3. Results

In Table 1, the anthropometric parameters of the participants were presented. The average age of all participants was 30.26±5.38 years. The mean height was 168.75±7.08 cm, the average weight was 64.76±7.32 kg, and their BMI was 22.71±1.19 kg/m^2.

AUC, T_{max}, and C_{max} of DHA in different formulation

The pharmacokinetic curves of free DHA levels in plasma from baseline to 6 hours post-consumption and pharmacokinetics parameters including AUC_{0-6}, C_{max}, and T_{max} were depicted in Figure 2. Both formulations resulted in an increase in DHA content in plasma. The AUC of circulating DHA as a free fatty acid form of DHA Gel Tablet over 6 h was 2.929 times larger compared with the DHA algal oil group (P= 0.0491, P < 0.05) (Figure 2). For peak concentration, the C_{max} of free DHA was 2.506 times higher with the DHA Gel Tablet compared with the algal oil form (P =0.0293, P<0.05). The time till maximum concentration, T_{max}, was determined to be 3.278 h and 3.600 h for DHA Gel Tablet and algal oil form, respectively.

The comparison of AUC_{0-6} values and C_{max} demonstrates that the free serum DHA levels were significantly higher after the DHA Gel Tablet treatment compared with the DHA algal oil.

No significant difference was observed in side effects (P=0.474).

Table 1. The Participants' Anthropometric Characteristics

	All(n=19)	*Reference Group (DHA algal oil，n=9)*	*Test Group (DHA Gel Tablet，n=10)*
Male:female, n	15:4	7:2	8:2
Age, years	30.26±5.38	31.69±5.87	29.00±4.85
Height, cm	168.75 ± 7.08	168.82±6.80	168.68±7.69
Weight, kg	64.76±7.32	66.78±6.61	62.95±7.78
BMI, kg/m^2	22.71±1.19	23.40±1.61	22.08±1.79
Plasma TG, mmol/L	1.19±0.48	1.13±0.31	1.25±0.61
Plasma HDL-C, mmol/L	1.17±0.23	1.25±0.23	1.04±0.14
Plasma LDL-C, mmol/L	2.54±0.49	2.54±0.55	2.54±0.46

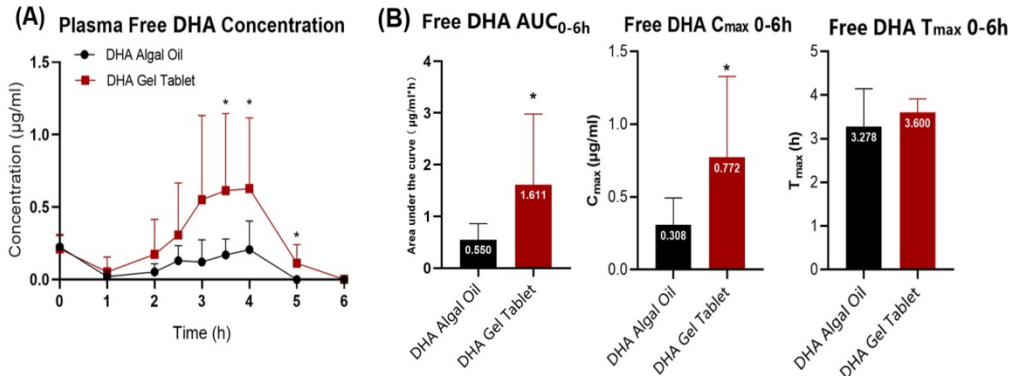

Figure 2. (A) Absolute free DHA in plasma concentrations in adults during 6 hours after taking DHA Gel Tablet and DHA algal oil. Plotted values were expressed as mean ± SD (μg/ml) (n = 19) (B) The incremental area under the curve from 0 to 6 hours (AUC0–6), Cmax, and Tmax after DHA Gel Tablet and DHA algal oil administration. T statistical test for unpaired samples was performed. Plotted values were expressed as mean ± SD. The asterisks (*) in the graphs indicate significant differences ($p < 0.05$) between the DHA Gel Tablet group and the DHA algal oil supplementation groups. One of the subjects' AUC0-6 from the DHA algal oil group exceeded the mean by more than two standard deviations. This result was therefore treated as an outlier, and data for this subject were excluded from subsequent analysis to ensure the integrity and accuracy of the statistical results. DHA, docosahexaenoic acid; AUC, area under the curve; Cmax, the maximum concentration of free DHA in plasma; Tmax, time taken to reach maximum concentration

4. Discussion

There are mainly two notable aspects of the present study. First, we measured circulating free DHA instead of total DHA, based on a previous report demonstrating that free DHA constitutes the primary plasma reservoir that provides the brain [19]. Second, oral intake of DHA Gel Tablet significantly increased the bioavailability of free DHA in circulation, a finding not previously reported.

It has been reported that emulsification of lipids increases the gastrointestinal absorption of long-chain polyunsaturated fatty acids [20,21,22], especially n-3 fatty acids such as EPA and DHA [22]. Generally, emulsification improves lipid bioavailability by reducing fat droplet size, generating a lipid-water interface [23], facilitating fat digestion by pancreatic lipase [24], and promoting fat absorption by the digestive tract [25]. Several studies have demonstrated increased EPA absorption in emulsified formulations compared to non-emulsified ones [11,26], although they did not report changes in circulating DHA. The exact reasons for the discrepancies with previous studies are unknown but likely due to the technical differences in DHA preparation and the measurement of free DHA rather than total DHA in circulation.

Emulsification provides a pathway to bypass the physiological step of forming the lipid-water interface before absorbing DHA in the gut, increasing bioavailability [23]. As Armand et al. illustrated [20], large oil droplets decrease the available surface area for lipase interaction, leading to a reduction in the rate of lipolysis. In addition, improving lipase activity in finer emulsions was illustrated by Borel et al [24] suggesting the potential benefit of emulsification. With the emulsion technology provided by SIRIO, the particle size of DHA is reduced to the sub-micron level in the dispersed phase, facilitating improved DHA absorption [18]. Figure 3 shows an electron microscope scanning image of the DHA Gel Tablet, indicating that most DHA particles have a diameter of less than 5 μm. According to our previous study, this formulation can also form a stable emulsion with concentrated particle size distribution after *in vitro* digestion [18]. The milk lipids of all mammals are contained in the form of fat globules [27]. Reducing the fat globule size of DHA to less than 5 μm through emulsification is both technically feasible and practically significant for optimizing bioavailability. This bionic method mimics the fat globule sizes found in mammalian milk, which range from 0.5 to 5 μm [27].

In conclusion, this randomized controlled study provides pharmacokinetic evidence that the bioavailability of free DHA is significantly improved when DHA algal oil is administered in the form of an emulsified gel tablet compared with conventional DHA algal oil.

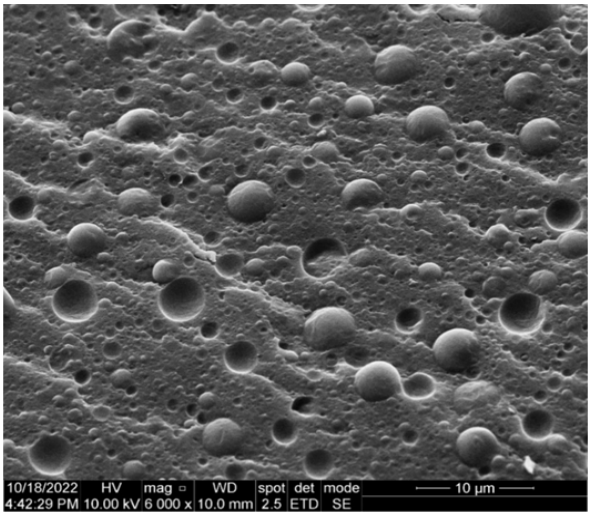

Figure 3. SEM image (magnification 1000T) showing the emulsified DHA oil globules within the gel matrix (scale bar: 10 μm). The average droplet diameter appears to be less than 5 μm

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Conflict of Interest Statement

All authors confirm they have no conflicts of interest to declare.

Author Contributions

The study was designed and performed by Sun Xuan, Huang Xiaomin, Xie Bingqi, and Chen Peng. The data analysis and visualization were conducted by Sun Xuan, Huo Shaofeng, and Chen Peng. Fang Suqiong, Zheng Yirui, and Huang Xiaomin provided emulsion technology support. The first draft of the manuscript was written by Xu Qiuyu and all authors commented on previous versions of the manuscript. Reviewing and editing were conducted by Zhang Weiguo, Xu Qiuyu, Huo Shaofeng, Sun Xuan, Chen Peng, Huang Xiaomin, and Fang Suqiong. The final manuscript was supervised by Zhang Weiguo and all authors have read and approved the final manuscript.

Abbreviations

ALA, α-Linolenic acid; AUC, area under the curve; BMI, body mass index; Cryo-SEM analysis, Cryo Scanning Electron Microscopy; DHA, docosahexaenoic acid (22:6n-3); K_2EDTA, dipotassium ethylenediaminetetraacetic acid; LC-MS/MS, liquid chromatography-mass spectrometry; LCPUFA, long-chain polyunsaturated fatty acid; SD, standard deviation.

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