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ORIGINAL CONTRIBUTION

A self-emulsifying Omega-3 ethyl ester formulation (AquaCelle) significantly improves eicosapentaenoic and docosahexaenoic acid bioavailability in healthy adults

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Abstract

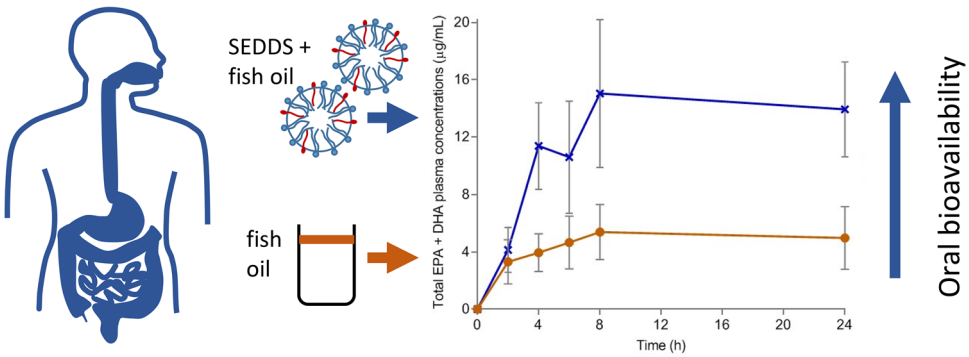
Purpose Application of intelligent formulation design has the ability to address the poor bioavailability and improve the fasted state bioavailability of fish oils. In this study we assessed the ability of a self-emulsifying drug delivery system (SEDDS), AquaCelle®, as an additive to enhance the oral absorption of Omega-3 ethyl esters (EE) in healthy subjects under low-fat diet conditions.

Methods Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) EE were formulated with AquaCelle®. A single dose (680 mg dose of oil containing 272 mg of EPA EE and 204 mg of DHA EE), randomized, double-blind, study measured uptake of EPA and DHA over 24 h in healthy adults. Participants were randomized into two groups, receiving either the SEDDS AquaCelle® fish oil formulation or the unformulated fish oil EE as control.

Results The AquaCelle® fish oil EE formulation demonstrated instant and complete emulsification on addition to water to produce an emulsion with an average diameter of 43 µm, compared to the oil alone which did not emulsify. The study revealed a significant difference in absorption (C_{max} and $AUC_{0–24h}$) between the AquaCelle® group and the control group. The AquaCelle® group was capable of increasing maximum plasma concentrations and absorption ($AUC_{0–24h}$) of total Omega-3 (EPA + DHA) 3.7- and 7.1-fold, respectively, compared to the control.

Conclusion Formulating Omega-3 EE with a SEDSS concentrate (AquaCelle®) demonstrated a significant improvement in the oral absorption of Omega-3 fatty acids without requiring a high-fat meal.

Graphic abstract



Keywords Omega-3 · Eicosapentaenoic acid ethyl ester · Docosahexaenoic acid ethyl ester · Bioavailability · Self-emulsifying delivery systems

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Introduction

Long-chain Omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), provide many health benefits including improved cardiovascular health [1, 2], reduced inflammation [3], brain, eye, skin and joint disorders and improved psychological outcomes [4]. Evidence suggests that EPA and DHA reduce triglyceride levels; a combination of both EPA and DHA has demonstrated complementary physiological effects [5]. To minimize the volume of PUFAs required per dose, EPA and DHA are available in concentrated form in either a free fatty acid (FFA) form, or as an ethyl ester (EE).

The FDA has approved a number of concentrated EPA and DHA formulations for the treatment of severe hypertriglyceridemia. The EE form has been found to be poorly absorbed when consumed either in a fasting state, or with a low-fat meal as recommended for people with cardiovascular disease, as sufficient absorption relies on the presence of the carboxyl ester lipase to aid digestion. Optimal Omega-3 absorption is achieved with a high-fat meal as a result of the digestion process stimulating the release of bile salts and digestive enzymes [6]. A recent study even suggested that the timing of Omega-3 administration relative to food intake influenced the bioavailability of EPA and DHA [7]. The digestive process promotes emulsification of fats resulting in increased access to digestive enzymes. Thus, for individuals on a low-fat diet, oral bioavailability of the EE form is incomplete, hence consumers require high doses of Omega-3 to achieve the recommended daily consumption. Emulsification of lipid drug delivery systems has demonstrated advantages for improving bioavailability [8, 9], and when occurring prior to ingestion of fish oil, it is known to increase absorption of Omega-3 lipids [10]. Emulsification reduces the oil droplet size and greatly increases surface area of the oil–water interface. This facilitates enzymatic activity, whereby the increased surface area of the lipid droplets promotes lipase interaction, thus impacting digestion [11, 12].

Self-emulsifying drug delivery systems (SEDDS) have been investigated as lipid dosage forms for delivery of drugs with poor aqueous solubility [13]. SEDDS consist of lipids, surfactants, co-surfactants and co-solvents that spontaneously form an emulsion in digestive fluids, aiding transportation through the intestinal epithelium. SEDDS have previously demonstrated improved uptake of Omega-3 EE's during fasting or with a low-fat meal due to the system's ability to mimic the conditions of the fed-state [14–17], and have demonstrated a mitigated food effect for Omega-3 EE's [18]. AquaCelle® is a customizable self-emulsifying technology, which has been clinically proven to optimize bioavailability and maintain product stability for numerous poorly water soluble active ingredients such as CoQ_{10}, vitamins A, D, E and K, lutein and curcumin [19]. Due to the successful application of AquaCelle® to a range of lipophilic moieties, it was predicted that AquaCelle® may be able to provide a superior enhancement in absorption and bioavailability of Omega-3.

This study was designed to compare the pharmacokinetics of a single dose of fish oil (containing 680 mg of oil with 272 mg EPA and 204 mg DHA as EE when dosed with and without AquaCelle® on increasing Omega-3 fatty acid concentrations (EPA + DHA) in healthy participants over a 24 h period. As both study groups received the same fish oil, the ability of AquaCelle® to improve bioavailability of EE forms of EPA and DHA on a low-fat diet will be assessed. In addition, selected physicochemical analyses have been undertaken and provided to elucidate the improved in vivo performance.

Experimental methods

Preparation and characterization of SEDDS Formulation

AquaCelle Omega-3 EE (AO EE) SEDDS were prepared in soft-gel capsules after mixing 15% (w/v) AquaCelle® (lime oil, coconut oil fractionated, lecithin (sunflower), lecithin (oat), olive oil, polyglycerol polyricinoleate, and dl-alpha tocopheryl acetate) and EE fish oil [85% (w/v)].

Droplet size and zeta potential

Size analysis of self-emulsifying formulations requires a standardized method, as typical sample preparation techniques may impact the droplet size due to application of shear either via mixing, sonication or filtration. In this study the droplet size and emulsification of the SEDDS was analyzed using a Mastersizer 3000 (M, UK), according to the method proposed by Vasconcelos et al. [20]. Briefly, SEDDS was added to 400 mL of purified water in the measurement beaker to obtain an obscuration between 3 and 20%. Continuous dispersion was maintained at 1750 rpm with no ultrasound. Droplet size measurements were recorded continuously for 330 s. Cumulative particle diameters corresponding to D_{10}, D_{50} and D_{90} were documented. Zeta potential of the emulsions were determined using phase analysis light scattering (PALS) method (Malvern Zetasizer Nano ZS, Worcestershire, UK) at 25 °C.

Clinical study design and procedures

A single equivalent dose, randomised, double blinded study was used to evaluate the absorption of 2 Omega-3 formulations administered in single 680 mg (272 mg of EPA and 204 mg of DHA) doses contained in a soft-shell capsule. Enrolled participants were allocated to 1 of 2 groups; Group 1–680 mg Omega-3 capsule with no additive (standard formulation) or Group 2–680 mg Omega-3 with AquaCelle® (AO EE). Omega-3 absorption was determined from blood samples taken prior to dosing ($t=0$), followed by intervals of 2, 4, 6, 8 and 24 h post supplementation.

All trial participants, investigators conducting the trial and the biochemist analyzing the samples were blinded to who received each product. Only upon the completion of all statistical analysis was the randomization code broken. This study was conducted in accordance with ethical approval from Bellberry Limited, an NHMRC accredited Human Research and Ethics Committee. All participants provided written informed consent and were screened for inclusion and exclusion criteria prior to the conduct of the study.

Subjects

A minimum sample size of 15 participants was required per group for the primary outcome analysis to be powered at 80%. This is calculated to detect a change in plasma Omega-3 of 100% (twofold) with a 5% chance of a type 1 error. A total of 62 subjects were enrolled in the study ($n=31$ per group). Two subjects withdrew during the study resulting in 60 subjects completing the study ($n=30$ per group). Subjects were adult male ($n=22$) and female ($n=38$); (non-pregnant and non-lactating) volunteers between the ages of 18–36 years. All participants were in normal physical health (BMI 18.5–24.9), as assessed through subject screening (e.g. medication use). There was no difference between groups in baseline characteristics. Refer to Table 1 for a summary of subject demographics for group 1 (standard fish oil) and group 2 (AquaCelle® fish oil).

Table 1 Baseline demographics of completed study participants

	Standard fish oil	AquaCelle® fish oil	Total
Number	30	30	60
Age (years)	24.2 (19–36)	24.8 (20–35)	24.4 (20–36)
Male	10	12	22
Female	20	18	38

Dosing and sample collection

All participants were advised to fast from 10:00 pm the night prior to the study commencing. A single 680 mg oral capsule of Omega-3 oil was administered to each participant, with half the participants receiving the standard fish oil and the other half provided with the AquaCelle®-containing fish oil. The participants were provided a low-fat breakfast and lunch 30 min and 4 h post administration, respectively. Snacks were also provided by the center. Meals were standardized and nutritionally balanced during the 0–8 h sample collection period. A full description of the diet can be found in Table 2.

Table 2 Food provided during the study

	Kilojoules	Fat (g)	Protein (g)	Carbs (g)
Breakfast				
Cereal, 45 g	662	0.8	3.9	31.3
Skim milk, 1 cup	381	0.3	9.4	12.5
Apple, 1 medium	396	0.7	0.5	19.5
Orange juice, 250 ml	283	0.2	2.1	14.2
Snack				
Banana, 1 medium	380	0.3	1.4	19.2
Lunch				
Bread (non-fortified), 2 slices	636	1.5	7.4	24.8
Lettuce, 1 large leaf	6	0	0.1	0.1
Tomato, 2 slices	18	0	0.2	1.1
Carrot, 50 g	72	0	0.5	4.5
Beetroot, 2 slices canned	33	0	0.4	2.5
Chicken, ½ cup	477	3.4	20.8	0
Mayonnaise (low fat), 1 tsp	29	0.2	0	1.3
Rice (white), ½ cup	561	0.1	2.3	30.1
Snack				
Biscuit (2 choc chip), 16 g	126	5.6	1.4	17.1
Total	4060	12.9	50.4	178.5

Blood samples were collected at 2, 4, 6, 8 and 24 h post-supplement ingestion from the antecubital fossa using a 21 G EclipseTM needle (BD, New Jersey) and 3 or 6 mL vacutainer containing lithium heparin (BD, New Jersey). Blood samples were immediately centrifuged at 4 °C for 10 min (2300 RPM). Plasma was collected and temporarily stored at − 20 °C (< 48 h) before being transported and stored at − 80 °C to await analysis.

Subjects remained on site for the full 8 h of sample collection. Only participants who provided at least 5 of the 6 samples collected between 0 and 24 h had their data analyzed.

Safety analysis

Subjects were monitored and asked to report any side effects experienced as a result of Fish Oil supplementation while at the research center. Upon returning for the 24-h sample, participants were again asked if they experienced any symptoms.

Bioanalysis

Plasma was transferred to a screw-cap glass vial which contained heptadecanoic acid as in internal standard (C17:0) and BTM (methanol containing 14% boron trifluoride, toluene, methanol; 35:30:35 v/v/v) (Sigma-Aldrich, St. Louis, MO). The vial was briefly vortexed and heated in a hot bath at 100 °C for 45 min. After cooling, hexane (EMD Chemicals, USA) and HPLC grade water was added. The tubes were vortexed and centrifuged to aid in layer separation. An aliquot of the hexane layer was transferred to a vial for analysis of plasma Omega-3 PUFA concentrations using gas chromatography (GC) with flame ionization detection.

GC was carried out using a GC-2010 Gas Chromatograph (Shimadzu Corporation, Columbia, MD) equipped with a SP-2560, 100-m fused silica capillary column (0.25 mm internal diameter, 0.2 um film thickness; Supelco, Bellefonte, PA). Fatty acids were identified by comparison with a standard mixture of fatty acids (GLC OQ-A, NuCheck Prep, Elysian, MN) which was also used to determine individual fatty acid calibration curves. The C17:0 was used to calculate recovery efficiency of the assay and applied to all fatty acids.

Statistical analysis

Plasma EPA and DHA concentrations were measured at each time-point (0, 2, 4, 6, 8 and 24 h). As there is endogenous EPA and DHA in the plasma, the absorption results were calculated as a change from baseline (Baseline corrected) for each participant at each time-point for the measured EPA and DHA values. Any data points that resulted in a negative number were given a value of "0".

Area under the curve (AUC_{0-24h}) for each treatment and each plasma was calculated in Stata (V14) using the trapezoidal model in Stata's PK module. Maximum concentration (C_{max}) and time to maximum concentration (T_{max}) were also calculated using the Stata module. Descriptive statistics for primary and secondary measures, including arithmetic mean, standard deviation mean, and geometric mean for each trial arm by plasma type (i.e. EPA, DHA and EPA + DHA) were calculated.

Results

Physicochemical characterization of Omega 3 formulations

In the absence of surfactants or emulsifiers and application of shear, the control fish oil was not expected to emulsify when added to water. While some oil drops were formed upon addition to water, the control fish oil did not emulsify under conditions used during particle size measurement as evident from an oil layer remaining at the air/water interface. In contrast, the AO EE formulation emulsified rapidly when added to water, forming a translucent solution. After 330 s measurement time, a mono-dispersed emulsion was produced (Fig. 1) with a D50 of 43 ± 2.58 µm. This was obtained under low agitation conditions and suggests emulsification in the gastro intestinal tract (GIT) to occur spontaneously. Zeta potential of AO EE emulsion after dispersion in water was − 27 mV. The negative charge results from the anionic lecithin molecules adsorbed at the oil–water interface, providing electrostatic repulsion between the oil droplets aiding in stability.

Clinical bioavailability study

Baseline concentrations of plasma EPA and DHA were measured for each individual in the trial. There was no significant difference between baseline plasma concentration or demographic features between the two groups. The single dose was well tolerated in both treatment groups, with no participants reporting any nausea, vomiting or diarrhea. No participants consuming the AO EE formulation reported a "fishy" aftertaste or burp, compared to five in the control group.

Baseline-adjusted plasma concentrations of EPA and DHA measured over 24 h after a single dose of 680 mg standard fish oil EE or AO EE indicated a significant increase ($p < 0.05$) in absorption of both EPA and DHA when formulated with the AquaCelle® technology (Fig. 2). Total Omega-3 (EPA + DHA) absorption also increased sixfold over the 24 h study (Fig. 3), with the AO EE group demonstrating a greater $AUC_{(0-24h)}$ compared to the control.

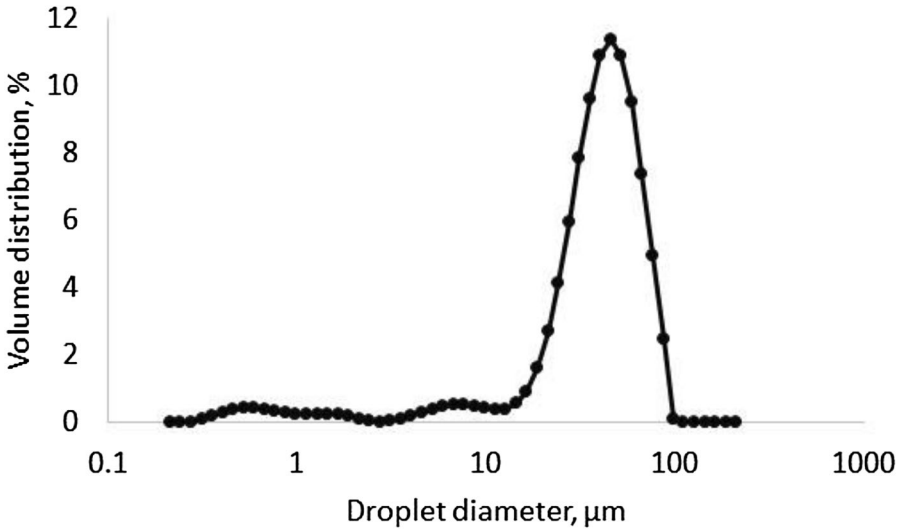

Fig. 1 Emulsion droplet diameter of AO EE formulation dispersed in water

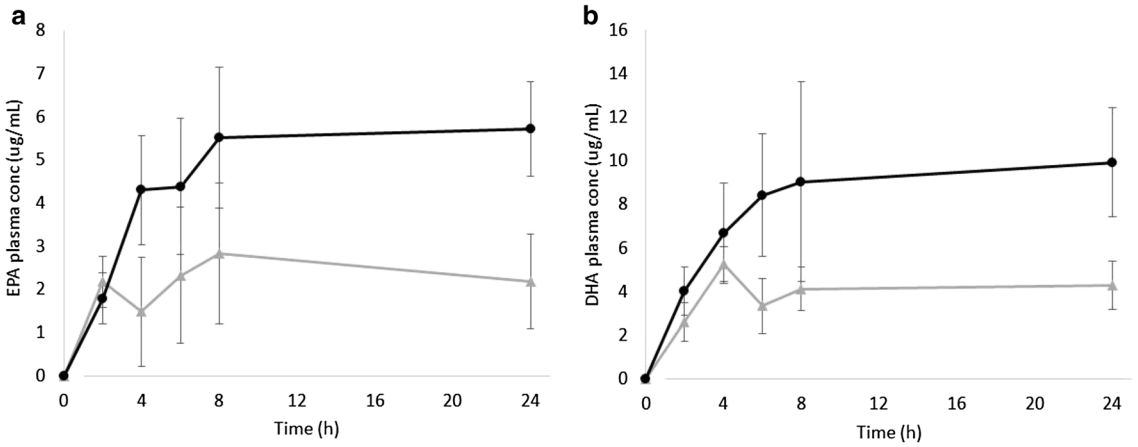

Fig. 2 EPA (**a**) and DHA (**b**) plasma concentration–time profiles (base-line adjusted change) after a single dose of standard fish oil (filled triangle) or AO EE fish oil (filled circle). Each value represents the geometric mean ± SE ($n = 30$)

Plasma concentration of EPA, DHA and EPA + DHA increased from baseline after ingestion of all formulations and was observed to plateau after approximately 8 h.

Pharmacokinetic analysis of the baseline-adjusted $AUC_{(0–24h)}$, C_{max} and T_{max} for EPA, DHA and EPA + DHA after a single dose of AO EE or control fish oil EE are presented in Tables 3, 4 and 5, respectively. Both C_{max} and $AUC_{(0–24h)}$ of the AO EE formulation increased significantly ($p < 0.052$) compared to the unformulated oil. For EPA, DHA and EPA + DHA, both groups had a medium T_{max} of approximately 6–9 h, and there was no significant difference observed between the two treatments.

A significant increase in C_{max} was observed for the AO EE cohort compared to the control group, with the C_{max} of EPA and DHA increasing 2.8 and 3.5-fold, respectively. Total EPA + DHA also increased significantly ($p < 0.05$) by 3.2 times compared to the unformulated oil. The AO EE formulation generated a significant response in the geometric mean of $AUC_{(0–24h)}$ for EPA (5.1 times higher) and DHA (6.9 times higher) compared to the control group (Fig. 4). There was also a significant increase in geometric mean of $AUC_{(0–24h)}$ for total absorption of EPA + DHA (6.1 times higher, $p < 0.05$) compared to the unformulated oil.

Discussion

Emulsification of fish oil prior to entering the intestine has been documented to improve intestinal absorption [10, 21]. Traditional SEDDS used in oral delivery for emulsification upon ingestion, form small vesicles, typically less than 1 µm diameter, as demonstrated schematically in Fig. 5. The high surfactant concentration (greater than 40%) promotes micelle formation, in which the oil phase resides in the

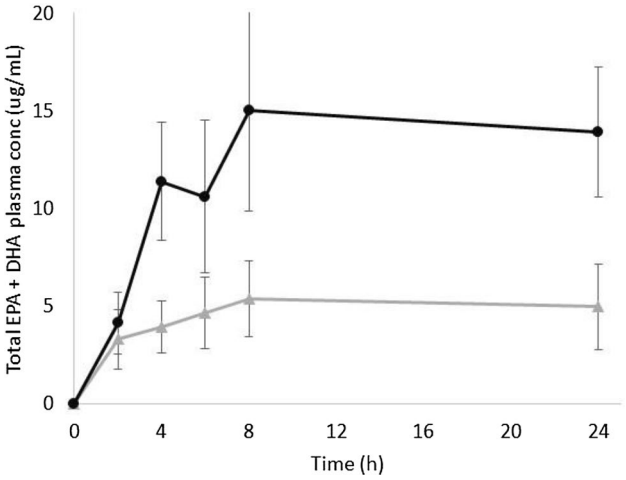

Fig. 3 Total EPA and DHA plasma concentration–time profiles (baseline adjusted change) after a single dose of standard fish oil (filled triangle) or AO EE fish oil (filled circle). Each value represents the geometric mean ± SE ($n = 30$)

micellar interior. AquaCelle® is a SEDDS formulation containing lipid and emulsifiers. When 15% (w/v) AquaCelle® was added to the Omega-3 EE fish oil, the emulsifiers are present at significantly lower concentration compared to traditional SEDDS, however, ability to spontaneously emulsify the fish oil on addition to solution was retained. As the emulsion progresses through the GIT into the small intestine, endogenous emulsifying molecules such as bile salts are encountered. Bile salts adsorb at the oil–water interface and promote lipolysis by further stabilizing new interfacial area and facilitate enzyme interaction with the lipids as digestion proceeds [22]. While the droplet size produced by the AO EE formulation is larger than typically reported for self-micro emulsifying drug delivery systems, the concentration of emulsifiers used is low (15%) compared to a more typical 40–80% [8].

It has been consistently reported in literature that when ingested on a fasting or low-fat diet, the chemical form of EPA and DHA (triglyceride, free fatty acid or EE plays a significant role in bioavailability. Of the three chemical forms, the EE form results in the lowest plasma levels of EPA and DHA [23]. This is due to the additional digestion required by carboxyl ester lipase which is stimulated upon the consumption and digestion of fat. However, the National Cholesterol Education Program (NCEP) recommends that patients with hypertriglyceridemia consume meals with a very low-fat content (< 15% fat content) [24]. This means that if following NCEP guidelines, patients who are taking fish oil will not achieve therapeutic Omega-3 concentrations. Lipid-based formulations, such as SEDDS, are known to mimic the pharmaceutical food effect; a phenomenon where the bioavailability of active compounds is increased when administered with a fatty meal.

In this study, the EE form of fish oil was employed and participants consumed the fish oil on a fasting stomach, followed by a low-fat breakfast and lunch containing no Omega-3′s. This minimized the dietary lipids contributing

Table 3 Summary of pharmacokinetic parameters for EPA by treatment

PK parameters	EPA						*R*
	Standard fish oil			AquaCelle® fish oil EE			
	AM	GM	SE	AM	GM	SE	
AUC $_{(0–24h)}$	68.60	23.14	24.81	158.29*	117.44*	24.90	5.08
C_{max} (µg/mL)	6.73	3.23	1.51	11.81	9.00*	1.62	2.79
T_{max} (h)	10.72	7.91	1.57	14.28	11.37	1.64	

R is the ratio of the geometric mean for the pharmacokinetic parameters, *AM* arithmetic mean, *GM* geometric mean and *SE* standard error

*Significant difference $p < 0.05$

Table 4 Summary of pharmacokinetic parameters for DHA by treatment

PK parameters	DHA						*R*
	Standard fish oil			AquaCelle® fish oil EE			
	AM	GM	SE	AM	GM	SE	
AUC $_{(0–24h)}$	81.59	27.38	22.69	302.03*	188.50*	57.69	6.88
C_{max} (µg/mL)	7.46	4.19	1.46	22.99*	14.49*	4.72	3.46
T_{max} (h)	9.92	7.31	1.48	11.93	9.41	1.53	

R is the ratio of the geometric mean for the pharmacokinetic parameters, *AM* arithmetic mean, *GM* geometric mean and *SE* standard error

*Significant difference $p < 0.05$

Table 5 Summary of pharmacokinetic parameters for the total EPA + DHA by treatment

PK parameters	DHA + EPA						*R*
	Standard fish oil			AquaCelle® fish oil EE			
	AM	GM	SE	AM	GM	SE	
AUC $_{(0–24h)}$	150.2	50.40	40.50	460.32*	305.94*	69.83	6.10
C_{max} (μg/mL)	12.94	7.45	2.61	34.81	23.49*	5.43	3.15
T_{max} (h)	10.24	7.61	1.32	13.10	11.12	1.34	

R is the ratio of the geometric mean for the pharmacokinetic parameters, *AM* arithmetic mean, *GM* geometric mean and *SE* standard error

*Significant difference $p < 0.05$

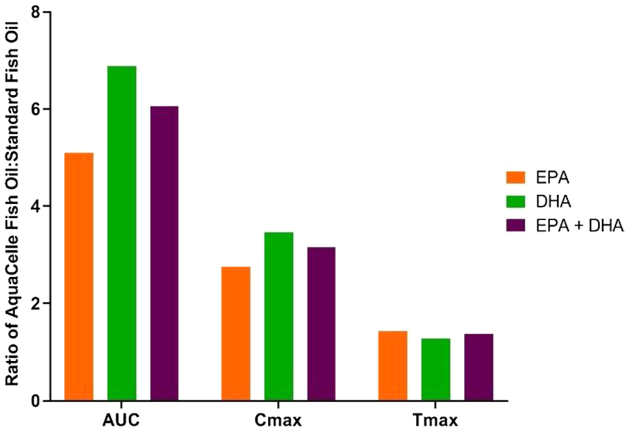

Fig. 4 Pharmacokinetic parameter ratio for EPA, DHA and total EPA + DHA of AO EE vs Standard fish oil. Bars represent the ratio between the geometric means

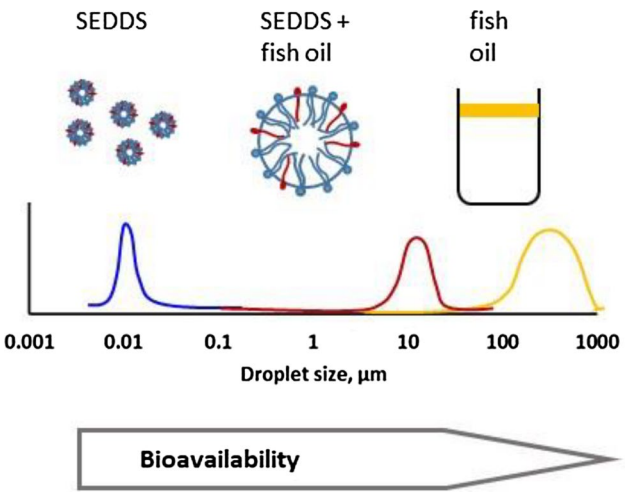

Fig. 5 Schematic of the influence of SEDDS on reducing the emulsion droplet size of fish oil and the relationship with bioavailability

to the measured Omega-3 concentrations. Formulating the fish oil EE with surfactants (AO EE) enabled rapid self-emulsification, as observed in in vitro analysis. The smaller emulsion drop diameter of the AO EE formulation provides a higher surface area to enable the carboxyl ester lipase access to the fish oil EE's for improved digestion and absorption of EPA and DHA. This process resulted in the higher plasma levels of EPA and DHA observed for the AO EE formulation in terms of C_{max} and AUC$_{(0–24h)}$ than measured for the control group. In the current study, formulation with AquaCelle® increased C_{max} significantly for EPA, DHA and EPA + DHA, by 2.8, 3.5 and 3.2 fold, respectively. This supports a recent study formulating an Omega-3 EE with emulsifiers where a 6.7- and 2.68- fold increase in C_{max} was observed for EPA and DHA, respectively [14]. Other recent studies formulating the EE fish oil as SEDDS also reported improved bioavailability of EPA and DHA EE's compared to other unformulated EE fish oil [16] or a commercial EE fish oil product, Lovaza [15, 17]. Thus, the incorporation of AquaCelle to fish oil allows for enhanced Omega-3 absorption without the requirement to consume a high-fat meal which is extremely beneficial.

A 6.1 times higher AUC$_{(0–24h)}$ for absorption of total EPA + DHA was achieved by formulation with AquaCelle® compared to the unformulated oil. The AquaCelle® emulsifier effect is similar to that reported by Qin et al. [14], and 6 times that of Lopez-Tolendo et al. [15]. Although a cross-over trial design was not followed in the current study, the randomized double blinded study was designed in accordance with good clinical practice guidelines with every effort made to account for variables in absorption differences between individuals in each group. Importantly, in this study the same fish oil was used for both the control and the AO EE group. Therefore, the increase in AUC$_{(0–24h)}$ and C_{max} can be solely attributed to the addition of AquaCelle® and the associated production of an emulsified state. Delivering the Omega-3 EE in a form that spontaneously emulsifies upon ingestion increased the surface area of the oil providing improved access to digesting lipases, increased efficiency in hydrolysis and ultimately, improved absorption.

Typically SEDDS formulations contain greater than 40% emulsifiers [8]; the high concentration of emulsifiers used in SEDDS has resulted in drug instability issues and irritation of the GIT with sustained use [25]. However, the AO EE formulation contains a low concentration (15%) of

added excipients, to 85% ethyl ester fish oil. Thus allowing a higher dose of fish oil to be delivered per capsule, and a decreased potential for intestinal irritation resulting from high doses of surfactants. The total Omega-3 acids present in the AO EE formulation was determined to be stable over 18 months storage. Thus, the increased efficacy and tolerability of Omega-3 EE formulated with AquaCelle® provides a promising approach for oral delivery of Omega-3 EE.

Conclusion

An Omega-3 EE SEDDS using AquaCelle® offered more extensive oral bioavailability of the long chain fatty acids, EPA and DHA, compared to the unformulated Omega-3 EE oil. Ability of the AquaCelle® formulation to emulsify the Omega-3 EE oil upon addition to the liquid environment in the stomach provided an increased surface area for improved digestion and long chain fatty acid absorption, without the requirement of a fatty meal. This SEDDS formulation is an effective approach to deliver EE forms of Omega-3 fish oil compared to currently available formulations.

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Compliance with ethical standards

Conflict of interest The author declares that they have no competing interests.

Ethical standards The manuscript was written through contribution from all authors who have given approval for the final manuscript.

References

1. AbuMweis S, Jew S, Tayyem R, Agraib L (2018) Eicosapentaenoic acid and docosahexaenoic acid containing supplements modulate risk factors for cardiovascular disease: a meta-analysis of randomised placebo-control human clinical trials. J Hum Nutr Diet 31(1):67–84. https://doi.org/10.1111/jhn.12493
2. Chandra A, Røsjø H, Eide IA, Vigen T, Ihle-Hansen H, Orstad EB, Rønning OM, Lyngbakken MN, Berge T, Schmidt EB, Omland T, Tveit A, Svensson M (2019) Plasma marine n-3 polyunsaturated fatty acids and cardiovascular risk factors: data from the ACE 1950 study. Eur J Nutr. https://doi.org/10.1007/s00394-019-02007-3
3. Calder PC (2017) Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochem Soc Trans 45(5):1105–1115. https://doi.org/10.1042/bst20160474
4. Sinclair AJ, Begg D, Mathai M, Weisinger RS (2007) Omega 3 fatty acids and the brain: review of studies in depression. Asia Pac J Clin Nutr 16(Suppl 1):391–397
5. Mozaffarian D, Wu JHY (2012) (n-3) fatty acids and cardiovascular health: are effects of EPA and DHA shared or complementary? J Nutr 142(3):614S–625S. https://doi.org/10.3945/jn.111.149633
6. Davidson MH, Johnson J, Rooney MW, Kyle ML, Kling DF (2012) A novel omega-3 free fatty acid formulation has dramatically improved bioavailability during a low-fat diet compared with omega-3-acid ethyl esters: the ECLIPSE (Epanova® compared to Lovaza® in a pharmacokinetic single-dose evaluation) study. J Clin Lipidol 6(6):573–584. https://doi.org/10.1016/j.jacl.2012.01.002
7. Shimada H, Nilsson C, Noda Y, Kim H, Lundström T, Yajima T (2017) Effects of food on the pharmacokinetics of Omega-3-carboxylic acids in healthy Japanese male subjects: a phase I, randomized, open-label, three-period, crossover trial. J Atheroscler Thromb 24(9):980–987. https://doi.org/10.5551/jat.38737
8. Pouton CW (2006) Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci 29(3):278–287. https://doi.org/10.1016/j.ejps.2006.04.016
9. McClements DJ, Decker EA, Park Y, Weiss J (2008) Designing food structure to control stability, digestion, release and absorption of lipophilic food components. Food Biophys 3(2):219–228. https://doi.org/10.1007/s11483-008-9070-y
10. Garaiova I, Guschina IA, Plummer SF, Tang J, Wang D, Plummer NT (2007) A randomised cross-over trial in healthy adults indicating improved absorption of omega-3 fatty acids by pre-emulsification. Nutr J 6(1):4. https://doi.org/10.1186/1475-2891-6-4
11. Chang Y, McClements DJ (2016) Influence of emulsifier type on the in vitro digestion of fish oil-in-water emulsions in the presence of an anionic marine polysaccharide (fucoidan): caseinate, whey protein, lecithin, or Tween 80. Food Hydrocoll 61:92–101. https://doi.org/10.1016/j.foodhyd.2016.04.047
12. Joyce P, Gustafsson H, Prestidge CA (2018) Enhancing the lipase-mediated bioaccessibility of omega-3 fatty acids by microencapsulation of fish oil droplets within porous silica particles. J Funct Foods 47:491–502. https://doi.org/10.1016/j.jff.2018.06.015
13. Singh B, Bandopadhyay S, Kapil R, Singh R, Katare OP (2009) Self-emulsifying drug delivery systems (SEDDS): formulation development, characterization, and applications. Crit Revi Ther Drug Carr Syst 26(5):427–451. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v26.i5.10
14. Qin Y, Nyheim H, Haram EM, Moritz JM, Hustvedt SO (2017) A novel self-micro-emulsifying delivery system (SMEDS) formulation significantly improves the fasting absorption of EPA and DHA from a single dose of an omega-3 ethyl ester concentrate. Lipid Health Dis 16(1):204. https://doi.org/10.1186/s12944-017-0589-0
15. Lopez-Toledano MA, Thorsteinsson T, Daak A, Maki KC, Johns C, Rabinowicz AL, Sancilio FD (2017) A novel ω-3 acid ethyl ester formulation incorporating advanced lipid technologies™ (ALT®) improves docosahexaenoic acid and eicosapentaenoic acid bioavailability compared with lovaza®. Clin Ther 39(3):581–591. https://doi.org/10.1016/j.clinthera.2017.01.020
16. West AL, Kindberg GM, Hustvedt SO, Calder PC (2018) A novel self-micro-emulsifying delivery system enhances enrichment of eicosapentaenoic acid and docosahexaenoic acid after single and repeated dosing in healthy adults in a randomized trial. J Nutr 148(11):1704–1715. https://doi.org/10.1093/jn/nxy127
17. Maki KC, Palacios OM, Buggia MA, Trivedi R, Dicklin MR, Maki CE (2018) 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. Clin Ther 40(12):2065–2076. https://doi.org/10.1016/j.clinthera.2018.10.014
18. Lopez-Toledano MA, Thorsteinsson T, Daak AA, Maki KC, Johns C, Rabinowicz AL, Sancilio FD (2017) Minimal food effect for

eicosapentaenoic acid and docosahexaenoic acid bioavailability from omega-3–acid ethyl esters with an Advanced Lipid TechnologiesTM (ALT)–based formulation. J Clin Lipidol 11:394–405. https://doi.org/10.1016/j.jacl.2017.01.017
19. PharmakoBiotechnologies (2019) http://www.pharmako.com.au. Accessed 9 April 2019
20. Vasconcelos T, Marques S, Sarmento B (2018) Measuring the emulsification dynamics and stability of self-emulsifying drug delivery systems. Eur J Pharm Biopharm 123:1–8. https://doi.org/10.1016/j.ejpb.2017.11.003
21. Raatz SK, Johnson LK, Bukowski MR (2016) Enhanced bioavailability of EPA from emulsified fish oil preparations versus capsular triacylglycerol. Lipids 51(5):643–651. https://doi.org/10.1007/s11745-015-4100-2
22. Sarkar A, Ye A, Singh H (2016) On the role of bile salts in the digestion of emulsified lipids. Food Hydrocoll 60:77–84. https://doi.org/10.1016/j.foodhyd.2016.03.018
23. Lawson LD, Hughes BG (1988) Human absorption of fish oil fatty acids as triacylglycerols, free acids, or ethyl esters. Biochem Biophys Res Commun 152(1):328–335. https://doi.org/10.1016/S0006-291X(88)80718-6
24. National Cholesterol Education Program (NCEP) Expert Panel on Detection E, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2002) Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final Report. Circulation 106:3143–3421
25. Neslihan Gursoy R, Benita S (2004) Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother 58(3):173–182. https://doi.org/10.1016/j.biopha.2004.02.001

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