ConCordix®

Omega-3 PUFAs

A whitepaper on supplementation

It is well known that omega-3 poly-unsaturated fatty acids (PUFAs) have numerous health benefits. Fish oil is a rich source of the omega-3 PUFA types eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Because these PUFAs are essential for a healthy heart and normal brain and eye function the World Health Organization (WHO) recommends to take at least 250 mg EPA + DHA per day.Fish oil supplements are a good alternative to meet this daily requirement. However, many fish oil dosing systems come across challenges such as taste masking, (fishy) belching or reflux, and swallowing problems with large sized capsules.

A solution to these challenges is ConCordix; a patented delivery system for the administration of nutra- and pharmaceuticals. It offers a novel approach to the administration of active ingredients by embedding the actives in a chewable soft tablet that overcomes the issues with swallowing and the necessity of water. ConCordix is available in a variety of sugar-free flavors and has excellent taste masking properties. In one soft chewable tablet both oil-and-water-soluble ingredients can be included without interfering with its homogeneity or stability. Moreover, ConCordix has a very high payload of lipophilic active ingredients, such as fish oil, in comparison with alternative dosage forms.

These unique features provide an oral delivery system that can be tailor made to any population.

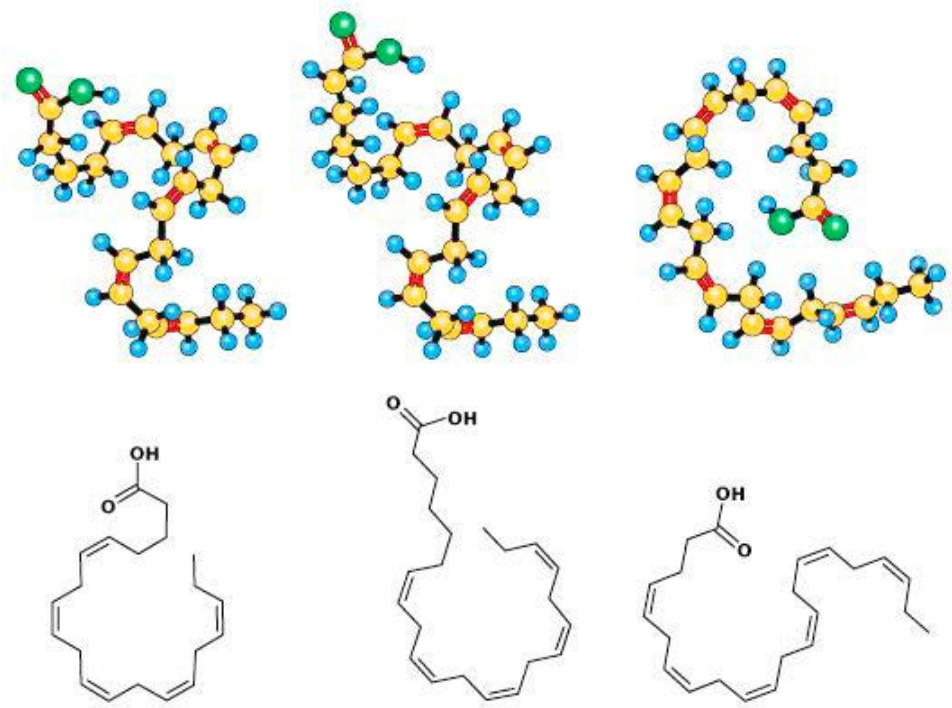
Omega-3 PUFAs: Eicosapentaenoic acid and Docosahexaenoic acid

The health benefits of omega-3 PUFAs are well known, and considered to be essential for good functioning of the human body (1-3). Humans are not able to synthesize omega-3 PUFAs, and therefore these PUFAs must be provided by the diet or by (fish oil) supplements.

Fish, and fish oil in particular, is a rich source of omega-3 PUFAs that mainly consists of two types (4, 5):

1. Eicosapentaenoic acid (EPA)
   and
2. Docosahexaenoic acid (DHA)

Figure 1: Chemical structures EPA and DHA



Eicosapentaenoic acid EPA (20:5n-3) | **Docosapentaenoic acid DPA (22:5n-3)** | **Docosahexaenoic acid DHA (22:6n-3)**

It has been demonstrated that both EPA and DHA drive most of the health effects (6-12). It is known that these PUFAs have different effects. For instance, EPA is metabolized to eicosanoids that regulate fundamental physiological processes such as cell division and growth, blood clotting, muscle activity, and the secretion of digestive juices and hormones (6, 9, 13, 14). Eicosanoids derived from EPA may reduce certain inflammatory processes that can lead to heart attacks and strokes (5, 6, 9, 13, 15).

DHA is not involved in eicosanoid formation but is highly concentrated in the brain and involved in normal neurological development and functioning. Next to that, DHA is an important part of the retina and plays a role in visual development and normal eye function (5, 8, 9, 13).

Scientific evidence of the numerous health benefits of omega-3 PUFAs is still growing. Studies suggest that intake of sufficient EPA and DHA can modulate the immune response, lower hypercholesteremia, reduce depression and ADHD, and improve insulin sensitivity (2, 8, 15-20). Interestingly, some of the health benefits have been acknowledged by the European Food Safety Authority (EFSA), which approved a number of health claims regarding EPA and DHA (Table 1) (21-25).

Table 1: Health Claims for Omega-3 PUFAs: EPA and DHA

Health Claim	Health relationship with Omega-3 PUFAs	Type of Omega-3 PUFAs
Heart health	Maintenance of normal heart function	DHA/EPA
Brain health	Contributes to the maintenance of normal brain function Maternal intake contributes to the normal brain development of the fetus and breastfed infants	DHA
Eye health	Maintenance of normal vision and normal visual development	DHA

Health claims approved by EFSA for maintenance of normal heart, brain and eye function were all based on a daily intake of at least 250 mg EPA + DHA.
Heart health reference numbers: 2010;8(10):1796. 2011;9(4):2078
Brain health reference numbers: 2010;8(10):1734. 2011;9(4):20178
Eye health reference numbers: 2010;8(10):1734. 2011;9(4):20178

To obtain significant health benefits from both EPA and DHA, the Food and Agriculture Organization (FAO) and the WHO, recommend a minimum daily intake for adults of 250 mg/d EPA + DHA (4, 22, 26, 27). This corresponds to approximately eating fish twice a week. However, for optimal fetal and infant development the daily recommendations are at least 300 mg/d EPA + DHA, of which at least 200 mg/d should be DHA (4).
This daily requirement seems small and feasible, but it has been estimated that the current EPA+DHA intake is only 15% of the recommended 250 mg/d. Moreover, the current DHA intakes in adults are low (only 20%]) which is even less in young children (approximately 19 mg/d) (4, 26, 28, 29).
A possible reason for these low numbers is that the consumption of fish, and in particular fatty fish, is not enough to meet the daily FAO/WHO recommendation, and increases the risk for neurological and cardiac diseases and reduced infant growth and development (1, 2, 4, 8, 9, 26, 30).

Omega-3 PUFA supplements

An alternative to meet the recommended daily omega-3 PUFA intake are fish oil supplements (7, 29).

However, many fish oil capsules encounter manufacturing challenges such as masking the typical fish smell and taste and belching. Because fish oil is encapsulated as a liquid, fishy belching or reflux are common 'side effects'. These challenges strongly influence the consumer's decision to comply with a supplement or not and demand a special manufacturing strategy.
Another challenge that might lead to non-compliance is the size of the dosing form. When a capsule or tablet is (too) large is can give problems with swallowing. Several studies have found that these problems occur in all kind of populations, but especially children and elderly encounter swallowing problems of large sized dosing forms (31-33). In one questionnaire study, 26% of the interviewed subjects reported to have problems swallowing large sized tablets, potentially leading to significant issues with patient-compliance and showing a demand for dosage forms that are easier to ingest (31).
A solution to all these challenges is an oral delivery system that is easy to ingest, has excellent taste masking properties, and does not trigger belching or reflux.

Soft chewable tablet: ConCordix

Vitux AS developed a patented dosage form for the administration of nutra-and pharmaceuticals: ConCordix soft chewable tablet.

ConCordix offers a novel approach to deliver active ingredients and is an alternative to other delivery systems such as capsules, tablets, and liquids as shown in the table 2.

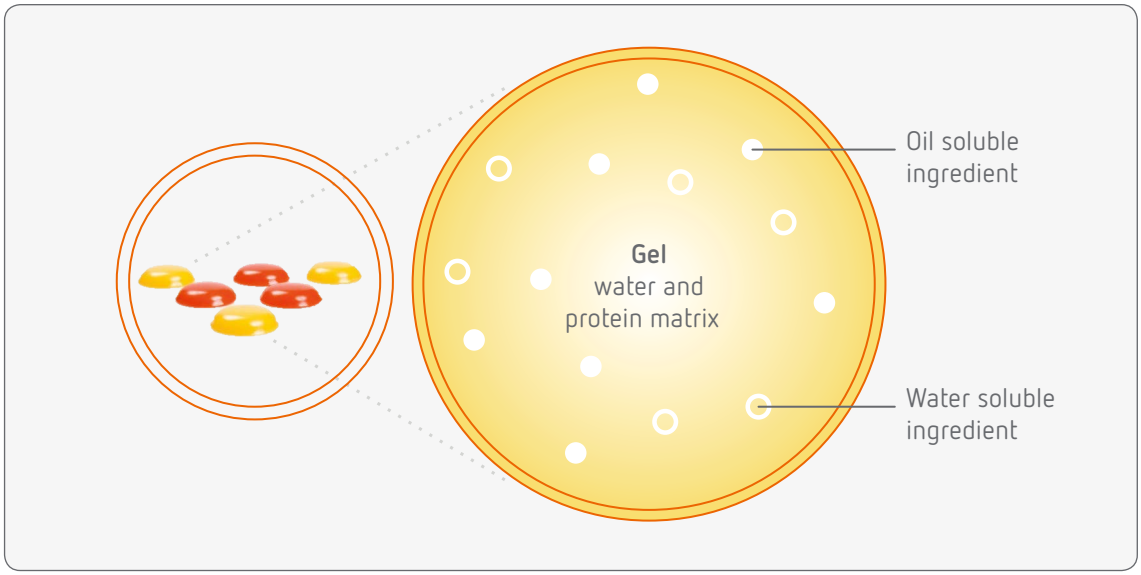
Table 2: Benefits of ConCordix compared with traditional dosage forms

	Liquid forms		Solid forms					
Characteristics oral delivery forms	Suspension (drinkable)	Elixirs (drinkable)	Tablet/ hard capsule	Oro-dispersal	Soft capsule	Gummies	CCx Delivery System	CCx Techno-logy Platform
Water soluble ingredients –in form of solution	Yes	Yes	No	No	No	Yes	Yes	Yes
Lipid soluble ingredients –in form of solution	**Restricted**	**Restricted**	No	No	Yes	Yes	Yes	Yes
Particulate materials	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Pre-emulsified	**Possible**	No	No	No	No	**Possible**	Yes	Yes
Protection from oxidation	**Only until opened**	**Only until opened**	**Extra packing step**	**Extra packing step**	**Extra packing step**	No	Yes	Yes
Allowed water content	Yes	Yes	No	No	**Max. 10%**	Yes	Yes	Yes
Chewable form	-	-	No	Yes	**Possible**	Yes	Yes	Yes
Taste masking/ flavouring	Yes	Yes	**Restricted**	**Possible**	**Possible**	**Restricted***	Yes	Yes
Easy to swallow / no water needed	Yes	Yes	No	Yes	**No / patient dependent**	Yes	Yes	Yes
Sugar free	**Possible**	**Possible**	**Possible**	**Possible**	**Possible**	No	Yes	Yes

* due to oxidation factor

ConCordix has a soft chewable gelatin matrix in which active ingredients such as fish oil (34), vitamins B, choline (35) and beta-glucan (10) are embedded. In one soft chewable tablet both oil-and-water-soluble ingredients can be included without interfering with its homogeneity or stability. Based on previous studies, the stability of active ingredients in ConCordix is excellent (36-38).

Figure 2: Oil- and water-soluble fraction ConCordix



Moreover, ConCordix has a very high payload of lipophilic active ingredients, such as fish oil, in comparison with alternative dosage forms. That is, a larger quantity of fish oil included per dosage compared with alternative delivery systems (36). Because ConCordix is formulated as a soft chewable tablet it eases intake and provides a solution to swallowing difficulties and overcomes the necessity of water for ingestion. In addition, ConCordix is available in a variety of sugar-free flavors that contribute to the exceptional taste masking properties (39).

In summary, the possibilities that ConCordix provides are:

- Combination of natural oil- and water-soluble ingredients;
- High payload of lipophilic ingredients (fish oil);
- Excellent stability;
- All natural excipients;
- Exceptional taste masking;
- Sugar-free;
- Chewable (no need to for water);
- High absorption and bioavailability of lipophilic (fish oil) active ingredients;
- Unique individual packaging ensuring freshness.

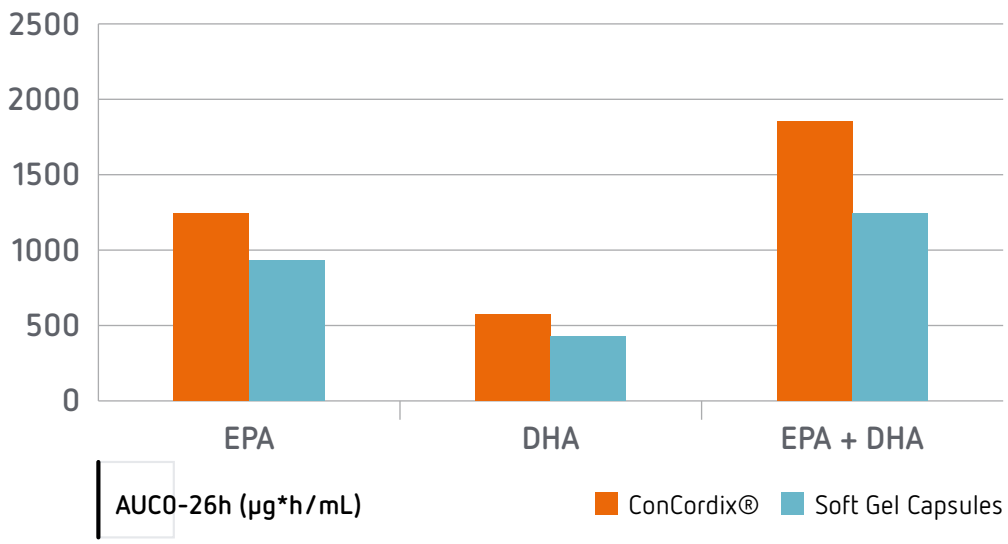
Taken all these outstanding features together, ConCordix provides a tailor made solution for oral supplementation.

Clinical studies with ConCordix and Omega-3 PUFAs

Several studies investigated ConCordix soft chewable tablets to test the bioavailability of EPA and DHA, taste masking properties and consumer acceptance (34, 39, 40).

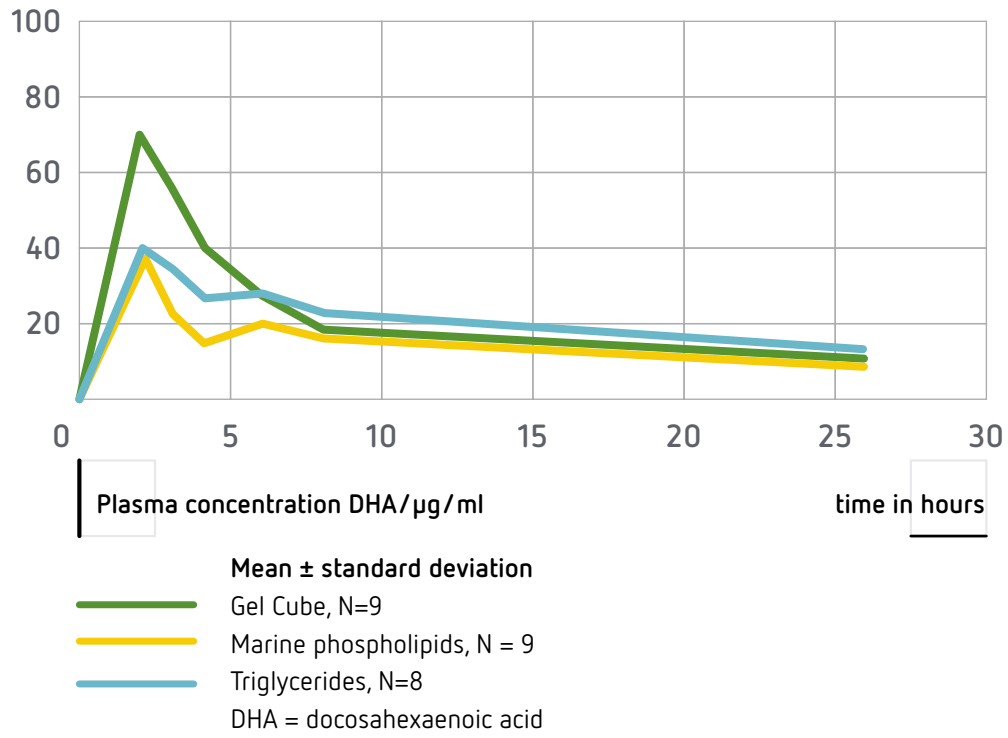
One study demonstrated a significant increase of short-term absorption of EPA and DHA in fish oil when healthy volunteers were administered with ConCordix soft chewable tablets compared with soft gel capsules. Both delivery forms contained a ratio of approximately 3:2 / EPA:DHA. After 26 hours a clear difference in plasma concentration of both EPA and DHA was observed and bioavailability increased significantly with 44% (34). It has been postulated that emulsified fish oil increases the absorption and subsequent bioavailability of EPA and DHA (4). If bioavailability of an active ingredient is improved, the same (health) effects can be achieved with a lower concentration of ingredients (34, 41, 42).

Figure 3: Differences of EPA and DHA in plasma between ConCordix and soft gel capsules



AUC: area under the curve. EPA: eicosapentaenoic acid. DHA: docosahexaenoic acid

Figure 4: Absorption of fish oil (DHA)



Another study was conducted with children (2 to 10 years of age) to investigate the taste masking properties of ConCordix. The children received fish oil supplements, which were formulated either as liquids, soft-capsules, or ConCordix. Compared with the alternative formulations, ConCordix was highly appreciated by the children because it tasted and looked like candy (39). This result indicated that ConCordix perfectly masks the taste of fish oil.

A randomized placebo-controlled double-blind study demonstrated that fish oil delivered by ConCordix did not affect the product acceptance in children. Of the 413 randomized children (aged 8.5 years) 204 children received ConCordix with fish oil and the rest of the children received a placebo ConCordix. After the 3-month intervention period, only 5.4% of children in the fish oil group stopped taking ConCordix before the end of the study. The main reasons for quitting were nausea, abdominal pain, and unpleasant soft tablet flavor and/or texture. Importantly, a comparable number of children (4.3%) in the placebo group stopped taking ConCordix before the end of the study. This observation indicated that ConCordix was accepted well in a very young population (40).

Conclusion

The health effects of omega-3 PUFAs are well known and extensively studied. Many people do not meet the daily intake recommended by the FAO/WHO.

Because omega-3 PUFAs and especially EPA and DHA, are essential for health, fish oil supplements are a good alternative to complement the diet. However, alternative dosing forms encounter several challenges that impact the manufacturing process and/or the consumer's willingness to comply. An innovative solution to tackle these challenges is a novel delivery system: ConCordix.

ConCordix chewable soft tablets are easy to take without the necessity of water, have excellent taste masking properties and are well accepted among children, adults and elderly. Moreover, both oil- and water-soluble ingredients can be combined in one soft chewable tablet providing a variety of opportunities for many nutra-and pharmaceutical manufacturers. Especially with lipophilic ingredients such as fish oil, this dosage system offers a very high payload compared with alternative dosage forms and has an excellent stability.

Vitux uses state-of-the-art BRC certified manufacturing methods. Only ingredients with high quality standards are used for the production of turnkey products and customized dietary supplements.

At Vitux we try to make health easy. We try to provide a solution that fits your needs.

A team of experts will assist you to produce a tailor made product based on your needs.

Feel free to get more information about our unique ConCordix soft chewable and visit our website: http://www.concordix.com or contact one of our experts.

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