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Supramolecular structures in lipid digestion and implications for functional food delivery

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Abstract
The daily diet is important for our survival, health, and wellbeing. Functional food materials, which tailor the digestion process, can help maintaining and even improving human health and lifestyle. Knowledge on how food products, particularly food emulsions such as milk, interact with the digestive system, where they transform into supramolecular structures, can have a direct impact on the rational design of such advanced materials for functional food delivery applications. These materials have the potential to be personalized to digestive conditions and dietary nutrient requirements of the consumer or patient. They could help maintaining the uptake of codelivered nutrients and drugs even under compromised digestion conditions such as a fat maldigestion, a low bile salt concentration, or a limited lipase action. Such conditions are found, for instance, in preterm infants or patients with digestive disorders such as chronic pancreatitis or pancreatic insufficiency. Tailored nanostructure formation and transformation in these materials may further trigger the digestion rate and thus have an impact on the related feeling of satiety, which may help curing eating disorders and reduce the societal challenges of obesity and related diseases. In this contribution, the specific focus is set on discussing the equilibrium and dynamic colloidal properties of food emulsion droplets during digestion and their implications for designing nature-inspired functional food materials. These investigations provide a perspective toward the design of personalized food colloids.

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Introduction

Designer-made supramolecular food materials may form the basis for personalized, health-promoting diets of the future [1]. Delivering a complete diet with a content of hydrophobic, amphiphilic, and hydrophilic nutrients, which is personalized to the needs of the consumers, could be beneficial for clinical, infant, and sport nutrition. A well-balanced nutrient content is important as, for instance, the overconsumption of lipid food components such as dietary triglycerides is related to major health disorders including heart disease, obesity, cancer, and diabetes [2]. In the ideal functional food material, the digestion-induced structural transformations and the produced types of colloidal structures tailor both the digestion rate and nutrient absorption by specific interactions with digestive enzymes and the absorptive cells in the gastrointestinal tract. Slowing down the digestion rate of colloidal food materials could support maintaining the feeling of satiety for longer and promoting the absorption of nutrients into the circulatory system of the body [3]. Ultimately, the designed supramolecular structures not only deliver health-promoting bioactive molecules but also protect them from chemical and physical degradation during the digestion process and storage. This is important to secure their delivery through the harsh conditions of the stomach into the small intestine and ultimately into the circulatory system of the body [4–6]. Examples for health-promoting molecules that are sensitive to degradation during the digestion processes include proteins, peptides, polyunsaturated fatty acids (PUFAs), vitamins, and drugs.

There is growing interest in the bioavailability improvement of poorly water-soluble drugs after coadministration with lipids as most of the recently discovered drug molecules are hydrophobic [7–10]. To highlight the benefit of lipid delivery systems, particularly colloidal lipid formulations, an exceptional case is the reported increase in the bioavailability of vitamin E up to around 400% on its administration with a lipid liquid formulation compared with soft gelatine capsules [11]. In another example, the bioavailability of the drug danazol, a medication used for

the treatment of endometriosis, was increased up to 900% *in vivo* in rats and in *in vitro* investigations, when provided in lipid-based formulations [12]. However, the underlying mechanisms at play that lead to this increase are still mostly unknown.

This review summarizes the recent achievements that may guide the design of nature-inspired supramolecular functional food structures as a step toward the development of nanocarriers for the personalized delivery of nutrients. The comprehensive design of functional food materials requires a fundamental understanding of the mechanisms at play, leading to structure formation, structural transformations, and morphological alterations during digestion. It is also important to gain insight into the role of interactions among the digestion-induced nanostructured materials and the digestive enzymes and cells in the gastrointestinal tract in facilitating the transfer of the nutrients in the body. This is only possible through recent advances in experimental techniques and sample manipulations that provide access to the mesoscopic length scale with a high spatiotemporal resolution such as time-resolved online small-angle X-ray scattering (SAXS) small-angle for the real-time monitoring of dynamic structural alterations within seconds. The further combination of these techniques with microfluidics can increase the time resolution to fractions of seconds for the *in situ* study of fast-digesting samples and molecular self-assembly processes in general, as demonstrated in a recent microfluidics–SAXS study on vesicle formation [13]. In real space, electron microscopy techniques such as cryogenic transmission electron microscopy (cryo-TEM–) are essential for gaining further insight into the morphological alterations and investigating possible coexistence of different self-assembled aggregates in the digested samples. At the same time, coupling of these methods with biochemical assays and advanced *in vitro* digestion models (e.g. relevant *in vitro* cell culture models) is crucial to bridge the colloidal structure to the biological activity. The investigations on the structural, morphological, and size alterations of food emulsions during the digestion process, as illustrated in Figure 1, are important for shedding light on this possible interplay between the colloidal length scale and the expected performance of digested emulsion droplets. Hence, thorough understanding of the mechanism behind the evolvement of self-assembled structures and the translation from the basic to personalized food delivery applications is highly dependent on multidisciplinary research efforts involving scientists from different backgrounds: physics, chemistry, biology, engineering, food science, and medicine.

Nature's own complete and personalized diet milk

The digestive behavior of nature's own personalized and functional food system, milk, which has been optimized over millions of years by evolution, is the key starting point in the design of advanced food materials and benchmark for nature-inspired functional foods. Milk is a complete diet that forms the basis for the survival and development of the offspring. Its lipid food components are emulsified in water in form of small micron-sized droplets, stabilized by biosurfactants such as phospholipids and amphiphilic proteins [14,15]. In addition to poorly water-soluble bioactive components, and metabolic messages such as human milk oligosaccharides that can modulate the gut development, milk contains components such as microRNAs that presumably regulate the further development of the offspring [16–18]. Extracellular vesicles in milk act as nanocarriers for these labile nutrients and protects them from degradation in the digestive tract and targets their delivery through a surface protein-mediated membrane binding [19,20]. This is of interest here as it highlights the presence of lipid-based nanocarriers in food designed by nature. PUFAs and their related diglyceride and monoglyceride forms, which are mostly released from the breast milk triglycerides during digestion in the gastrointestinal tract, are key elements in the development of the brain and central nervous system as well as normal vision in the infants [16,21]. The digestion process is a highly complex multistage bioprocess that secures survival by facilitating the effective delivery of the required nutrients [9,15,22–26].

During their digestion, food emulsions such as milk undergo a range of molecular and colloidal transformations that are triggered by enzymatic reactions and stimuli such as metabolites, ions, and pH that secure the bioavailability of the nutrients and survival of the offspring [27–30]. Inspired by this dynamic self-assembly structure formation in milk, a detailed understanding of the fate of food emulsions during digestion can guide the design of advanced food systems that are personalized to the needs of the consumers. This is also important as milk is targeted to the specific species, and an increasing number of patients are diagnosed with allergies against specific milk proteins or lactose in bovine milk, which is also used as basis in many infant formulas [31,32].

Physiology of the human digestive tract

The knowledge of how food molecules interact during their digestion may be key for controlling the feeling of hunger and the delivery of essential lipid amphiphilic food components such as lipids, hydrophobic vitamins, drugs, or peptides with functional foods. The lipolysis of lipids is catalyzed by enzymes called lipases that hydrolyze the ester bonds between glycerol and fatty acids, mainly in the stomach and small intestine [33]. Lipases are fascinating enzymes that are soluble in water but practically insoluble in their substrate, oil [34]. When the lipases such as pancreatic lipase in the small

intestine adsorb onto the oil–water interface of the emulsified oil droplet in normal food emulsions, a flap protecting its hydrophobic site is displaced in a process called interfacial activation, and the substrate, therefore, can reach the active site of the lipase for initiating the enzymatic reaction [35–37].

The major part of lipid digestion that enhances the solubilization of lipophilic molecules occurs in the stomach and the small intestine by gastric and pancreatic lipases [7,38]. In the stomach, the pH (typically the local pH in the range of ~2.0–3.0), the osmolality, and the viscosity of the digested lipid foods are adjusted [28,39]. For food emulsions, gastric lipase in the stomach is on average responsible for the hydrolysis of up to 25% of the ester bonds between the fatty acid and glycerol moieties of administered triglycerides, generating mainly diglycerides and free fatty acids (FFAs) that accumulate on the emulsion droplet surfaces and promote the action of the pancreatic lipase in the following small intestine [9,34]. The major part of lipid digestion then takes place in the small intestine by lipases including the pancreatic lipase and phospholipases together with various cofactors (colipase, bile salts, and calcium) at typical pH in the range of 6.0–8.0 [28]. Gall bladder contractions lead to secretion of biliary juice containing mainly bile salts and phospholipids that help stabilizing the emulsion droplets and further modify their oil–water interfaces for enhancing the adsorption of the pancreatic lipase–colipase complex [40–43]. It was proposed that the interactions among bile salts and colipase facilitate anchoring of a less interfacial active pancreatic lipase presumably in the form of ternary complex that is mainly stabilized by van der Waals interactions [43,44]. Adsorbed onto the emulsion droplet surfaces, pancreatic lipase stereospecifically hydrolyzes the two outer ester bonds of the triglycerides, denoted as *sn-1* and *sn-3* resulting in the generation of the *sn-2* monoglyceride and the corresponding FFAs [29]. In this process, it was reported that the triglyceride composition affects the size distribution, the surface charge, and the microstructure of the digested emulsion droplets [45]. This indicates the presence of a link between the used oil type in food emulsions and the bioaccessibility of digestion-induced hydrophobic nutrients. Once incorporated into self-assembled structures in the presence of bile salts, the digestion products together with poorly water-soluble food components are transferred through the aqueous system of the small intestine. The generation of supramolecular structures owing to the presence of amphiphilic lipids (e.g. monoglycerides and diglycerides in combination with FFAs) and biosurfactants may also play a crucial role in facilitating the delivery of health-promoting nutrients through the intestinal cell membranes and into the circulatory system of the body.

Self-assembly of lipid digestion products—the phase diagram approach under equilibrium conditions

Dietary fatty acids and monoglycerides are composed of hydrophobic moieties (e.g. saturated, - or unsaturated hydrocarbon chains) and hydrophilic headgroups (e.g. carboxylic or glycerol functional groups); Figure 2 presents the triolein digestion products *sn-2* monoolein (monounsaturated monoglyceride) and oleic acid. Depending on pH for oleic acid, and the lipid composition of systems based on monoolein, these surface-active molecules display inverse lyotropic nonlamellar liquid crystalline phases, including the inverted-type hexagonal phase (H_2), the bicontinuous cubic phases (*Pn3m* and *Im3m* types), and the discontinuous micellar cubic *Fd3m* phase, and inverse micelles (L_2 phase) on exposure to excess water [46–48]. In a recent study, the polyunsaturated eicosapentaenoic acid monoglyceride was reported to self-assemble into H_2 structure in excess water [49,50]. These self-assembled, fluid-like lipid nanostructures are held together by noncovalent, intermolecular forces such as van der Waals, hydrophobic, hydrogen bonding, and electrostatic interactions between the amphiphilic molecules, and the molecular shapes of oleic acid and monoolein play an important role in modulating their structural features [51]. Dispersions of these inverse (oil-continuous) structures in excess water that form cubosomes, hexosomes, and related dispersed systems provide attractive drug and functional food nanocarriers owing to their capability to solubilize not only hydrophobic but also hydrophilic and amphiphilic bioactive molecules [52–58]. The encapsulation of degradation-sensitive molecules such as PUFAs, proteins, and peptides into these structures can protect them from degradation in the biological milieu, which may be crucial for facilitating their transport through the low-pH and protease-rich gastric fluid into the small intestine for absorption [55,59]. The solution conditions such as pH and ionic strength, that are significantly changing during digestion, are important to be taken into account as they affect the intermolecular forces and thereby modify the dynamic self-assembled structural features [47,53,60,61]. For instance, in pH-tunable systems, the protonation and deprotonation of the fatty acids embedded in the water–lipid interface modify the geometric packing of the amphiphilic molecules, leading to significant alterations in the self-assembled structure. Such pH-responsive nanocarriers may act as sustained release systems, targeting the nutrient delivery to certain pH regions in the digestive tract. In fact, it is hypothesized that one of the driving forces for the absorption of lipid food components from the self-assembled structures into the enterocytes is the pH gradient between the bulk intestinal fluid and the local reduced pH environment of the unstirred water layer that may induce colloidal transformations in close proximity to the intestinal wall [9,26,61].

Figure 1

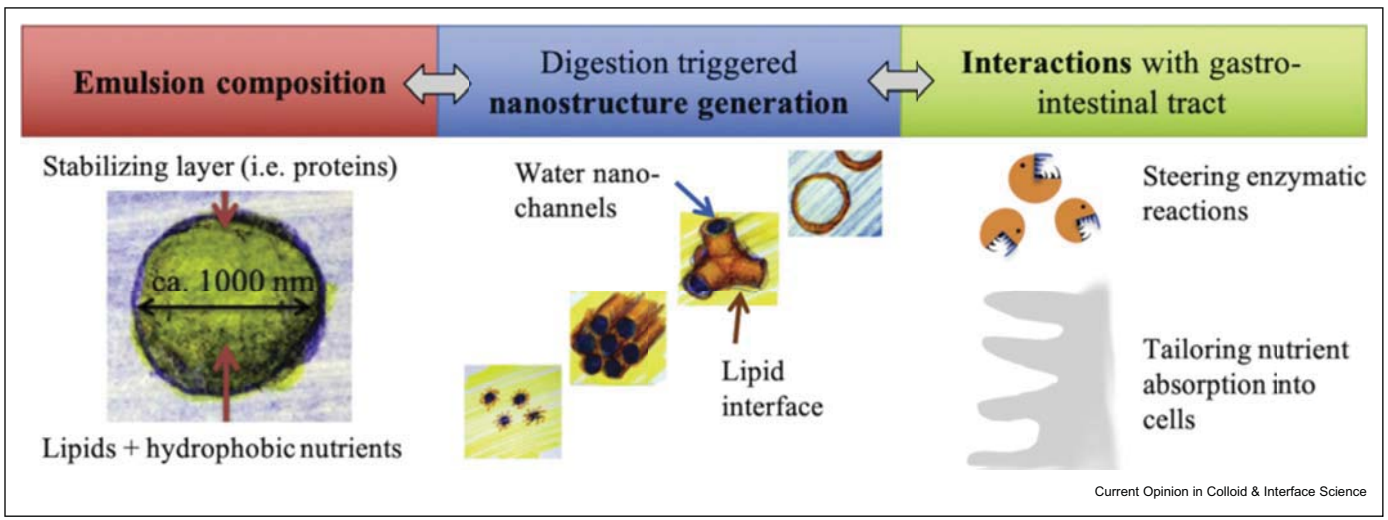


Illustration of the composition–nanostructure–activity relationship during digestion. The fundamental understanding of the link among the emulsion composition, the related digestion-generated lipid-based nanostructures in the gastrointestinal tract, and their interactions with components such as enzymes and epithelial cells in the digestive tract are crucial for the rational design of functional food materials.

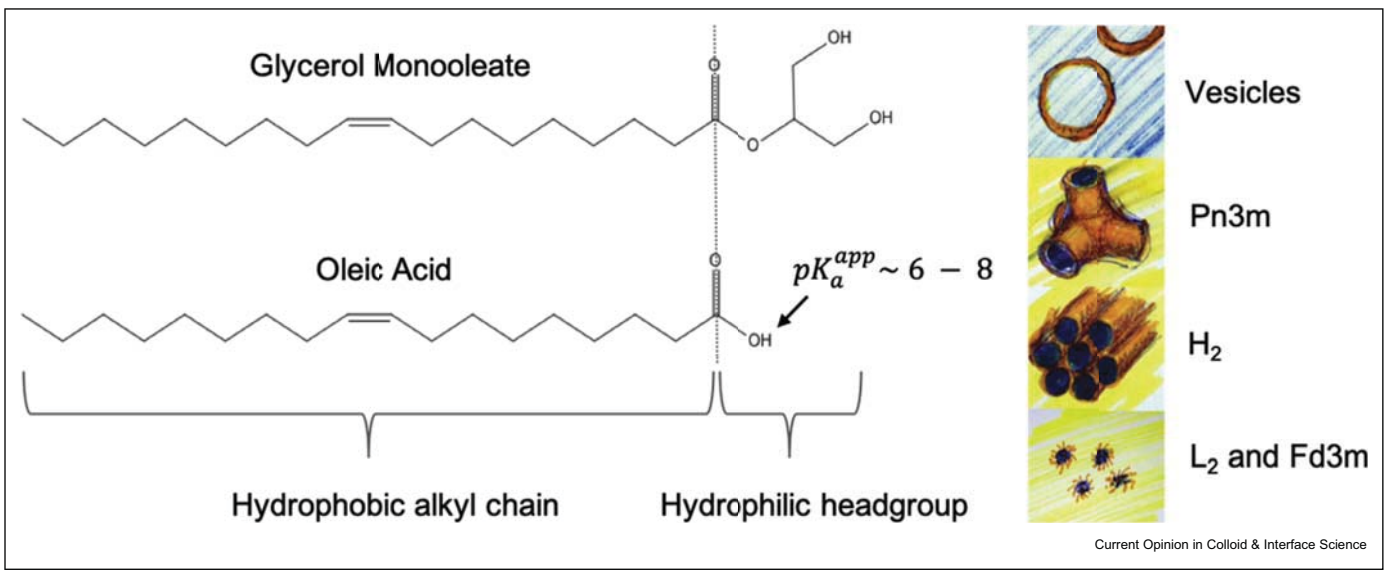
In addition to the role of the generated amphiphilic digestion products in the formation of self-assembled structures, bile salts together with amphiphilic lipids are also known to self-assemble into supramolecular structures that can solubilize hydrophobic molecules and facilitate their transport to the adsorptive cells of the small intestine [42,62,63]. On their own, bile salts form small micelles with aggregation numbers between 4 and 6 for sodium cholate and 7 and 12 for sodium deoxycholate [64]. Bile salts also participate in the self-assembly of the amphiphilic digestion products, mainly monoglycerides and fatty acids, in water through localization into the lipid–water interface of their structures [65,66]. For instance, the addition of bile salts to an aqueous solution of hexosomes at a monoolein/oleic acid weight ratio of 8/2 at pH = 6.8 led to a swelling of their internal H_2 structure followed by transformation to cubosomes at lipid/bile salt ratio of 17, and eventually to vesicles and direct micelles at a lipid/bile salt ratio of 8, within the reported bile salt concentrations found in the small intestine [65]. These results suggest that the addition of bile salts within the pancreatic juice during digestion in the small intestine favors the formation of more hydrophilic interfaces and ultimately direct micelles. It is worth noting that, contrary to the structure-forming lipid digestion products such as *sn-2* monoglycerides and fatty acids, bile salts are not uptaken by the enterocytes in the small intestine but later in the ileum [67]. Hence, significant changes in the self-assembled structures, potentially even a back-tuning to inverse liquid crystalline phases, may occur also at the enterocyte membrane on bile salt 'removal', on the basis of the composition of the lipid digestion products and the reduced local pH environment.

Dynamic self-assembly during emulsion digestion studied *in situ*

Lipid digestion is a dynamic process with constant modifications in the lipid composition overtime including triglycerides, diglycerides, monoglycerides, and fatty acids. This section discusses the dynamic assembly of these products during digestion *in situ*. These research studies require suitable *in vitro* digestion models coupled with highly contemporary small-angle scattering approaches and electron microscopy techniques to unravel the dynamic nanostructure formation and the structural transition mechanisms with high resolution in time and space [65,68–70].

Structural changes on the surface of the digesting olive oil droplets were first demonstrated with an *in vitro* intestinal digestion model coupled with light microscopy [71]. However, a detailed structural assignment was not possible with this technique due to the nanoscale-dimensions of the structures. The dynamic formation and assignment of highly ordered lyotropic liquid crystalline structures in model triolein-in-water emulsion droplets was then demonstrated using a suitable *in vitro* intestinal digestion model coupled with online SAXS and cryo-TEM [65]. Recently, these structural transformations were also observed in bovine and human breast milks and the triglyceride-based food product mayonnaise, in which oleic acid is also a dominating lipid component [30,68]. Considering that the self-assembled structures are very sensitive to modifications in their environment such as composition, salt concentration, and pH, it is a surprising result to find them in such digested complex food systems in the presence of multiple hydrophilic, hydrophobic, and amphiphilic components including proteins, carbohydrates, lipids, DNA, and even cells. The discovered biogenerated structures and their transformations with time of digestion are in line with the expectations from the composition- and pH-dependent self-assembly of oleic acid and monoolein under equilibrium conditions, as discussed previously. With time of digestion at pH 6.5, transitions from normal emulsion droplets through a variety of colloidal objects with differently internally ordered nanostructures, including the L_2 phase, the *Fd3m* structure, the H_2 phase, and the bicontinuous cubic *Pn3m* and *Im3m* phases, to vesicles and normal micelles were observed in absence and at low bile salt concentrations (Figure 3). Figure 4 shows the time-resolved SAXS data for mayonnaise and cow milk during digestion with pancreatin extract from the porcine pancreas without added bile salts. The sequence of structures is similar between the different food systems. The up to four times slower rate of structure formation in mayonnaise compared with the homogenized cow milk may be mainly caused by the larger emulsion droplet size in the mayonnaise providing less oil-water surface area for the lipase to attach, and variation in composition. SAXS data during the digestion of triolein emulsions at elevated bile salt levels and elevated pH of 7.5 indicated their transformation to normal micelles and vesicles without intermediate nonlamellar liquid crystalline structures [65,69]. However, as SAXS is a statistical method providing an average over all nanoparticles in the sample volume, the presence of a minor fraction of liquid crystalline nanoparticles as intermediate structures cannot be excluded even at high bile salt or pH levels. These transformations from normal emulsions to fatty acid and monoglyceride-based inverse liquid crystalline structures and further to vesicles and direct (normal) micelles also imply that water molecules start to diffuse into the droplets' interiors and create water pockets, which are eventually transformed into a network of hydrophilic domains in the internal oil-continuous liquid crystalline structures of the formed colloidal objects, see illustration in Figure 3. The lipase-driven transfer of water into the triglyceride (oil) phase at the macroscopic oil–water interface was recently demonstrated experimentally with ellipsometry [72]. The location and activity of the lipase may be triggered by the formation of nanostructures with the extensive water domains inside

Figure 2



The triolein digestion products *sn-2* monoolein and oleic acid. Both molecules are amphiphilic, containing a hydrophobic tail and hydrophilic headgroup covalently linked in one molecule. Self-assembled structures including inverse micellar phases (L_2 and *Fd3m*), inverse hexagonal phase (H_2), bicontinuous cubic (*Pn3m* type) structure and vesicles are schematically presented in the figure with water in blue and oil in yellow and orange. The structures arise from intermolecular forces and electrostatic interactions among the amphiphilic molecules in excess water. Related to electrostatic interactions, the 'apparent' pK_a of oleic acid in self-assembled structures was found between about 6 and 8, that is, within the physiological pH range found in the small intestine [47]. Thus, if the solution pH is changed, the electrostatic forces and, consequently, the colloidal structures are modified.

the oil droplets during digestion. These highly ordered nanostructures were mainly observed during the digestion of long-chain triglycerides; medium-chain triglycerides (MCTs) were found to be digested much faster, and direct transformations to vesicles and micelles were reported [65]. The bioaccessibility of hydrophobic nutrients such as vitamin D was found to strongly depend on the carrier-emulsion oil type, with MCTs resulting in low- and long-chain triglycerides, resulting in high bioavailability of the hydrophobic vitamin D [73]. Furthermore, clinical nutrition studies with formulas containing MCTs, where liquid crystalline structures are not present during digestion, showed a decrease in the uptake of fat-soluble vitamins in patients [74].

Toward this end, the question arises if designer-made nanostructured particles with liquid crystalline interiors can be engineered to induce specific phase transformations that tailor the digestion process and the delivery of loaded nutrients in defined and specific locations in the digestive tract, for instance, the induction of certain phase transitions through responses to specific enzymes. Recently, particles with liquid crystalline *Fd3m* digestion structure (micellar cubosomes) were formulated with lipase-specific phase transition patterns [75]. In a system containing nanoparticles with a 1/1 mixture of phospholipid and diglycerides, the cubic *Fd3m* structure was transformed into more hydrophobic inverse micelles (L_2 phase) with phospholipase and into more hydrophilic vesicles with pancreatic lipase. Also pH has a significant effect on the dynamic structural transformations as it was demonstrated during the digestion of monoolein-based cubosomes by using thermomyces lanuginosus lipase [76]. The inner cubic *Im3m* structure transformed to H_2 phase, cubic *Fd3m* phase, and L_2 phase at pH between 6.5 and 7.5. Contrarily, at increased pH above 8.0, transformations from cubosomes with an internal cubic *Im3m* phase to sponge-like structure (L_3 phase) and multilamellar vesicles (MLVs) were reported [76]. These differences in structures were discussed in relation to the protonation of the produced oleic acid that may trigger a more negative curvature of the oil—water interface further supporting the role of the pH as one of the key parameters for nanostructure formation and structural transformations in the digestion process of emulsified lipid systems such as food emulsions [30,47,61,77]. In this context, further important parameters include the ionic strength, specifically, also the calcium concentration during digestion as calcium ions can form insoluble complexes with fatty acids (soaps) that precipitate from the solution and thus impact the digestion rate and extent of digestion [78]. Hence, these approaches pave the path towards the design of enzyme- and pH-triggered biointerfaces with potential for sustained nutrient release and tailored interactions with the cells in the digestive tract. However, the important impact of these structures on lipid absorption and its implications for the rational design of new healthy functional foods is still poorly understood. [9,79].

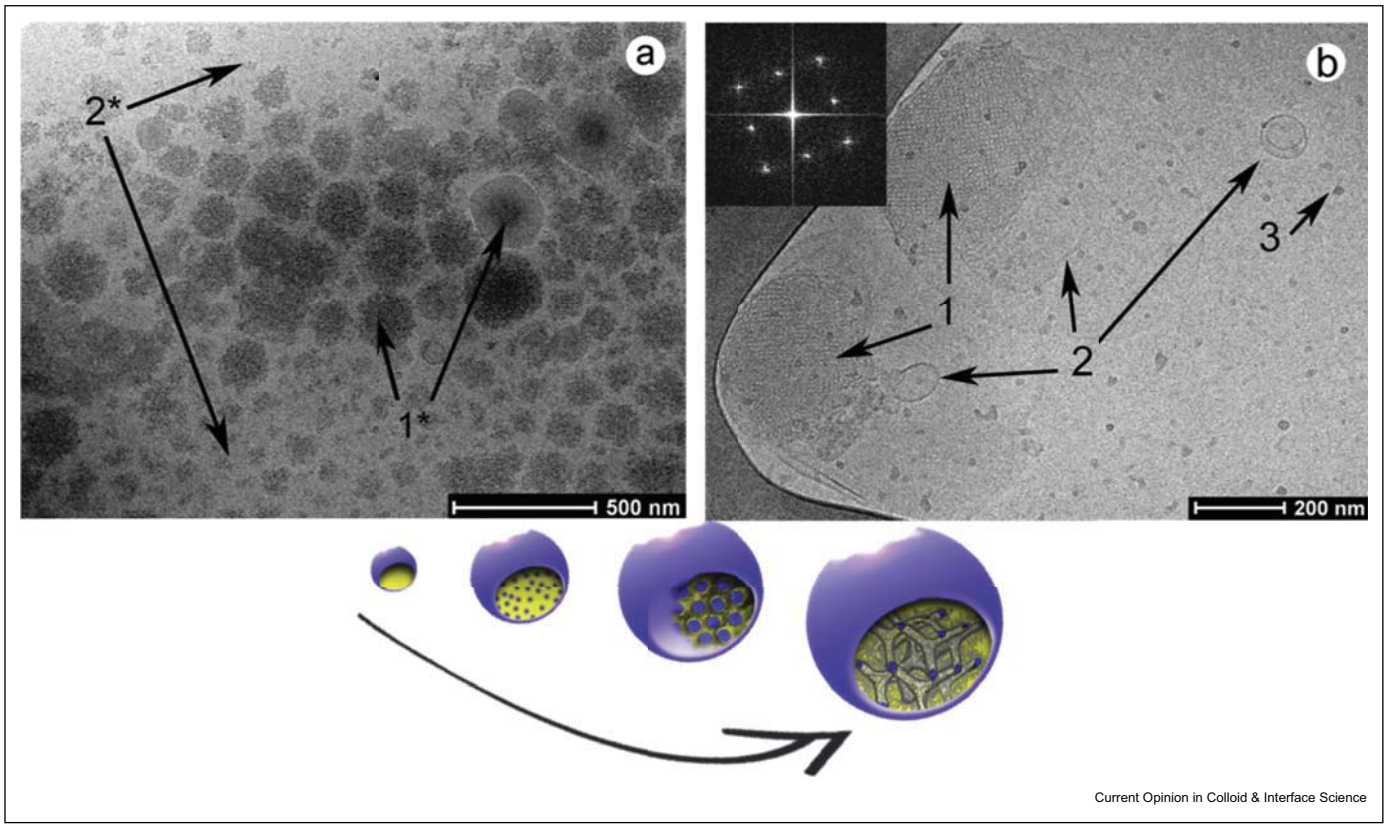
It is worth highlighting at this point that the current *in vitro* digestion models applied for the study of nanostructure formation so far in food emulsions and other related lipid dispersions neglect the dynamic changes in composition through the absorption of the digestion products into the absorptive cells of the intestine, occurring during the *in vivo* digestion. Overall, as the *in vivo* conditions are highly complex, a comprehensive understanding of the role of individual process parameters is only possible with well-defined *in vitro* models at reduced complexity. Such parameters include emulsion properties, digestive juice composition, pH, selected lipases, and interactions with cells. In this research area, the next major step toward a more thorough understanding of the digestion-triggered nanostructure formation and its implications on nutrient uptake requires coupling the current online SAXS *in vitro* digestion model with gastric predigestion and physiologically relevant cell culture models. These cell culture models should approximate the structure of the intestinal epithelium such as Caco-2 cells cocultured with mucus-secreting cells [80—84].

Implications of supramolecular structures for healthy food

Enzyme- and pH-responsive supramolecular food materials are interesting concepts for tailoring the delivery of specific nutrients and the digestion profile to the needs of the consumer. For instance, switching from the protected mode to the active mode as the developed nanocarrier migrates from the stomach into the small intestine could be used to transport labile molecules through the harsh and degradative environment of the stomach to the small intestine for uptake into the circulatory system. Related to this, pH-responsive nanocarriers of antimicrobial peptides have been designed with the triolein digestion products glycerol monooleate and oleic acid as structure-forming molecules [53,55]. In this system, cubosomes did not interact with bacteria cells as the encapsulation of the antimicrobial peptides within the curved bilayers of the internal cubic phase in cubosomes was discussed to hinder their access to the bacterial membrane. However, in form of micelles and vesicles at pH around 7.0, the peptides are exposed at the outer interface and the nanostructures are highly antibacterial active.

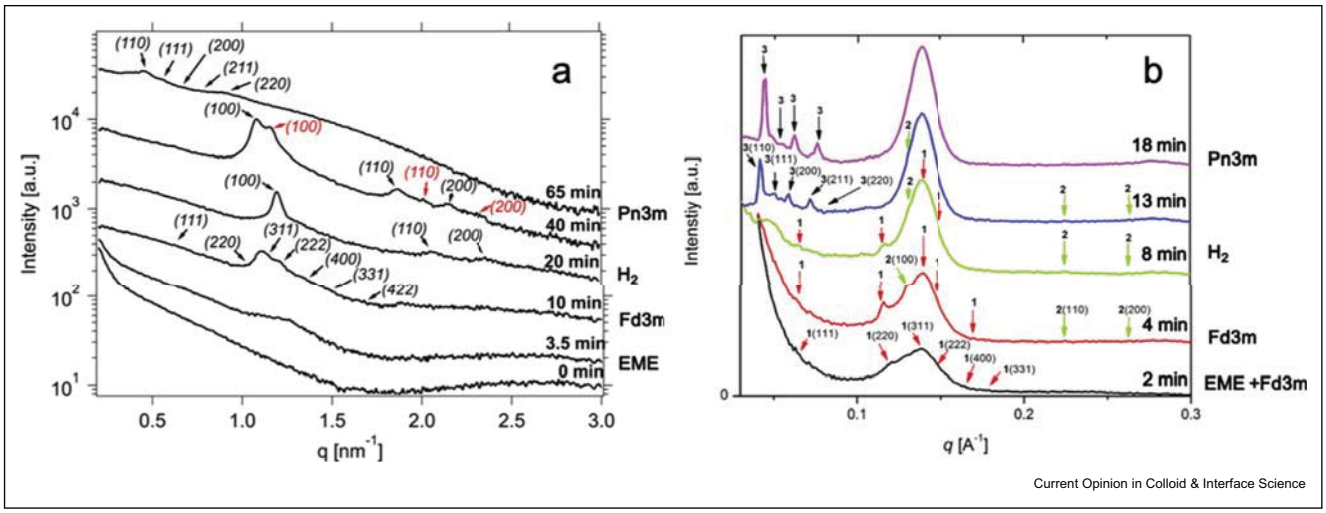
These lipid-based supramolecular materials may help maintaining the transport and absorption of lipid food components including hydrophobic vitamins, carotenoids, and drugs under compromised digestion conditions such as in preterm infants and patients with exocrine pancreatic insufficiency or chronic pancreatitis [85]. Here, pancreatic lipase—loaded functional food structures could be designed to transport the pH-sensitive

Figure 3 The digestion of milk visualised using cryogenic transmission electron microscopy (cryo-TEM).



(a) Cryo-TEM image of store-bought homogenized milk showing milk emulsion droplets in water (1*) in combination with casein micelles (2*). **(b)** Shows the appearance of internally nanostructured particles, containing a bicontinuous cubic phase (1), that coexist with vesicles (2) and direct micelles (3) at the final state of milk digestion in porcine pancreatin solution without additional bile salts. The inset shows the fast Fourier transform of the structured region in the cryo-TEM with the diffraction pattern that is characteristic for the bicontinuous cubic structure. The graphical illustration sketches the nanostructure formation inside the milk emulsion droplet during digestion. The internal oil structure of the normal emulsion is dynamically transformed via inverse micellar phases to inverse hexagonal and bicontinuous cubic structure during digestion. cryo-TEM, cryogenic transmission electron microscopy. Figure adapted from Refs. [68,70].

Figure 4



In situ small-angle X-ray scattering (SAXS) data recorded during the digestion of mayonnaise **(a)** and store-bought homogenized cow milk **(b)**. The formation of highly geometrically ordered liquid crystalline structures was observed in both food emulsions. However, the Bragg reflections of the lamellar phase may most likely be attributed to a difference in the lipid type and composition in mayonnaise compared with milk. For instance, milk contains a significant amount of saturated fatty acids that may form coexisting multilamellar structures. Figure adapted from Refs. [30,70].

enzyme through the stomach into the small intestine, where it can exert its activity. A concept for pancreatic lipase delivery based on pH-responsive hydrogel beads has been demonstrated recently [5]. The major advantage of the lipid-based nanocarriers is the potential for coadministering further hydrophilic and hydrophobic nutrients and the lipid building blocks of the nanocarriers that are of high demand for the body under these conditions.

Tailoring digestion rates through structure formation and transformation with designer-made food materials may provide also an interesting approach to trigger the feeling of satiety and hunger for improved diets [86]. Clinical studies showed that the consumption of milk significantly increased satiety and decreased energy intake in a second follow-up meal [87]. The underlying mechanisms are not yet understood but the formation of lipid structures in combination with proteins may play a major role in this process. A detailed understanding of the nanostructure formation and transformation in milk and its implications on the activity and interaction with the lipases during digestion can guide the development of functional food materials. This may open an alternative route to current approaches that mainly focus on engineering the surfaces of emulsion droplets, for instance, with hydrogels, that inhibit or delay lipase access *in vitro* [86,88].

Conclusions

The self-assembly of the triglyceride digestion products of food emulsions such as milk leads to a rich variety of nanostructures including highly geometrically ordered liquid crystalline structures, depending on the composition, temperature, and environmental conditions during digestion such as pH, bile salt levels, and ionic strength. These supramolecular structures possess unique properties including extensive lipid–water interfacial areas and ultralow surface tensions, allowing the spontaneous nanostructure formation. Hence, the formation of these structures *in situ* during digestion of these emulsions may not only help solubilizing poorly water-soluble nutrients but also tailor the interactions with cell membranes in the intestine and secure lipid digestion under compromised conditions such as low bile salt levels. Toward this end, a detailed understanding of the fate of the nature's personalized diet milk during digestion with focus on composition, nanostructure generation, and interactions with the epithelial cells of the digestive tract may provide crucial inspirations for advanced functional food materials.

Similar to milk, designer-made lipid-based nanocarriers may be optimized for the transport and absorption of lipid food components into the epithelial cells in the small intestine under compromised digestion conditions. This would allow the tailored delivery of degradation-sensitive nutrients such as vitamins, PUFAs, and peptides through the stomach to the epithelial cells of the small intestine for absorption. In this context, the adaption of *in situ* scattering techniques for the time-resolved study of nanostructural transformations opens a new research area on the colloidal aspects of food digestion and the design of novel functional food delivery systems.

In the future, ideal supramolecular food nanocarriers are expected to be personalized by considering the digestive conditions of the consumer that include composition, pH profile, and lipase activity. Combined with a detailed understanding of the self-assembly of the food components during digestion, as well as their specific interactions with lipases and the intestinal cells, this will allow tailoring the digestion profile and the formation of most efficient structures for the delivery of essential nutrients and drugs to the epithelial cells of the small intestine.

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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