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Whitepaper

Emulsions, their science and physiology

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An emulsion is a mixture of two immiscible liquids, most commonly oil and water, where one liquid (discontinuous phase) is dispersed as droplets throughout the other (continuous phase), with droplet diameters usually in the range of 0.1 – 100 µm.

When an emulsion is made of oil droplets dispersed in water, the emulsion is called an oil-in-water emulsion (O/W-emulsion). Water droplets dispersed in oil are called water-in-oil emulsions (W/O-emulsion) [1].

Stable emulsions

Emulsions made from oil and water are commonly found in food, such as milk and mayonnaise (O/W-emulsions), or butter (W/O-emulsion) [2]. Many common food ingredients are water soluble, including salts, acids, some vitamins, flavoring agents, proteins, etc. By dissolving these ingredients in an aqueous phase and forming an emulsion, these ingredients can easily be combined with oils and fats, as well as fat-soluble nutrients. The resulting food products can have more complex taste combinations and more complete nutritional profiles.

Unstable emulsions

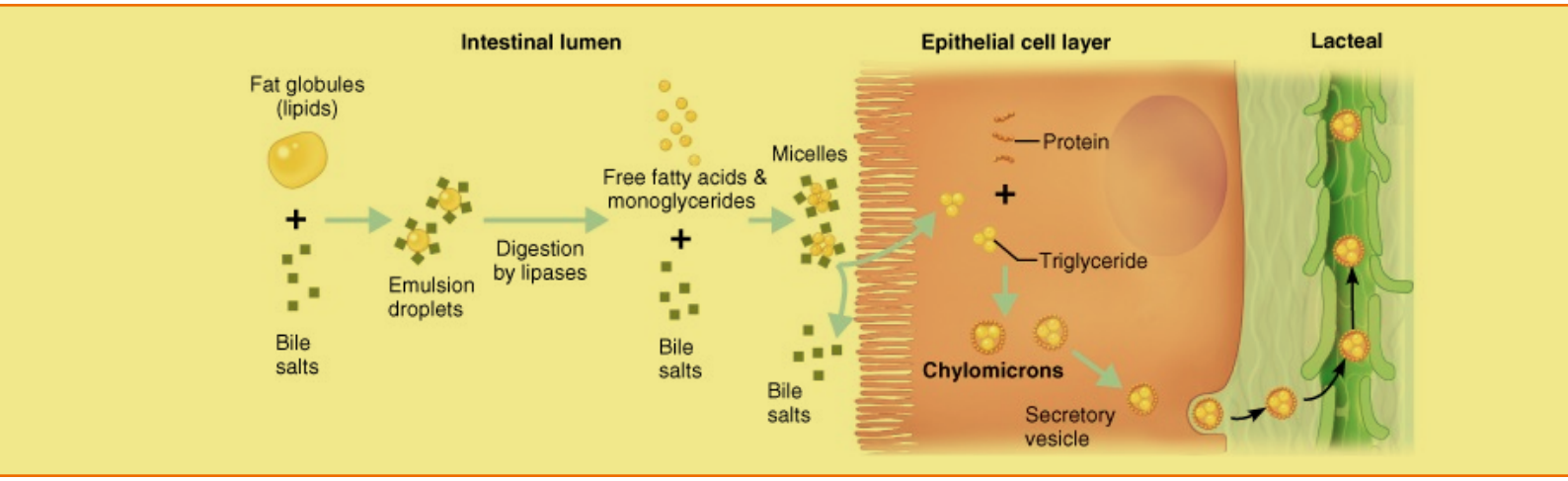
Emulsions are inherently unstable and require some form of stabilization to prevent spontaneous rapid coalescence (i.e., re-merging of droplets). This stabilization is usually achieved through addition of emulsifiers, stabilizers, and/or thickeners. Added emulsifiers adsorb directly onto the surfaces of emulsion droplets to provide stabilization. Stabilizers and thickeners instead thicken or gel the continuous phase, indirectly stabilizing the droplets by reducing droplet movement and collisions [1].

Emulsions in the digestive system

Triglycerides (TG), i.e. oils/fats, cannot be taken up from the intestine directly. Their successful intestinal absorption depends on multiple steps through the digestion process, as outlined below.

After chewing and swallowing, food is rapidly transported through the esophagus to the stomach. The acidic stomach fluids contain digestive enzymes, including the proteolytic enzyme pepsin and gastric lipase. This lipase is responsible for 10 – 30% of total gastrointestinal TG lipolysis (i.e., TG hydrolysis/breakdown) in humans, and it breaks TG down to primarily fatty acids and diglycerides [3]. In the lower part of the stomach, shearing forces provide sufficient energy to coarsely emulsify ingested bulk oil, with surface active components such as fatty acids generated by gastric lipase, or components from co-ingested foods/drinks acting as emulsifiers. This means that bulk oil to some degree will get emulsified naturally when moving through the GI tract, with resulting droplet diameters of 15 – 30 µm [4]. However, this is significantly larger than the droplet sizes that can be achieved in emulsion-based products, where down to sub-micrometer sized droplets easily can be prepared. In addition, ingested bulk oil tends to form a phase separated layer on top of the stomach fluids, while emulsions tend to mix throughout the stomach contents. This leads to a more linear and predictable rate of gastric emptying for emulsified formulations, which may also be beneficial for optimal lipid digestion and uptake [5, 6].

As the oil enters the small intestine, the pH is neutralized and digestive enzymes and bile salts are secreted. When emulsions and bile salts are mixed, the bile salts will adsorb onto the oil-water interface, potentially displacing existing emulsifiers [7]. The primary enzyme for digestion of TG is pancreatic lipase. With the help of the co-enzyme colipase, it adsorbs to bile salt covered emulsion droplets and starts the process of lipolysis. Pancreatic lipase breaks each TG down into 2 fatty acids and 1 monoglyceride. These digestion products are continuously removed from the droplets through formation of aggregate particles called mixed micelles.



A mixed micelle consists primarily of bile salts and TG digestion products along with other surface-active compounds, such as phospholipids [7]. The inner lipophilic part of the micelles can solubilize lipid-soluble compounds such as cholesterols and fat-soluble vitamins and pharmaceuticals. These mixed micelles can then diffuse through the highly hydrated mucus layer coating the intestinal cell wall, bringing their payload into close proximity of the enterocytes for uptake. After uptake, the TG digestion products are re-combined into TG and packed into protein coated particles called chylomicrons. These are then secreted into the lacteals (intestinal lymphatic vessels) which transport the chylomicrons and their TG load to the blood circulation.

The mixed micelles also solubilize and help the absorption of other fat-soluble components. For this reason, co-administration of TG with fat-soluble nutrients is essential to maximize the uptake of these nutrients. This has been shown for e.g., fat-soluble vitamins such as vitamin E [8] and vitamin K [9], as well as carotenoids such as lycopene [10], astaxanthin [11] and beta-carotene [12, 13].

The pancreatic lipase enzyme can only work at the oil-water-interface (i.e., oil droplet surfaces), and the total size of this interface is highly dependent on droplet size. Each time the average droplet radius is decreased to half, the total surface area of the emulsion is doubled. This means that emulsion based products, with droplet sizes potentially much smaller than those achieved by natural gastrointestinal emulsification, can be digested much more rapidly, efficiently, and thoroughly when compared to ingested bulk oil.

More efficient lipid digestion may be especially important for TG containing very long chain FA such as EPA and DHA. The reason for this is that pancreatic lipase digests these TG significantly slower than TG containing shorter FA [14]. This may explain why emulsion-based systems have outperformed bulk oil systems in multiple clinical studies regarding uptake of triglyceride fish oil.

Conclusion

Emulsions are mixtures of oil and water, where one of the liquids is dispersed as droplets throughout the other. Bulk oil is naturally emulsified when passing through the gastrointestinal system. However, these natural emulsions have large droplet sizes, and significantly smaller droplets can be achieved in emulsified products. Each time the average droplet radius is decreased to half, the total surface area of the emulsion is doubled. This is important, because oil-digesting enzymes, lipases, can only work at the surfaces of oil droplets. Thus, the smaller oil droplets of emulsion-based delivery systems may lead to more rapid and efficient digestion, due to the larger available surface area for enzymes to work at. This may be why multiple clinical trials have shown enhanced bioavailability of some lipids, e.g. fish oils for emulsified systems compared to e.g. bulk oil capsules. In conclusion, it seems clear that emulsification is beneficial in regards to bioavailability of fish oils.

Emulsified vs non-emulsified fish oil – clinical trials

The most relevant clinical trials on fish oil oral delivery are summarized here.

- **Conus et al. (2019)** [15] performed a randomized, 2-period crossover study with 47 healthy adults, where they compared plasma levels of omega-3 fatty acids after a single dose of an emulsified omega-3 supplement compared to bulk oil. The emulsified supplement used biopolymers as emulsifiers (xanthan gum, propylene glycol alginate). They measured 1.66 – 1.74 times higher total uptake (AUC24h) of DHA and EPA for the emulsified formulation compared to the bulk oil supplement.
- **Garaiova et al. (2007)** [14] performed a randomized cross-over study with 24 participants (healthy adults), where they compared the plasma uptake of fatty acids after ingestion of either emulsified or non-emulsified oil as part of a meal. The emulsified oil resulted in significantly higher uptake (AUC) of very long chain fatty acids such as EPA (3 times higher) and DHA (2.2 times higher), but not e.g. C18 and C16 fatty acids
- **Raatz et al. (2009)** [16] performed a randomized cross-over study on 10 participants, comparing an emulsified omega-3 supplement to bulk omega-3 oil capsules. They measured a statistically significant increase in EPA uptake (plasma phospholipid FA), as well as a significant change in plasma phospholipid omega-3: omega-6 ratio, both in the emulsified supplement's favor.
- **Raatz et al. (2016)** [17] again performed a randomized cross-over study on 10 participants. It was found that emulsion-based supplements led to a significant increase in incorporation of EPA into plasma phospholipids compared to non-emulsified oil (capsules) over 48 hours after a single dose.
- **Haug et al. (2009)** [18] performed a single-dose clinical study with 17 participants, and saw a significant increase in uptake of EPA and EPA + DHA for an emulsified gelatin-based product compared to bulk oil capsules. In the 5 studies reviewed, with 108 total subjects, looking at the uptake of fish oil (EPA and DHA), clear evidence showing the benefit of emulsification in omega-3 fish oil supplementation is presented. The studies all show a significantly increased uptake of EPA for emulsified products compared to non-emulsified, while two of the studies also show increased uptake of DHA.

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