Bioaccessibility of lipophilic micro-constituents from a lipid emulsion

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ABSTRACT

Digestion is an important process, the first one in the conversion of food to energy. From this angle, digestion of nutrients was extensively studied, and this process was found to be very efficient. Nevertheless, many molecules contained in food do not bring energy but are essential as they allow maintaining normal body functions. These are the micro-nutrients, including vitamins and minerals. On top of that, recent nutrition research identified many other bioactive molecules (termed micro-constituents as they only represent a small part of the food) playing a role in the health status, e.g. contributing to the prevention of chronic diseases. However, it was shown that their digestion is much less efficient, especially that of lipophilic micro-constituents (such as lipophilic vitamins, carotenoids, cholesterol and other steroids) depending on food structure and composition. Enhancing their health effects through optimal absorption and bioavailability thus requires a comprehensive knowledge of their release from food within the gastrointestinal tract. To study this step, of which the endpoint is termed bioaccessibility, *in vitro* digestion methods proved to be well adapted to fundamental research. This review reports the effects of the physicochemical parameters controlling the bioaccessibility of various lipophilic micro-constituents from emulsion. Notably, it appears that this bioaccessibility is related to the bioaccessibility of lipid nutrients, as their kinetics are interrelated. This knowledge will enable the formulation of food in terms of structure and composition to obtain optimal bioaccessibility. As the latter likely controls bioavailability, prevention of some metabolic disorders could be targeted in the long term.

Introduction

The digestion of food has always been studied, from the observations of ancient philosophers to the most advanced techniques of contemporary scientists. Nutritional sciences allowed major progresses during the 20th century and still do, but generally neglected the role of food composition and structure, focusing on an entire meal, implying too many interactions or, on the other hand, on an isolated nutrient or micro-nutrient.

Actually, recent studies and reviews have shown that identical foods processed differently (solid, semi-solid or liquid) exhibit discriminated micro-constituent bioavailability, demonstrating the role of food structure.[1] Also, the bioavailability of a given micro-nutrient in various foods is highly variable, what is thought to be due in part to contrasted structures and compositions of the foods.[2,3] It was thus recognized that the study of the physicochemical processes of food digestion within the gastrointestinal tract was an important topic, as they constitute the first and indispensable step before absorption.

Among the numerous food micro-constituents, lipophilic ones received much interest because they are not molecularly soluble in the gastrointestinal aqueous environment, being originally in the dispersed phase constituted of lipid droplets or transferring into them. In the second case, the transfer is thought to follow from the gastric breakdown of the native food structures, releasing these lipophilic molecules.[4] Their bioaccessibility in this case is thus achieved in four steps, first by their release by breakdown, then by their transfer into lipid droplets, then by their co-digestion with triglycerides and other lipids (e.g. phospholipids), and finally by their co-transfer (solubilization) into intestinal mixed micelles.

In this review, only the two latter steps are discussed, as the gastric breakdown step was already reviewed,[4] and the following transfer step was rarely studied.[5,6,7] Moreover, gastric hydrolysis only plays an indirect role in bioaccessibility, mostly important for triglyceride

digestion. This review is thus limited to foods with an emulsion structure, that is with a dispersed lipid phase containing the micro-constituents. The digestion of the lipid nutrients is not described as it was already studied thoroughly and reviewed recently.[8,9,10] Most bioaccessibility results were obtained *in vitro*, and the *in vivo* ones are not included. For an overview of the factors (including the biological ones) influencing *in vivo* bioavailability, see ref. 2. The main objective of this review is the identification of the physicochemical parameters (composition and structure) controlling bioaccessibility. Systematic and mechanistic studies on model systems are highlighted, in which the effect of each parameter is clearly evidenced.

Definitions and historical perspective

The term bioaccessibility was first introduced in the early 1990s by environmental scientists to quantify the proportion of a mineral released from ingested soil within the gastrointestinal tract and thus potentially absorbable.[11,12] The term was used by food scientists in the early 2000s, applied to any bioactive molecule released from food in its absorbable form within the gastrointestinal tract. The notion of the absorbable form is important because many bioactive molecules also need a chemical process within the gastrointestinal tract to be released. For example, fatty acids and monoglycerides are the products of triglyceride hydrolysis, and amino acids are the products of protein hydrolysis.

For lipophilic molecules, the bioaccessibility endpoint is their incorporation into intestinal mixed micelle composed of bile salts and digested lipids, which is the transporter towards the intestinal absorption site.[10] This bioaccessibility is determined as the percentage ratio of the quantity of a given molecule in the micellar phase (usually isolated by ultracentrifugation) to the total quantity of this molecule in the sample. Note that a few early studies referred to *in vitro* (bio)availability, release, or transfer for the concept of bioaccessibility.[14,15,16] Using

bioavailability is incorrect because it refers to the distribution into the systemic circulation. When cultured cells are used *in vitro*, the terms absorption, uptake, and crossing should be used, even when both apical and basolateral membranes are studied.

The terms micro-constituent and micro-component are equivalent and were used to include molecules that are not strictly classified as micro-nutrient, such as carotenoids or phytosterols. Like micro-nutrient, they carry the notion of a microgram amount in foods. The term bioactive molecules or simply bioactives is less precise, as it includes all nutrients, micro-nutrients and absorbable molecules having a biological effect (including on the gastrointestinal tract itself).

The main lipophilic micro-constituents studied in the literature are listed in table 1, with their chemical class and their partition coefficient log P. The latter is an important indicator of their lipophilicity, as it is the logarithm of the ratio of their solubilities in octanol and in water. A high log P indicates a lipophilic (or hydrophobic) molecule whereas a low or negative log P indicates a hydrophilic molecule.

Although a few earlier studies exist,[14,15] the work of Garrett et al.[16] reported in 1999 was seminal, launching an era of intensive but independent development of *in vitro* digestion protocols. This made the results of the 2000s studies difficult to compare, as many digestion parameters were different.[10] A standardized static protocol was only reached recently after an international consensus based on workshops and conferences of an international network (COST Infogest).[17]

A summary of the intestinal digestive processes of a lipid droplet leading to bioaccessibility is presented and described in fig. 1. In the following, the effects of the main parameters affecting the bioaccessibility of lipophilic micro-constituents from emulsion are reported.

Effect of triglyceride

Most food emulsions have a dispersed phase made of triglycerides. Their fatty acids composition, which depends on the type of oil used, is known to influence digestion processes.[9,10]

Malaki Nik et al.[18] compared the bioaccessibility of β-carotene from emulsions stabilized by tween 20, and made of hydrogenated solid canola oil or normal liquid canola oil. Bioaccessibility was respectively of 5% and 60%, which was linked to the degree of triglyceride hydrolysis, respectively of 4% and 67%.

Qian et al.[19] reported that the bioaccessibility of β-carotene from emulsions stabilized by tween 20 was much higher using corn oil (long chain triglycerides, LCT) than using MCT (medium chain triglycerides) or orange oil (a non-digestible essential oil).

Moelants et al.[20] added olive oil (emulsified by phosphatidylcholine or not emulsified) to carrot or tomato purées of varying particle size distribution and found that this addition, especially the emulsified form, increased the bioaccessibility of β-carotene (from carrot) or lycopene (from tomato). Moreover, a higher bioaccessibility for the smallest particle sizes was related to the breakdown of the cell wall during the manufacturing process.

Salvia-Trujillo et al.[21] studied β-carotene bioaccessibility from emulsions stabilized by tween 20 with varying MCT/LCT mixtures. In a low-fat case (1%), the bioaccessibility was found to increase progressively with the proportion of LCT, although there was a decrease of the free fatty acids released. This release trend was also reported in a high-fat case (4%), but the bioaccessibility did not increase with the proportion of LCT in this case, with an especially high value for pure MCT.

Rao et al.,[22] for similar emulsions stabilized by sucrose monopalmitate and lysolecithin, and based on lemon oil/corn oil mixtures (lemon oil is a non-digestible essential oil), reported a linear relationship between the free fatty acids released and the β-carotene bioaccessibility (both increased with the proportion of corn oil).

Yang et al.[23] studied the bioaccessibility of α-tocopheryl acetate from emulsions stabilized by Quillaja saponins using MCT or LCT. The bioaccessibility as well as the conversion to α-tocopherol were higher using LCT.

Mun et al.[24,25] compared the β-carotene bioaccessibility from LCT emulsions stabilized by whey protein isolate, the aqueous phase being water or a starch hydrogel. In all cases, bioaccessibility was higher with the starch system (termed filled hydrogel). Increasing the LCT content greatly increased the bioaccessibility in both systems, with an optimum for a LCT content of 6%. In contrast, replacing whey protein isolate by tween 20 or changing the type of starch did not have any effect on bioaccessibility. The hydrogel effect was interpreted as a stabilization of emulsion droplets against aggregation during the mouth and stomach digestion steps.

Xia et al.[26] studied the bioaccessibility of β-carotene solubilized (non-crystallized form) in the corn oil of an emulsion stabilized by tween 20, or added to the whole emulsion in its crystallized form. A very low bioaccessibility was obtained for the crystallized form (5%), only slightly higher than its bioaccessibility for the crystallized form in a phosphate buffer (1.5%), showing that β-carotene had to be non-crystallized in order to transfer efficiently into mixed micelles (about 55%).

Ozturk et al.[85] compared the vitamin D (cholecalciferol) bioaccessibility from emulsions made of various oils and stabilized by Quillaja saponins. The lowest bioaccessibility was obtained using MCT whereas the highest one was obtained using LCT (corn oil or fish oil). Non-digestible oils (orange oil or mineral oil) yielded intermediate bioaccessibility values.

In summary, bioaccessibility was always found to increase with the triglyceride chain length. The main reason for this effect is the higher solubilization capacity of mixed micelles composed of unsaturated long chain fatty acids and monoglycerides compared to saturated medium chain ones. Moreover, the concentration of triglyceride generally enhances

bioaccessibility up to an optimal concentration. These effects will be discussed further in the multi-parameters studies section.

Effect of interfacial molecules

To stabilize food emulsions, amphiphilic molecules are necessary. These are molecules having both hydrophilic and lipophilic parts, thus adsorbing at the oil-water interface, such as proteins, some polysaccharides, and some lipids (all of these molecules may be named emulsifiers). Note that some non-amphiphilic polysaccharides may also be located near the oil-water interface by binding to other molecules (such as proteins) by electrostatic complexation, forming a layer around the droplet.

By adding 6% partially hydrolyzed guar gum in an emulsion stabilized by egg yolk, Minekus et al.[27] could modulate the bioaccessibility of cholesterol from about 82% to about 64%. This decrease was explained by a depletion flocculation of the droplets.

Fernandez-Garcia et al.[28] could vary the bioaccessibility of total carotenoids from emulsified paprika oleoresin from about 2% to about 20% using various emulsifiers (nine) and their mixtures (restricting the combinations with an experimental design and a statistical analysis).

White et al.[29] reported a higher bioaccessibility of α-tocopherol using a lipid emulsifier (tween 20) rather than a protein (whey protein or oil body oleosin) at the oil-water interface. This was explained by a coalescence process during the gastric step for the protein systems.

Malaki Nik et al.[30,31] added different amphiphilic physiological components in the classical intestinal juice (lipase, colipase, bile salt), obtaining a higher bioaccessibility of β-carotene when phospholipids were included together with phospholipase A_2. They suggested that mixed micelles containing lysophospholipids could solubilize more β-carotene than those containing non-hydrolyzed phospholipids.

Wu et al.[32] added *ι*-carrageenan in an oil body emulsion, reporting a marked decrease of tocopherol bioaccessibility as *ι*-carrageenan amount increased. The droplet sizes of the initial emulsions were dissimilar as moderate amounts of *ι*-carrageenan promoted droplets flocculation, what could explain the bioaccessibility decrease. When comparing emulsions without *ι*-carrageenan and with the maximum amount of *ι*-carrageenan, with similar initial droplet size distributions and no flocculation, the bioaccessibility decrease was attributed to lipase inhibition by steric hindrance.

Yu et al.[33] compared the bioaccessibility of curcuminoids from MCT emulsion containing span 20 and monostearin, with additional tween 20 or whey protein isolate or modified starch. The bioaccessibility of curcuminoids from the two latter systems was about 15% whereas from the two former it was about 45%.

Liang et al.[34] studied β-carotene bioaccessibility from MCT emulsions stabilized by different modified starches. They could modulate the bioaccessibility between 35% and 20%, and this effect was attributed to the thickness and the density of the interfacial layer. In all cases, bioaccessibility was much higher than that for non-emulsified MCT (about 3%).

Pinheiro et al.[35] studied the effect of the emulsifier charge (positive, negative or neutral) on the bioaccessibility of curcumin from corn oil emulsion. Instability during digestion was reported with the positively charged emulsifier, leading to droplet flocculation and coalescence and a low bioaccessibility. Conversely, the emulsions with negative or neutral charge were stable, yielding a much higher bioaccessibility.

Mayer et al.[36] reported that α-tocopheryl acetate bioaccessibility from MCT emulsions stabilized by tween 80 was high and did not change significantly with the tween 80 amount.

Xu et al.[37] modulated β-carotene bioaccessibility from MCT emulsions stabilized by whey protein isolate by adding unconjugated or conjugated beet pectin. Both cases resulted in a

reduction of the bioaccessibility (23% instead of 45% without beet pectin), presumably due to inhibition interactions with lipase and bile salt.

A complementary result was reported almost simultaneously by Verrijssen et al.,[38] modulating β-carotene bioaccessibility from olive oil emulsions stabilized by citrus pectin with different degrees of methyl-esterification (DM). Only the low DM case resulted in a reduced bioaccessibility (35% instead of 59% for high DM values). The reduced bioaccessibility was attributed to an increase of the size of the pectin gel particles encapsulating the oil droplets, during the gastric step.

Verrijssen et al.[39] reported β-carotene bioaccessibility from olive oil emulsions stabilized by phosphatidylcholine at various concentrations. Bioaccessibility of β-carotene increased from 33% to 80% with increasing concentration from 1% to 4%. In contrast, triglycerides were always fully hydrolyzed and the fatty acid and monoglyceride incorporation into mixed micelles was always around 26.5%. However, the phosphatidylcholine incorporation into mixed micelles increased linearly with the phosphatidylcholine concentration, what could explain the increased β-carotene bioaccessibility, as mixed micelles containing phospholipid enhance the solubilization capacity of lipophilic molecules.[40,41]

Vinarova et al.[42] studied the effect of various saponins on the cholesterol bioaccessibility from emulsions stabilized by tween 80. They found that only a Sapindus trifoliatus extract (50% saponins) or a Quillaja saponaria extract (26% saponins) had an effect on cholesterol bioaccessibility, decreasing from 78% to 44% or 19%, respectively. This was attributed to a displacement of cholesterol from the mixed micelles by saponins or polyphenols contained in the extracts.

In summary, all interfacial molecules have a specific activity affecting digestion processes and in turn bioaccessibility. The main mechanisms implied are 1) droplet flocculation leading to coalescence and/or creaming (for partially hydrolyzed guar gum, and for *ι*-carrageenan,

which do not adsorb, or for milk proteins, which adsorb), and 2) interfacial competition with other molecules, including those in digestive juices at the emulsion interface or at the micelle interface (e.g. by steric hindrance or desorption). Note that these mechanisms tend to decrease bioaccessibility, and that both may be implied, e.g. for the *ι*-carrageenan case reported here.

Effect of droplet size

The droplet size distribution of food emulsions can be modulated via various manufacturing processes, and is known to influence emulsion stability and digestion.[9,10]

Salvia-Trujillo et al.[43] changed the mean droplet diameter of a corn oil emulsion stabilized by tween 20 from 23 µm to 0.21 µm, what increased the bioaccessibility of β-carotene from 34% to 59%, related to the free fatty acids release around 80% and 96%, respectively.

By varying the mean droplet diameter of emulsions stabilized by sodium caseinate between 0.124 µm and 0.368 µm, Yi et al.[44] could decrease linearly the hydrolysis extent of corn oil from 84% to 66%. This resulted in a linear decrease of β-carotene bioaccessibility from 73% to 50%. The linearity did not hold for a very large mean droplet diameter of 10 µm, resulting in a low bioaccessibility of 15%, although the hydrolysis extent was still high (59%).

Zou et al.[45,46] studied the bioaccessibility of curcumin from corn oil emulsions stabilized by tween 80 with different mean droplet diameters of 0.18 µm, 0.52 µm, or 14 µm. The bioaccessibility was not influenced in the first two cases (around 70%). A lower value of 54% was reported for the largest mean diameter, although not significant in terms of statistics. When pure oil was compared to an emulsion, the curcumin concentration solubilized in the micellar phase was higher in the emulsion case.

Malaki Nik et al.[30,31] reported two studies where the only varying parameter was the type of protein used to stabilize emulsion. For soy protein isolate, there was an extensive droplet flocculation during the gastric step, deflocculating during the intestinal step, whereas for

whey protein isolate, there was a minor droplet flocculation during the gastric step, but a major one during the intestinal step. This may explain the lower β-carotene bioaccessibility reported in the case of whey protein isolate, as flocculated droplets in the intestinal phase possess a reduced interfacial area compared to individual droplets.

In summary, this droplet size effect can be identified as an interfacial area effect, explained by the fact that most digestion processes occur at the oil-water interface, thus more efficient when more interfacial area is available. This aspect will be discussed further in the next section.

Multi-parameters studies

It was evidenced in the previous sections that some factors are interdependent, so that the bioaccessibility could actually be explained by a factor that was not expected to change initially. This is often the case when interfacial molecules are compared, which can affect the interfacial digestive process itself, but also the droplets interaction, such as flocculation and coalescence, and thus the interfacial area available for digestion (as deduced from the apparent droplet size distribution).

The studies cited above were conducted with care, gathering all important properties, which are 1) particle size distribution, and zeta potential (interfacial charge, related to droplet instability when positive or close to zero) before and during digestion (sometimes including mixed micelle properties), 2) fatty acid release from triglyceride (or even better, the kinetics for all neutral lipid classes), 3) micro-constituent final bioaccessibility (or even better, the bioaccessibility kinetics). This allowed the identification of the main parameters controlling bioaccessibility.

Nevertheless, as most systems were different in terms of emulsion composition and of digestive juices composition, a direct comparison between the bioaccessibility values is

problematic. Thus, research articles reporting the effects of several parameters are valuable. The study of Tyssandier et al.[47] was the first of this kind, where six parameters were varied independently for carotenoids bioaccessibility (named transfer). They found that only the bile concentration, the pH, and the carotenoid partition coefficient had a significant influence (the two former increased the bioaccessibility whereas the latter decreased it). The type of triglyceride, the presence of pancreatic lipase, and the mean droplet size did not have a significant effect.

Wright et al.[48] studied the bioaccessibility (named transfer) of β-carotene from canola oil directly emulsified in an artificial intestinal juice. The bile concentration increased the bioaccessibility progressively up to an optimum, whereas the pancreatin concentration had a threshold effect depending on the bile concentration. In fasted state, they found that bioaccessibility was increased progressively by the pH, whereas in fed state there was a threshold at pH 5.0. When a higher quantity of oil or of β-carotene was added to the system, the bioaccessibility was decreased, highlighting the saturation of the mixed micelles.

Malaki Nik et al.[49] conducted a thorough study of the bioaccessibility kinetics of four lipophilic micro-constituents (individually or in mixtures) from soybean oil emulsion stabilized by soy protein isolate. First, the absence of pancreatic lipase resulted in a much lower bioaccessibility for all micro-constituents, although for cholecalciferol (vitamin D) and phytosterols, bioaccessibility was not negligible. In the presence of pancreatic lipase, triglyceride hydrolysis was influenced by the type of micro-constituent, the final degree of hydrolysis being lower than average for β-carotene and higher than average for coenzyme Q_{10}. The bioaccessibility for all micro-constituents increased linearly with the hydrolysis degree, except for a mixture of cholecalciferol/phytosterols, for which the bioaccessibility of each micro-constituent was enhanced. For a mixture of β-carotene/cholecalciferol, there was no enhancement.

Wang et al.[50] studied the bioaccessibility of β-carotene from soybean oil emulsion stabilized by decaglycerol monolaurate. The bioaccessibility increased with the bile concentration and with the pancreatic lipase concentration (reaching a maximum at an intermediate concentration for the latter). The optimal pH range was between 4.0 and 6.0. The bioaccessibility decreased significantly with increasing mean droplet diameter from 0.684, 0.873, and 1.978 µm, then no longer significantly for 18.315 µm. Nano-particles of mean diameters 0.060 and 0.045 µm were also prepared by hexane evaporation from hexane/water emulsion, yielding much higher bioaccessibility values than emulsions. When the quantity of β-carotene was increased, its bioaccessibility was decreased.

Ahmed et al.[51] studied the bioaccessibility of curcumin from emulsion stabilized by β-lactoglobulin, varying its droplet size, the type and concentration of oil. Although not always significantly, bioaccessibility tended to increase: 1) with increasing oil concentration, 2) with increasing mean droplet diameter (0.18 µm versus 18 µm), 3) with increasing triglyceride chain length (SCT < MCT < LCT). A mixture of SCT/LCT gave bioaccessibility values between those of SCT and MCT.

A series of articles by the team of Yanxiang Gao reported the bioaccessibility kinetics of β-carotene from MCT emulsions stabilized by various emulsifiers. In the first two studies,[52,53] decaglycerol monolaurate (ML750), whey protein isolate (WPI), or soluble polysaccharides from soybean (SSPS) were compared to stabilize emulsions with fine or coarse droplet size distributions (mean diameter of 0.58 µm versus 1.24 µm). Pancreatin, pancreatic lipase, and bile concentrations all tended to increase bioaccessibility, although optimal and threshold concentrations were evidenced. Bioaccessibility was very low in the gastric juice, except for the fine emulsion stabilized by ML750. In the duodenal and the intestinal juices (differing only by the pH, 5.3 or 7.5), the β-carotene bioaccessibility ranked according to the emulsifier in the order WPI > ML750 > SSPS, and was always higher in the intestinal juice.

Bioaccessibility was always higher for the fine emulsions. In the third study,[54] various milk proteins were compared as emulsifiers. Again, bioaccessibility was very low in the gastric juice, and droplet flocculation was always observed, greater for β-lactoglobulin and sodium caseinate than for lactalbumin and lactoferrin. These flocculation differences were also observed in the duodenal juice. However, in the intestinal juice, the flocculation was the same for all systems. β-carotene bioaccessibility was again much higher in the intestinal juice than in the duodenal juice, highlighting the role of pH. The highest bioaccessibility (about 90%) was obtained with β-lactoglobulin, whereas the lowest one (about 75%) was obtained with lactalbumin. An intermediate bioaccessibility (about 80%) was reported using the other proteins.

Marze[55,56] conducted two studies of vitamins A and E bioaccessibility from a single triglyceride droplet based on dynamic multi-agents simulation. The basic simulation was based on triglyceride hydrolysis and micellar solubilization (for which the fundamental data of hydrolysis rates and solubilization ratios were reviewed). The bioaccessibility kinetics of triglyceride digestion products and of vitamin could be investigated simultaneously. The static *in vitro* case where bile salt micelles get saturated with these solubilizates was treated. When bile concentration was increased, vitamin final bioaccessibility and half life (time at which half of the final bioaccessibility is reached) were increased. When the droplet size increased, vitamin final bioaccessibility was increased and half life was unchanged. In fact, as the simulation was based on a single droplet, a droplet size increase implied an interfacial area increase (when changing the droplet size, it is not possible to keep the droplet volume fraction constant, in contrast with emulsion). Thus this result confirmed that the droplet size effect should be expressed in terms of an interfacial area effect, of which the increase leads to a bioaccessibility increase. The different cases of this interfacial area effect are summarized and described in fig. 2. When simple bile salt micelles were considered, vitamin A final

bioaccessibility decreased with the triglyceride chain length and half life was unchanged. When mixed micelles (bile salt and triglyceride final digestion products) were considered, vitamin A final bioaccessibility and half life increased with the triglyceride chain length. A mixture of two triglycerides resulted in an increased vitamin A final bioaccessibility compared to each pure triglyceride. Increasing proportions of limonene (a non-digestible essential oil) in triglyceride/limonene mixtures resulted in lower vitamin A bioaccessibility and longer digestion time values. The retinol form of vitamin A yielded a higher final bioaccessibility compared to the retinyl ester form and half life was unchanged. Adding gastric hydrolysis of the triglyceride did not change the final vitamin A bioaccessibility. Overall, the relationship between vitamin and fatty acid bioaccessibilities was found to be identical in various digestion conditions, but not strictly linear. An illustration is given in fig. 3.

These results confirmed that the type of triglyceride mostly plays a role for the solubilization in mixed micelles, those containing unsaturated long chain fatty acids and monoglycerides having a higher capacity than those containing saturated medium chain ones. This effect likely explicates the results of Salvia-Trujillo et al.,[21] compensating the decrease of the fatty acids available for mixed micelles as MCT is progressively replaced by LCT in the initial emulsions. This solubilization capacity effect is sometimes explained by the larger size of the mixed micelles containing long chain fatty acids and monoglycerides, but molecular hydrophobic interactions might also be involved, and a role of the (lyso)phospholipids was also demonstrated.[30,31,39,40,41]

In many articles, higher concentrations of bile and pancreatic lipase led to increased bioaccessibility with an optimal or a threshold concentration. Increasing the concentration of the micro-nutrient led to a lower bioaccessibility. All these concentration effects were understood in our numerical simulations by a solubilization ratio approach,[55,56] stating that a

specific quantity of bile salt is needed to solubilize a specific quantity of micro-constituent. This is also true for the final products of triglyceride digestion, fatty acid and monoglyceride, which moreover increase the micro-constituent solubilization capacity of bile salt micelles. The fact optimal concentration values appear is due to competitions for adsorption at the oil-water interface (lipase and bile salt) and for solubilization (digestion products and micro-constituents for a given quantity of bile salt). This effect is expected to be especially critical for static *in vitro* methods, where the bile salt pool is not renewed, contrary to some dynamic *in vitro* methods.

Effect of the micro-constituent molecular properties

In the pharmaceutical field, many studies were conducted to predict drug absorption and bioavailability from molecular descriptors. Although there are still some debates about the appropriate descriptors, the most influent ones were reported to be log P (or log D for ionizable molecules), the numbers of H-bond donors and acceptors, the polar surface area, and the molecular weight (debated).[57,58,59,79]

In order to test these molecular properties for lipophilic micro-constituents from food, we gathered all bioaccessibility data from the studies that used real foods containing or with added fat, with the criterion of having sufficient data for each micro-constituent. When data were scarce, we included those for the model emulsion systems. All bioaccessibility values were included, regardless of the micro-constituent sources and of the parameters that were varied in the studies. The molecular properties listed above were obtained from the ChemSpider database (www.chemspider.com).

Only one significant correlation was found, a linear relationship between bioaccessibility and log P (see fig. 4). Such a correlation was already reported for five carotenoids with an excellent coefficient of determination $R^2 = 0.983$.[47] With nine lipophilic micro-constituents,

the R^2 of 0.908 reported in fig. 4 indicates a strong correlation between bioaccessibility and log P. Coenzyme Q_{10} and curcumin were left out of this correlation as they positioned very differently than the other micro-constituents (it might be related to the fact they are the only two micro-constituents not belonging to the terpenoid class), and had larger standard deviations. When the data for vitamin A (from only three studies) were also left out, R^2 increased to 0.972. Fig. 4 shows that micro-constituent lipophilicity plays a major role in bioaccessibility, whatever the sources, forms, and other parameters are (at least within the framework of real, mostly non-processed foods). Nevertheless, when properly controlled, the structural parameters play an important role, e.g. the bioaccessibility of β-carotene (one of the most studied micro-constituents) could reach up to 60-70% by decreasing the emulsion droplet size. Fig. 4 also constitutes an overview of the data available, indicating the ranges of the values (large for coenzyme Q_{10} and curcumin), and a lack of *in vitro* studies for vitamin A (three), vitamin D (two), and vitamin K (none).

Note that phytosterols were not included because only one study was found with phytosterols alone (i.e. without cholesterol).[49] All other studies actually showed that cholesterol competes with phytosterols for solubilization in mixed micelles, resulting in large bioaccessibility variations.[64,65,81,82] Nevertheless, a study of different phytosterols solubility in bile salt micelles reported that it decreases with increasing molecule hydrophobicity, in qualitative agreement with the trend reported in fig. 4.[83]

More generally, the data reviewed by Wiedmann and Kamel also support this trend, indicating a decrease for the solubilization ratio of drug into bile micelle or mixed micelle with increasing log P for various drugs.[84] Hence, the effect of the partition coefficient is likely related to the incorporation in the mixed micelle, of which the properties could be affected by all the other parameters discussed here, except the emulsion droplet size.

Conclusion

In this review, the bioaccessibility of lipophilic micro-constituents contained in the triglyceride droplets of emulsions was shown to depend on several physicochemical parameters. In all studies, it was found to increase with the triglyceride chain length. The concentration of triglyceride generally enhanced bioaccessibility up to an optimal concentration, what is likely an effect of the limiting quantity of bile salt in static *in vitro* protocols. Most of the studies indicated that different interfacial molecules stabilizing the emulsion droplets led to different bioaccessibility values. This effect may be indirect, influencing emulsion stability (droplet flocculation and coalescence, and thus interfacial area), or direct, by lipase inhibition or solubilization hindrance. In general, to discriminate those effects, dispersion stability should be studied during *in vitro* digestion. All articles but one reported that bioaccessibility increased with decreasing droplet size (or more correctly with increasing interfacial area). Bioaccessibility was also often reported to increase with pH, which could be explained by the ability of many lipids to form micelles at high pH.

At the molecular level, the partition coefficient (log P) is confirmed to be a reliable descriptor for the bioaccessibility prediction of many lipophilic micro-constituents (mostly from non-processed foods). The control of the other physicochemical parameters is nevertheless able to modulate the digestion kinetics and the mixed micelle properties. Together, these parameters could help to focus on the appropriate micro-constituents when developing specific encapsulation and delivery systems.

The next step in the study of the bioaccessibility of lipophilic micro-constituents is the consideration of more digestion processes related to all nutrients. For example, only a few articles reported protein hydrolysis, although it could influence lipid hydrolysis, and in turn micro-constituent bioaccessibility. Similarly, hydrolysis and gastrointestinal metabolites of the micro-constituent were rarely taken into account, whereas they can modify

bioaccessibility. The digestion inhibition property of dietary fibers was sporadically studied and, maybe to a lesser extent, starch hydrolysis could also play a role, so both should be investigated further.

Finally, the knowledge of the effects and interactions of the parameters discussed here could be used to formulate processed foods with optimal bioaccessibility. Moreover, as dynamic digestion systems develop, one can expect more realistic *in vitro* conditions, spanning the whole gastrointestinal tract, regulating digestive juices quantities and flows, controlling digestate pH and transit, and taking mechanical processes into account. This will enable the study of the effect of the food native macroscopic structure, which is important for the release of micro-constituents from non-processed foods.

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Author biography

Sébastien Marze started his higher education in polymer science and engineering. He then had significant experiences in numerical simulation and in polymer rheology. He prepared his PhD thesis on foam physicochemical properties (surface and bulk rheology) in the Laboratoire de Physique des Solides (CNRS/Université Paris-Sud), supervised by Dr. Arnaud Saint-Jalmes, in the team of Dr. Dominique Langevin. In November 2006, he obtained a PhD degree in physics. He then had further experiences in soft matter modeling, and took a two years postdoctoral position at the Nestlé Research Center to investigate emulsion and foam physics. In October 2009, he obtained his current scientist position at INRA, focusing on experimental and numerical methods to understand the physicochemical mechanisms controlling the digestion of lipids in emulsion. He is the writer or co-writer of various articles related to these topics.

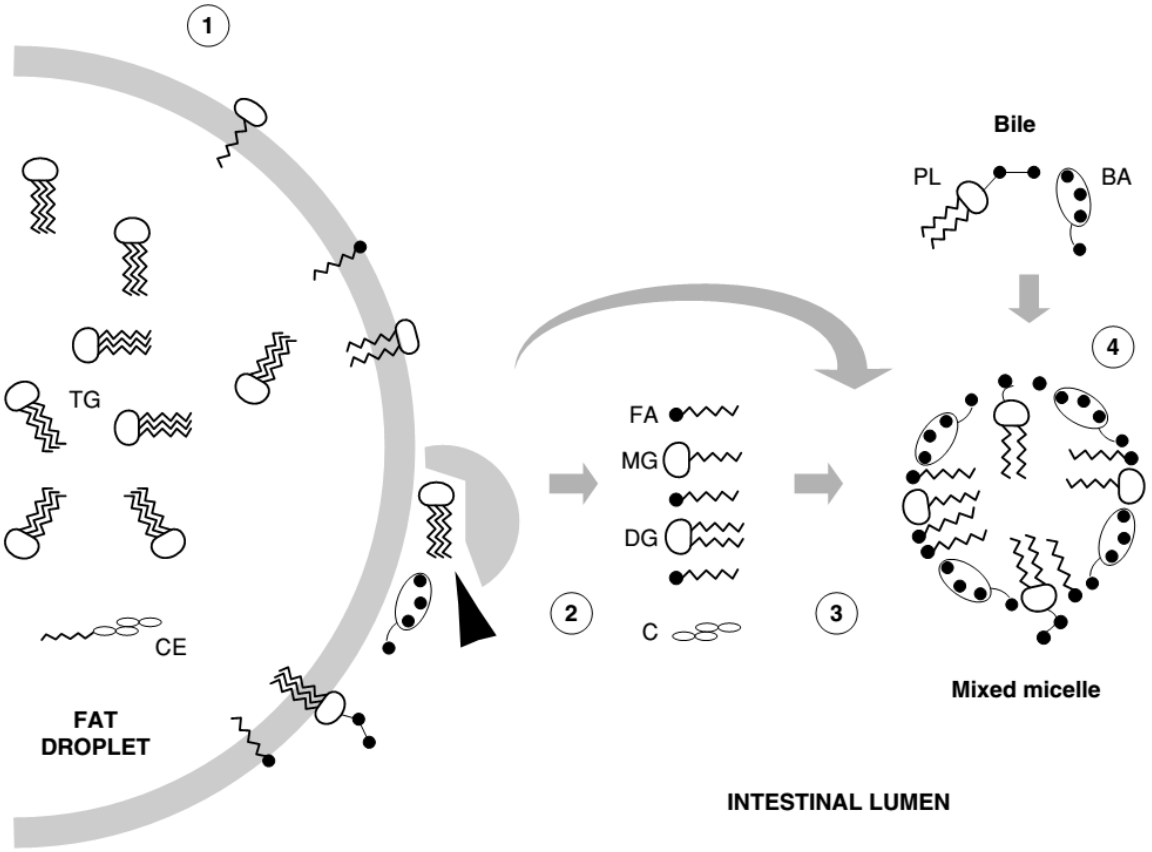


Figure 1: Summary of intestinal digestion processes of lipids, in this case a triglyceride (TG) droplet containing cholesteryl ester (CE). Pancreatic lipase and colipase (triangle) hydrolyze TG at the oil-water interface, yielding a fatty acid (FA) and a diglyceride (DG), the latter being hydrolyzed into a monoglyceride (MG) and a FA. Being insoluble in water, these final digestion products form a mixed micelle with bile acid (BA) and phospholipid (PL). Vesicles or liquid crystal phases are also formed in small proportion, or in specific digestion conditions (e.g. absence of bile). In the present example, CE is hydrolyzed by pancreatic lipase and carboxyl ester lipase into cholesterol (C). The latter should be represented in the mixed micelle as it transfers during digestion. Note that phospholipids are hydrolyzed by phospholipase A_2. From ref. 13 with permission of Elsevier.

Micro-constituent	Chemical class	log P
Lycopene	Carotenoid (carotene)	14.5
α-carotene	Carotenoid (carotene)	12.6
β-carotene	Carotenoid (carotene)	12.8
Zeaxanthin	Carotenoid (xanthophyll)	11.1
Lutein	Carotenoid (xanthophyll)	10.9
Vitamin E (α-tocopherol)	Tocopherol	10.5
Vitamin D (cholecalciferol)	Steroid (secosteroid)	8.0
Cholesterol	Steroid	7.4
Vitamin A (retinol)	Retinoid	5.8
Coenzyme Q_{10} (ubiquinone)	Quinone	18.7
Curcumin	Curcuminoid	3.2

Table 1: List of the most studied lipophilic micro-constituents. The partition coefficients log P are the Actelion simulated values using ALOGPS (www.vcclab.org/lab/alogps). Note that all molecules are part of the terpenoid class, except coenzyme Q_{10} and curcumin.

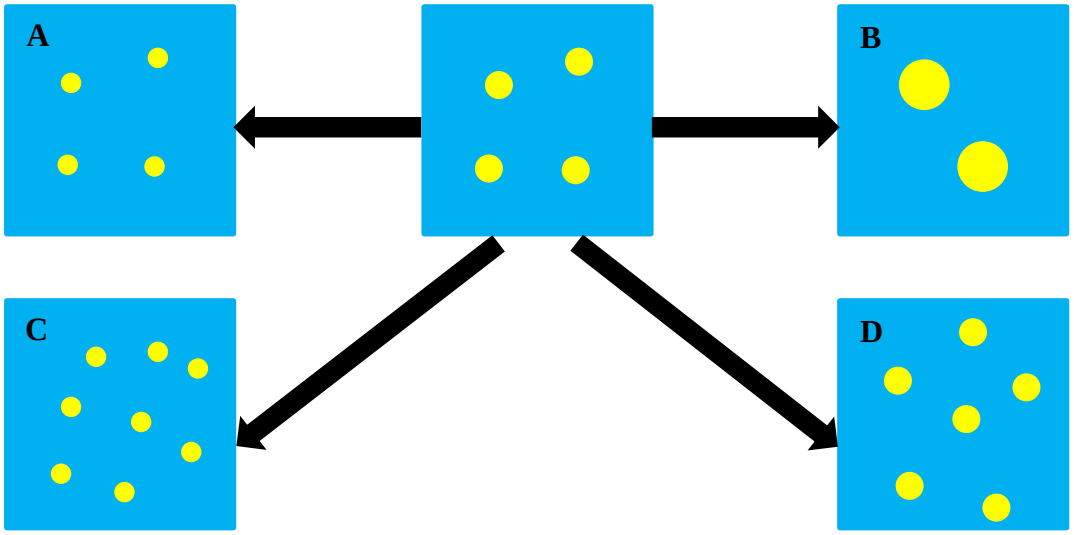


Figure 2: The different cases of interfacial area change in a monodisperse emulsion. A) All droplets decrease in size, leading to a decreased interfacial area. This is the case when matter exits the droplets, as during the solubilization step of digestion. B) Droplets aggregate or merge, leading to a decreased interfacial area. This is the case when droplets flocculate and finally coalesce during digestion. C) Droplets break up into smaller ones, leading to an increased interfacial area. This is the case during an emulsification process, which occurs during emulsion fabrication, and also during digestion. D) Droplet size is unchanged and the droplet volume fraction (equivalent to oil concentration) is increased, leading to an increased interfacial area. This is the case when droplets concentrate in a given volume, for example in the duodenum. The reverse way is also possible and represents the case of dilution.
Note that the droplet volume fraction is unchanged in cases B) and C), so the interfacial area available for hydrolysis and solubilization is directly related to droplet size. In contrast, the droplet volume fraction changes in cases A) and D), so the interfacial area available for hydrolysis and solubilization should be scaled by the droplet volume fraction.

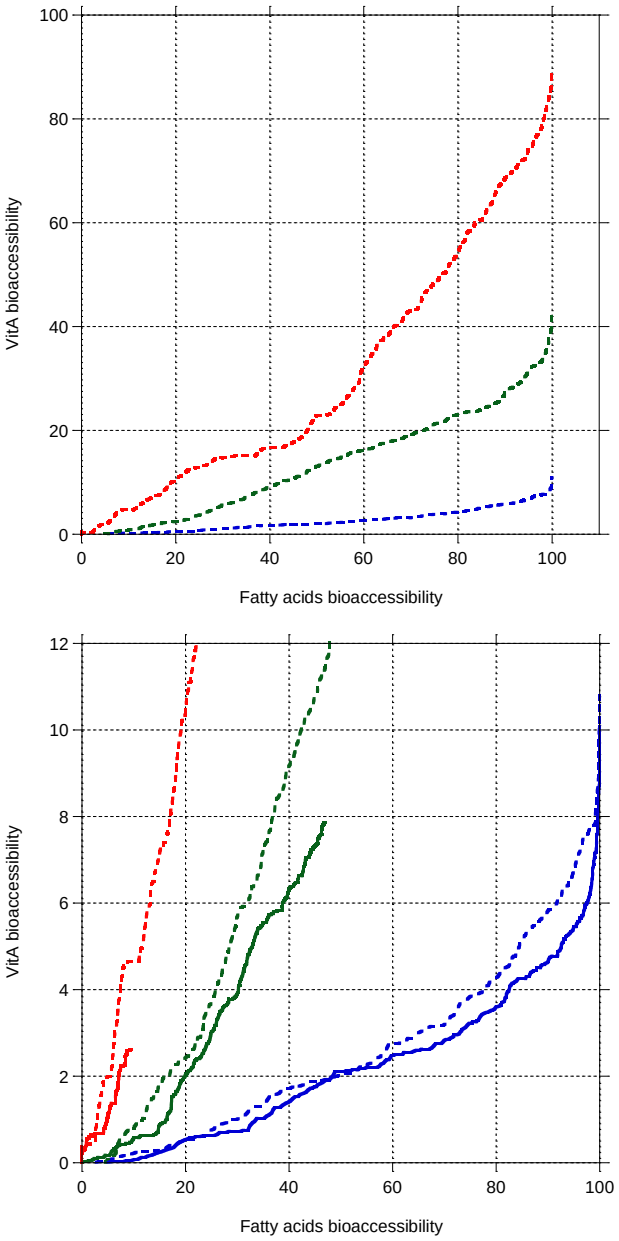


Figure 3: Relationship between fatty acids and vitamin A (vitA) bioaccessibilities by numerical simulations of the digestion of tricaprylin (blue), triolein (green), and a triglyceride representing an average of trieicosapentaenoin and tridocosahexaenoin (red). Top: bile micelle is recycled (it does not get saturated with solubilizates). Bottom: close-up of the recycled case, compared to the case where bile micelle does get saturated (full lines). From ref. 55, reproduced by permission of The Royal Society of Chemistry.

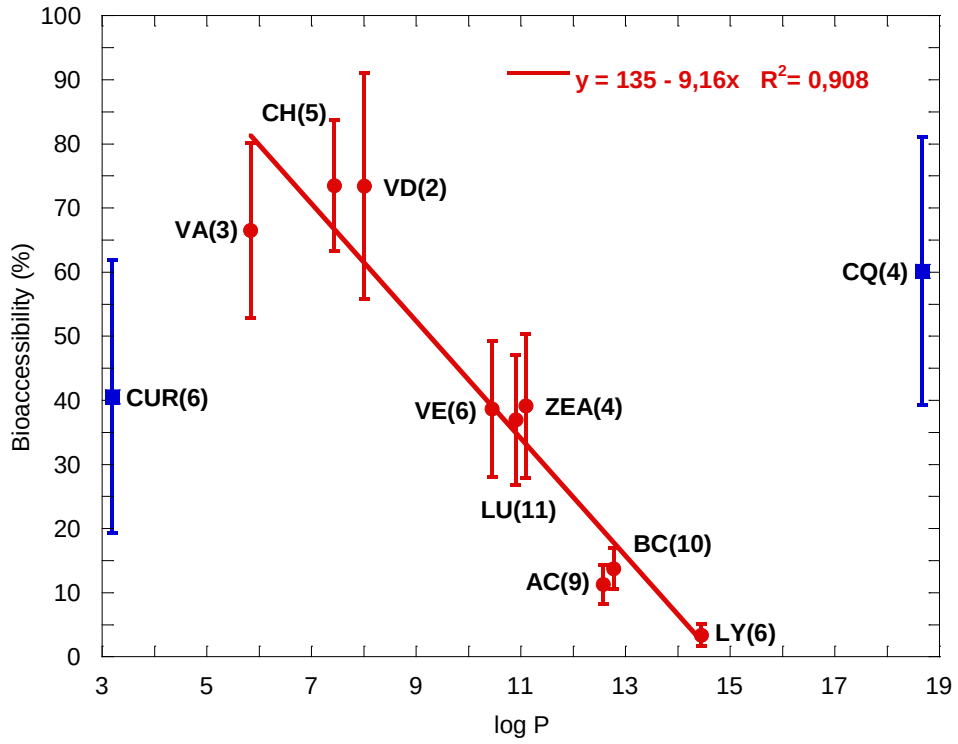
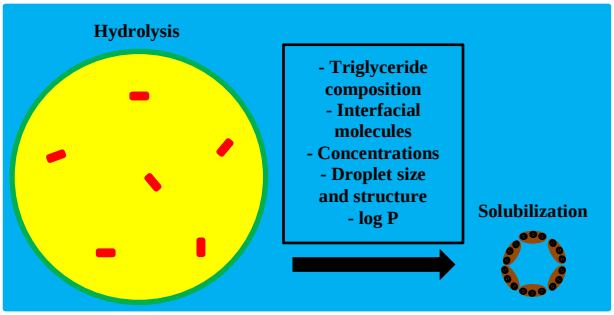


Figure 4: Correlation between the bioaccessibility and the log P of several food lipophilic micro-constituents (see text for precisions). The figure in brackets gives the number of studies where the data were extracted to calculate the mean and the standard deviation (reported as m ± sd). References 33,35,46,51,60,61 for curcumin (CUR), 62,63,80 for vitamin A (VA), 27,42,64,65,81 for cholesterol (CH), 49,85 for vitamin D (VD), 3,29,32,62,66,67 for vitamin E (VE), 3,16,67-75 for lutein (LU), 67,69,71,72 for zeaxanthin (ZEA), 3,16,67-69,72-75 for α-carotene (AC), 3,16,67-70,72-75 for β-carotene (BC), 3,67-70,72 for lycopene (LY), and 49,76-78 for coenzyme Q_{10} (CQ).



Graphical abstract: The physicochemical parameters controlling the transfer of lipophilic micro-constituents from emulsion droplets to mixed micelles (bioaccessibility) are reviewed.