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Review

Biophysical insights into modulating lipid digestion in food emulsions

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ABSTRACT

During the last decade, major scientific advances on understanding the mechanisms of lipid digestion and metabolism have been made, with a view to addressing health issues (such as obesity) associated with over-consumption of lipid-rich and sucrose-rich foods. As lipids in common foods exist in the form of emulsions, the structuring of emulsions has been one the main strategies for controlling the rate of lipid digestion and absorption, at least from a colloid science viewpoint. Modulating the kinetics of lipid digestion and absorption offers interesting possibilities for developing foods that can provide control of postprandial lipaemia and control the release of lipophilic compounds. Food emulsions can be designed to achieve considerable differences in the kinetics of lipid digestion but most research has been applied to relatively simple model systems and in in vitro digestion models. Further research to translate this knowledge into more complex food systems and to validate the results in human studies is required. One promising approach to delay/control lipid digestion is to alter the stomach emptying rate of lipids, which is largely affected by interactions of emulsion droplets with the food matrices. Food matrices with different responses to the gastric environment and with different interactions between oil droplets and the food matrix can be designed to influence lipid digestion. This review focuses on key scientific advances made during the last decade on understanding the physicochemical and structural modifications of emulsified lipids, mainly from a biophysical science perspective. The review specifically explores different approaches by which the structure and stability of emulsions may be altered to achieve specific lipid digestion kinetics.

1. Introduction

Lipids, derived from plant and animal sources, are important constituents of the human diet as they are essential nutrients required for growth and development. In the normal diet, lipids contribute between 20 and 40% of the total calories and provide a source of essential fatty acids, such as linoleic acid and α-linolenic acid, which are not synthesized by the human body. In addition, lipids are carriers of fat-soluble vitamins (vitamins A, D, E and K) and bioactive molecules, such as hydrophobic polyphenols. Lipids are also structural components of cell membranes, are involved in cell signalling pathways and are precursors of steroid hormones [1–7]. All these functions of dietary lipids contribute to human health but, when dysregulated, dietary lipids can also contribute to diseases, such as obesity, metabolic syndrome, diabetes, cardiovascular disease and cancer. For instance, overconsumption of saturated fatty acids, trans fatty acids and cholesterol in the diet can lead to hyperlipidaemia, i.e. elevated levels of blood triacylglycerols and cholesterol, which are important risk factors for atherosclerosis [8]. Elevated levels of fatty acids in the plasma have been associated with insulin resistance and obesity [8,9].

These complex diet-related health issues have triggered extensive multidisciplinary research, particularly over the last two decades, on understanding the mechanisms of lipid digestion and metabolism. Traditionally, the scientific contributions to this field have come from nutrition, biochemistry and physiology disciplines; however, in recent years, food science has come into the picture, providing different perspectives. The food science approach has relied largely on in vitro digestion experiments that purport to mimic the human digestion processes. The development of advanced in vitro digestion methods has allowed precise replication of the biochemical environment (such as pH,

Abbreviations: DAG, diacylglycerol; NEFA, non-esterified fatty acid; FHSO, fully hydrogenated soybean oil; GIT, gastrointestinal tract; HGS, human gastric simulator; HPC, hydroxypropylcellulose; HPMC, hydroxypropylmethylcellulose; MAG, monoacylglycerol; MC, methylcellulose; MFGM, milk fat globule membrane; MPC, milk protein concentrate; MRI, magnetic resonance imaging; NaTC, sodium taurocholate; NaTDC, sodium taurodeoxycholate; OSA, octenyl succinic anhydride; RBX, rice bran wax; SO, soybean oil; TAG, triacylglycerol; VLDL, very-low-density lipoprotein..

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ionic conditions and enzyme addition) and the hydrodynamic conditions within a single region of the gastrointestinal tract (GIT). These studies continue to provide fundamental understanding of the physicochemical and biochemical factors that affect lipid digestion in different food systems.

The food industry is also responding to the well-founded concern over the adverse health implications of the overconsumption of certain types of lipids by developing alternative "low fat" and "reduced fat" food products that do not compromise the consumer's organoleptic experience. In addition, good progress in designing products in which saturated and trans fats have been replaced with "healthy" fats has been made. Some high fat products with added plant sterols are commercially available to reduce the absorption of cholesterol. However, the concept of engineering the extent and the rate of lipid digestion within a food system has not yet been translated into commercial food products.

In terms of their chemical composition, storage lipids generally occur in the form of triacylglycerols (TAGs), which are formed by combining glycerol with three molecules of fatty acid. Depending on the chain length, fatty acids are classified into long-chain fatty acids with >12 carbon atoms, medium-chain fatty acids with 6–12 carbon atoms and short-chain fatty acids with <6 carbon atoms [10]. Another class of lipid is phospholipids, which are the major component of cell membranes and contain one or more phosphate groups. This presence of a phosphate group at the sn3 position confers a polar character on this region of the phospholipid, giving these molecules a distinctly amphipathic structure, i.e. each molecule consists of a distinct hydrophilic portion and a hydrophobic portion [10]. Other complex lipids include sterols and glycolipids that contain fatty acids, sphingosines and carbohydrates.

The physical state and the structure of a lipid in foods vary depending on whether it is of animal or plant origin. In plants (seeds, nuts etc.), the lipids in their natural state are stored as oil bodies, which are oil droplets that are stabilized by a monolayer of phospholipids with embedded specific proteins called oleosins [11]. Most seed oil bodies range in diameter from 0.5 to 2 μm and are composed mainly of nonpolar TAGs that form the core of the oil bodies. All mammalian milk lipids are contained within fat globules (with diameters ranging from 0.5 to 5 μm), which are stabilized by a milk fat globule membrane (MFGM) [12]. The MFGM consists of a phospholipid trilayer along with proteins, glycoproteins and cholesterol. The membranes of oil bodies and fat globules are designed by nature to protect them from endogenous lipases and external environmental conditions. In meat and muscle foods (e.g. "marbled" steak), TAGs are gathered as droplets in the adipocytes of the adipose tissue, whereas phospholipids are found mainly as the typical bilayers of the cell membranes [13].

In the manufacture of modern processed foods, lipids (oils) are extracted from plant and animal sources and are then combined with other food ingredients to create different food products (e.g. yoghurt, cheese, spreads, imitation creams, salad dressings, gravies, sauces, ice cream and confectionary products). In these foods, the lipids exist either as oil-in-water emulsions or as water-in-oil emulsions or as a combination of both. The emulsion droplet size and the nature of the interfacial layer in these systems vary enormously; the droplet size may range from the nano- to the micro-metre scale, and the interface is often stabilized by proteins and/or phospholipids, but more complex interfaces containing solid particles and biopolymeric multilayers can also be found [12,14]. The emulsified lipids in processed foods not only play a major role in determining the texture and flavour of processed foods but also provide structural attributes to food products.

The digestion and the absorption of lipids from different food products/diets are complex processes involving lipase actions and physicochemical processing along the length of the GIT [2,3,12,15,16]. As lipids are mostly insoluble in water, they need to be emulsified to make them accessible to the various lipolytic enzymes that are present in the stomach and the small intestine. These enzymes, which act at the lipid–water interface, include gastric lipase, colipase-dependent pancreatic lipase, pancreatic-lipase-related protein 2 and bile-salt-stimulated lipase [17,18]. The products of digestion are solubilized by bile acids and phospholipids in the intestinal lumen into self-assembled structures such as bile salt micelles and phospholipid vesicles, which are then transported to intestinal epithelial cells for absorption.

The rate at which lipids from individual foods are digested and absorbed depends on several factors, including the type and structure of the lipids, their organization within the food matrix, the presence of other compounds in the digestion medium (e.g. dietary fibres, polyphenols) and the volume of digestive secretions, which depend on age, health status and amount of meal consumed [19,20]. The rate of appearance and clearance of lipids in the bloodstream following the consumption of a lipid-containing food/meal is commonly referred to as "postprandial lipaemia". Postprandial lipaemia is due to an increase in both intestine-derived chylomicrons and liver-derived very-low-density lipoproteins (VLDLs) [21]. A sharp and prolonged postprandial lipaemia has been shown to be associated with modulation of endothelial function and homeostatic variables and is considered to be an independent cardiovascular risk factor [22].

Modulating the kinetics of lipid digestion and absorption through the design of food structures, matrices and compositions offers interesting possibilities for developing novel foods that can provide control of postprandial lipaemia, can control the release of lipophilic compounds and may offer new routes to trigger satiety. The past decade or so has seen substantial growth in research directed towards understanding the dynamics of lipid digestion and absorption in connection with the structure and composition of food emulsions. The trend is illustrated by the bibliometric data in Fig. 1, showing the annual number of publications and citations for the combined topics of "lipid digestion and emulsion" over the period 2009–2020. Ongoing developments have been presented in recent reviews [2–5,7,23].

The present review paper focuses on key scientific advances made during the last decade on understanding the physicochemical and structural modifications of emulsified lipids, mainly from a biophysical science perspective. The review specifically explores different approaches by which the structure and stability of emulsions may be altered to achieve specific lipid digestion kinetics.

2. Fate of dietary lipids in the GIT

As discussed above, the lipids in our diet exhibit a wide diversity of supramolecular structures and chemical compositions and they usually occur in an emulsified state in a liquid or solid food matrix. In this section, we will focus on the digestion and absorption of TAGs. Moreover, the physical structures of lipids change continually under the dynamic environment of the GIT, which in turn influence digestion and the metabolic fate of the digestion products. In healthy adults, the digestion

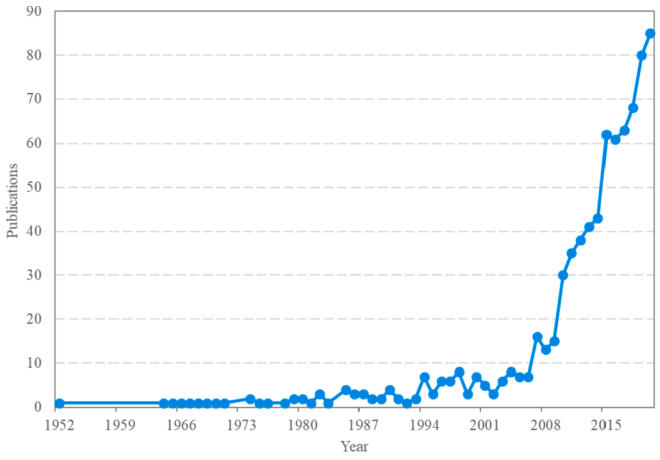

Fig. 1. Number of documents by year found in the Scopus database using the keywords "emulsion" and "lipid digestion".

and absorption of lipids is very efficient, with about 95–98% of lipids in the diet being absorbed in the small intestine, but lipid digestion varies considerably between different types of food [24,25]. Several approaches have been used to modulate the kinetics of lipid digestion in simple emulsions, including controlling the binding of lipases to the interface of emulsified lipid droplets, inhibiting the activity of enzymes, modifying the composition and structure of the interface and controlling the surface area of the interface and the surrounding matrix structure [2–4]. Some of these approaches are discussed later. The known mechanisms of lipid digestion and absorption from a physiological viewpoint are briefly described below and are also depicted in Fig. 2.

The first step in lipid digestion is oral processing, which involves the initial mechanical breakdown of lipid-containing semi-solid and solid foods. Saliva is incorporated into the bolus, which helps lubrication as it lowers the friction between food particles because of the action of salivary proteins [26]. Liquid food emulsions spend a relatively short time in the oral cavity but could still be affected by interactions with salivary enzymes, proteins, mucins and various ions. The existence of a lingual lipase, an enzyme that has been shown to be present and active in rat and mice tongues, in humans is questionable [27].

Upon entering the stomach, the action of intense peristaltic waves in the antrum induces the mixing of the food with gastric juices. The presence of dietary and endogenous surface-active compounds further facilitates the emulsification of lipids. The adsorption of gastric lipase at the oil–water interface of lipid droplets/particles initiates the hydrolysis of TAGs, forming primarily diacylglycerols (DAGs) and non-sterified fatty acids (NEFAs). The human gastric lipase (molecular weight 50 kDa) is co-localized with pepsinogen in the chief cells in the proximal stomach [28,29] and its secretion rate depends on the type and the amount of food intake. Gastric lipase is stable at pH values between 2 and 7, with maximum lipolytic activity at pH 5–5.4 [30]. It preferentially hydrolyses TAGs at the sn3 position, leading to the formation of

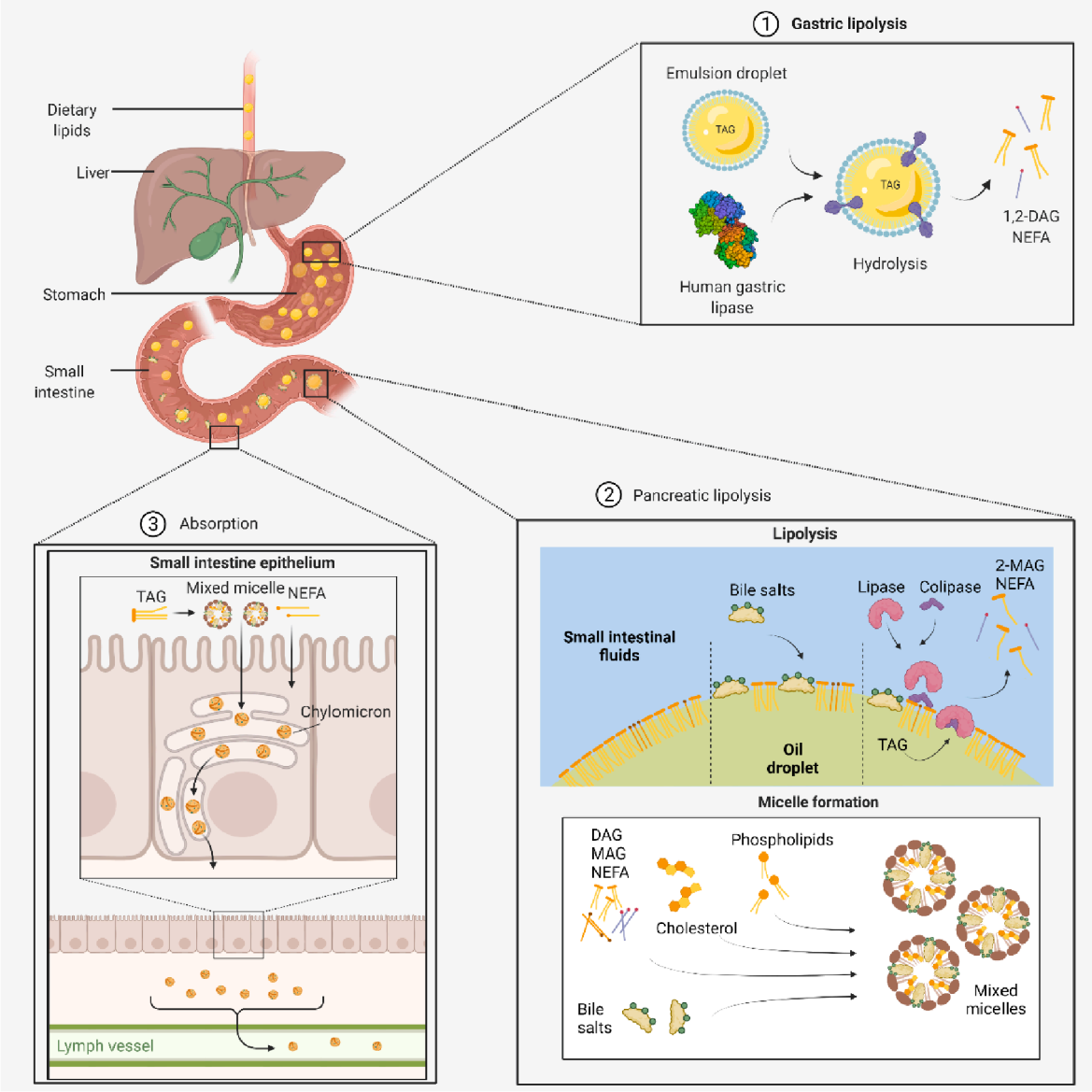

Fig. 2. Lipid digestion in the human GIT. (1) Gastric lipolysis: gastric lipase binds to emulsion oil droplets and partially hydrolyses TAGs into 2-MAGs and NEFAs. Long-chain NEFAs tend to accumulate at the droplet surface resulting in limited lipolysis. (2) Pancreatic lipolysis: a two-step process involving lipolysis (lipases and colipase action) and subsequent solubilization of NEFAs by bile salts (mixed micelles assembly), particularly for long-chain NEFAs. (3) Absorption: mixed micelles or NEFAs are transported across the small intestinal epithelium; mixed micelles are transformed into chylomicrons and are absorbed in the lymphatic system. Adapted from "liver, pancreas and gallbladder" and "Lipid Handling in the Small Intestine Modulates Immune System Homeostasis", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates

sn1,2-DAGs [31]. The lipolysis of TAGs comprising medium-chain fatty acids is considered to be more efficient than that of TAGs containing long-chain fatty acids, as the activity of gastric lipase is inhibited by the accumulation of long-chain fatty acids at the lipid–water interface [32]. The mechanism of action of gastric lipase relies on its adsorption at the lipid–water interface, which involves a conformational change in the lid domain at residues 215–244, allowing access to the hydrophobic areas both surrounding the active site and interfacing the lid. These areas are thought to draw lipids and to promote docking [33,34]. The active site of gastric lipase consists of a catalytic triad of serine, histidine and aspartate residues, as commonly found in serine proteases and other lipases.

Gastric lipase contributes to 10–30% of overall lipolysis in adult humans but plays a more important role in lipid digestion in infants. The fasting pH (2.0–6.0) of an infant's stomach is higher than that of an adult's stomach (pH 1.4–2.0), probably contributing to a more efficient lipid digestion by gastric lipase. The remainder of lipid digestion is dependent on the action of pancreatic lipase in the lower GIT.

The stomach also mediates the direct absorption of short- and medium-chain (< 12 carbon atoms) fatty acids through the gastric mucosa [35]. It is hypothesized that long-chain fatty acids released in the stomach by gastric lipase are the first to trigger the secretion of hormones, such as cholecystokinin (which mediates downstream food effects). The transfer of the gastric contents to the duodenum is controlled by the process of gastric emptying.

In the small intestine, TAGs and DAGs are further processed into absorbable 2-monoacylglycerols (2-MAGs) and NEFAs mainly by the action of human pancreatic lipase (optimum pH range 7.5–8.5), which has a co-factor, called colipase. Pancreatic lipase has been extensively reviewed [36,37]. It is a glycosylated serine hydrolase with a molecular weight of 50.5 kDa and is synthesized by the acinar cells of the pancreas in the form of an active enzyme and not as an inactive zymogen like most pancreatic enzymes. It is delivered into the intestinal lumen via the pancreatic duct.

The colipase binds to the oil–water interface with the help of the bile acids and anchors pancreatic lipase at the surface [38]. In the absence of colipase, bile acids remove pancreatic lipase from the lipid surface and thereby inhibit lipolysis. Pancreatic lipase hydrolyses positions 1 and 3 of TAGs, releasing NEFAs and 2-MAGs (Fig. 2) [37]. As the surface activity of these products is higher than that of the starting TAGs, they consequently aid in the dispersion of lipids in the intestinal lumen. The pancreatic enzymes phospholipase A_2 (molecular weight 13.6 kDa) and cholesterol esterase also have the ability to adsorb on to the oil–water interface. Pancreatic phospholipase A_2 hydrolyses the fatty acyl ester bond at position 2 in phospholipids, releasing an NEFAand lysolecithin, i.e. lysophosphatidylcholine [39]. As in the case of NEFAs, lysolecithin assists in the dispersion of the lipid droplets. Cholesterol esters are cleaved by pancreatic cholesterol esterase and are absorbed into enterocytes as free cholesterol.

As most of the products of lipid hydrolysis are essentially insoluble in water, they are solubilized by the liquid luminal contents of the intestine [40]. Bile acids, phospholipids and cholesterol have the ability to increase the solubility of lipolytic products in the intestinal lumen by forming a range of self-assembled structures, called mixed micelles (Fig. 2). Mixed micelles are disc-like aggregates that contain bile salts, fatty acids, MAGs, phospholipids and cholesterol and are about 4 nm in diameter [41]. These mixed micelles in the intestinal lumen co-exist with unilamellar liquid crystalline vesicles or liposomes [42].

NEFAs with chain lengths of ≤12 carbon atoms are absorbed directly via the enterocytes into the portal vein, but NEFAs with longer chain lengths follow a different pattern. After uptake into enterocytes, they are re-esterified into TAGs, incorporated into chylomicrons and, subsequently, enter the lymphatic transport pathway [43–45]. The absorption process encompasses the uptake of digestion products, intracellular trafficking, TAG synthesis and TAG packaging for either secretion as chylomicrons or storage in cytoplasmic lipid droplets by enterocytes (Fig. 2). All regions of the small intestine are capable of the uptake and absorption of the digestion products of TAGs; however, the jejunum is responsible for the majority of uptake and absorption [46,47]. Enterocytes are polarized epithelial cells with an apical and basolateral membrane that is responsible for the uptake and absorption of most nutrients. The apical membrane, or brush border membrane, has an unstirred water layer through which the digestion products are transported. There is a low pH that is generated by an H^+/Na^+ antiport exchange system, creating an acidic environment that allows the digestion products to dissociate from the micelles. NEFAs cross the apical membrane by either passive diffusion or protein-mediated transport [43].

After absorption from the small intestine, the products of lipid digestion appear in the blood via the lymphatic system. The appearance of chylomicrons in the circulation is followed by an increase in liver-derived VLDLs because of competition for lipolysis between VLDLs and chylomicrons [48]. Postprandial lipaemia is considered to be a result of an increase in both intestine-derived chylomicrons and liver-derived VLDLs. As chylomicrons are more readily targeted by lipoprotein lipase and the liver receptors, VLDLs tend to increase postprandially to a greater extent than chylomicrons [49]. The rate at which lipids from individual foods and meals are digested, absorbed, incorporated into the bloodstream and cleared depends on the structure and composition of the food consumed as well as various non-modifiable factors (pathological conditions, genetic background, age, gender and menopausal status) [19,50].

3. Approaches for controlling the rate of lipid digestion in emulsions

To develop scientific approaches to controlling the rate of lipid digestion, we first need to understand how the structure and properties of emulsions influence lipid digestion behaviours in the various interconnected compartments of the GIT, each with its own biochemical and physical environments. The response of emulsions to these different environments depends on their original characteristics, such as interfacial structure and composition, droplet size distribution, nature of the lipid phase and continuous phase composition. The changes in the physical structure of emulsions (colloidal effects), and the biochemical modification of emulsion components (molecular effects) occur simultaneously and play a key role the determining the overall kinetics of lipid digestion.

As the food digestion process is extremely complex, most of the research in this area has been carried out using model or highly controlled oil-in-water emulsion systems [2,3,14–16]. Through this approach, it is becoming apparent that the structure and stability of food emulsions can be used as a tool to alter the rates of lipid digestion in simple model systems. It must be pointed out that most of the studies on emulsion digestion have used static in vitro models, which are not able to fully replicate the dynamics of biochemical secretions, gastrointestinal emptying and motility. This is particularly important for understanding the digestion behaviour of emulsions in the gastric environment, where mechanical and shear processes, caused by peristaltic movements, may contribute to their instability.

Here, we first discuss key structural features that influence the behaviour of emulsions in the gastric environment. The most important aspects of the behaviour of emulsions in the gastric environment are schematically represented in Fig. 3. Because lipolysis occurs mostly in the small intestine (as discussed earlier), most of the in vitro studies have focused on the gastric behaviour of emulsions from a structural and stability perspective rather than on lipid digestion. Gastric lipase has not been included in the simulated gastric juice used in most studies, mainly because of its non-availability until recently. Thus, the main consideration has been the changes in the structure and stability of an emulsion system in the gastric environment and how this may impact on the migration of lipids to the small intestine for a more complete digestion. This is based on the hypothesis that gastric-stable emulsions will retain

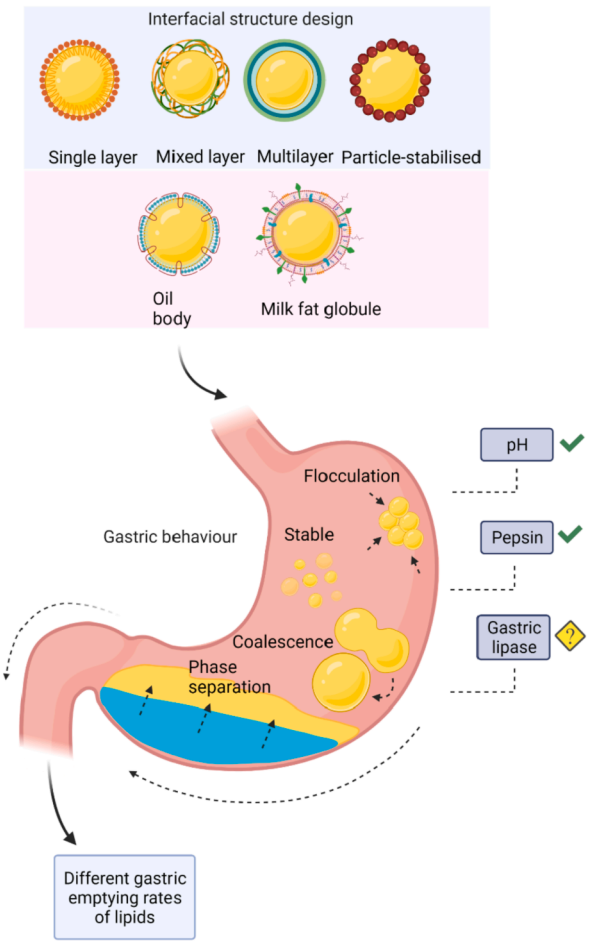

Fig. 3. Schematic representation of the behaviour of oil-in-water emulsions in the stomach; different interfacial structures that can be designed to influence gastric stability of emulsions; gastric stable emulsions show uniform rate of emptying of lipids, whereas gastric unstable emulsions show phase separation and uneven rate of emptying of lipids. Created with https://biorender.com/.

their homogeneous particle size distributions and will pass into the duodenum, delivering lipids at a gradual rate. In contrast, unstable emulsions will exhibit flocculation, coalescence, creaming and phase separation, which will lead to heterogeneous lipid compositions being transferred to the duodenum (Fig. 3).

In the duodenum, the emulsions are further transformed to allow efficient lipid digestion through a range of processes that allow optimized lipolysis and absorption of the products of digestion, as discussed earlier. The high digestion efficiency of the duodenum makes it challenging to devise a robust approach to control or delay lipid digestion and absorption. We discuss potential emulsion design strategies based around the design of interfacial structures and continuous phase/matrix components that may be applied to formulate lipolysis-resistant food emulsions. The focus is on the biophysical events that occur in the intraluminal phase of lipid digestion and absorption, i.e. lipolysis, solubilization (micelles, vesicles) and transport of lipolytic products towards the enterocyte membrane.

3.1. Behaviour of emulsions in the stomach

3.1.1. Interfacial structure and stability of emulsions

The instability of an emulsion is reflected as a change in the spatial arrangement or size distribution of the oil droplets, such as creaming, flocculation or coalescence. As the destabilization of an emulsion is due mainly to changes in the interfacial layer, the nature of this interface and its modification in the gastric environment play key roles in determining the state of the emulsion in the stomach. Therefore, it seems obvious that interfacial structures can be created using different biopolymers for controlling emulsion stability in the stomach. The interfacial layer is formed when emulsifier molecules adsorb on to an oil–water interface, and this interface varies in its thickness, charge density and viscoelasticity, depending on the molecular dimensions, packing and interactions of the adsorbed emulsifier molecules [51–53].

The thickness of the interface has a marked impact on the strength and range of the steric interactions between emulsion droplets, and the charge density has a strong influence on the strength of the electrostatic interactions. Emulsifiers that form thick interfaces (such as polysaccharides) are often able to stabilize emulsions entirely through steric repulsion, whereas those that form thin interfaces (such as globular proteins) require a combination of both electrostatic and steric repulsion to stabilize the droplets [54]. The digestion behaviour of food emulsions with different interfacial characteristics (such as surface charge, thickness, steric repulsion and surface rheological properties) and formed using various emulsifiers, including low-molecular-weight surfactants, phospholipids, proteins, polysaccharides and colloidal particles, have been studied extensively.

The digestion behaviour of protein-stabilized emulsions as affected by structural and biochemical factors has been covered in previous reviews [55–57]. As the interfaces consisting of adsorbed protein layers in most food emulsions are negatively charged at neutral pH, the decrease in pH to below 2.0 in the stomach causes a decrease in the negative charge (i.e. a loss of electrostatic repulsion), resulting in considerable droplet aggregation/flocculation. In addition, the interfacial protein layers are hydrolysed by the action of pepsin, although the ability of pepsin to hydrolyse different food proteins varies somewhat. The hydrolysis of the protein interfacial layer has been shown to decrease the net surface charge in model emulsions stabilized with a range of food proteins, such as whey protein isolate, sodium caseinate, β-lactoglobulin and β-casein, resulting in droplet aggregation [58]. In addition, the loss of rigidity of the interfacial layer because of hydrolysis makes the droplets more susceptible to coalescence.

The gastric stability of protein-stabilized emulsions can be improved by forming multilayered interfaces [59], often consisting of proteins and polysaccharides. The assumption is that the adsorbed multilayers provide enhanced steric stabilization, restricting the access of pepsin to the interface. For example, during gastric incubation, multilayered whey protein/pectin emulsions showed an improved stability against droplet flocculation and coalescence compared with whey-protein-stabilized emulsions. Apparently, the presence of a pectin layer affected the activity of pepsin, thereby limiting proteolysis and preventing flocculation/coalescence [60]. Another interesting observation is that emulsions stabilized by strong multilayered structures produced by combining pectin with whey protein fibrils [61] were physically stable at low pH (pH 2.0–3.5). Enzymatic cross-linking of gelatin and pectin using laccase has been shown to generate interfaces that are resistant to gastric destabilization [62].

The use of modified starches to stabilize emulsions against gastric conditions is feasible, as the branched amylopectin chains located at the interface can provide steric stabilization against droplet coalescence. Lin, et al. [63] showed that the gastric stability of emulsions stabilized by octenyl succinic anhydride (OSA)-modified starches was dependent on the degree of substitution, i.e. the average number of hydroxyl groups that are substituted by the OSA group per glucose unit in the starch. An increase in the degree of substitution of OSA-modified starch contributed to greater stability of the emulsion against the changes in ionic strength, low pH and enzymes in the gastric fluid; the extent of increase in the droplet size was negatively correlated with the degree of substitution.

Particle-based interfaces have also been shown to affect emulsion stability under gastric conditions [64,65]. Emulsion droplets stabilized by spherical whey protein microgel particles (300 nm) showed more

resistance to droplet coalescence than conventional whey-protein-stabilized emulsions. Similarly, emulsions formed with lactoferrin nanogel particles were less responsive to gastric conditions [66]. The emulsion stability was further improved when lactoferrin nanoparticles were complexed with polysaccharide, such as alginate and carrageenan. The coating of a whey protein nanogel particle interface with dextran sulphate (500 kDa) produced stable droplets with a lower degree of pepsin hydrolysis of the adsorbed layer than the uncoated protein-nanogel-stabilized interface after 120 min of digestion [67].

The susceptibility of interfaces formed by low-molecular-weight surfactants varies considerably. When Tween 80 was compared with sucrose esters, the Tween-80-stabilized emulsion remained stable in the gastric environment, whereas the sucrose-ester-stabilized emulsion tended to be easily destabilized [68]. Instability of sucrose esters in the gastric environment can occur because of their interactions with gastric enzymes via hydrophilic binding and their inversion at low pH [69]. High stability of polyoxyethylene sorbitan esters under simulated gastric conditions has also been observed in emulsions stabilized with whey protein/surfactant mixtures, in which increasing the Tween 80 fraction in the mixture increased the gastric stability of the emulsions [70]. Other surfactants, such as polyglycerol esters, can increase the stability of an emulsion under simulated gastric conditions when the degree of polymerization and the proportion of hydroxyl groups in the molecule are high. This is because the interfacial hydration properties are improved and so is the strength and thickness of the oil–water interfacial layer [71].

Most of the studies mentioned earlier were carried out using static in vitro gastric digestion methods in simple emulsion systems. In recent years, the development of dynamic gastric systems and the adoption of the standard INFOGEST digestion protocol have progressed our understanding of the dynamics of gastric digestion of both simple and complex emulsion systems. Recently, Wang, et al. [72] compared the gastric behaviours of emulsions stabilized by different types of milk protein [milk protein concentrate (MPC), calcium-depleted MPC and sodium caseinate] using a dynamic in vitro gastric digestion model – the human gastric simulator (HGS). Confocal micrographs of the gastric digesta obtained at different digestion times are shown in Fig. 4. The MPC-stabilized emulsions, which contained some intact casein micelles and whey proteins at the interface, showed extensive droplet flocculation within 20 min of digestion (at pH > 6), because of the hydrolysis of κ-casein at the surface of the adsorbed casein micelles. The flocculated droplet network became more open and porous with an increase in the digestion time and the proportion of coalesced oil droplets within the network also increased, possibly because of more extensive hydrolysis of the adsorbed protein layers by pepsin. For the calcium-depleted-MPC-stabilized emulsion, droplet flocculation was less pronounced, because of the presence of fewer intact casein micelles in the calcium-depleted MPC. The sodium-caseinate-stabilized emulsion also showed droplet flocculation at a digestion time of 60 min, when the pH approached the isoelectric point of casein, because of electrostatic interactions between the oil droplets. The cluster of flocs disappeared completely at a digestion time of 120 min and numerous tiny, evenly dispersed flocs and some free oil droplets were visible at the end of the gastric digestion. Flocculation of the emulsions in this system was driven mainly by low pH rather than by pepsin action [72].

Naturally occurring emulsions, such as mammalian milks, are stabilized by complex interfacial layers, often consisting of phospholipids and membrane proteins [12]. For example, in milk, TAGs are contained within fat globules ranging from 0.1 to 15 μm in diameter and are stabilized by the MFGM, which is a trilayered structure containing phospholipids, various glycoproteins, enzymes and cholesterol [12,73]. The structural changes in the MFGM of milk fat globules during static in vitro gastric digestion have been previously reported [74–76]; the MFGM proteins were hydrolysed by pepsin to varying degrees, but the phospholipids and some of the highly glycosylated MFGM proteins were not affected. The fat globules appeared to retain their integrity under in vitro gastric conditions [74].

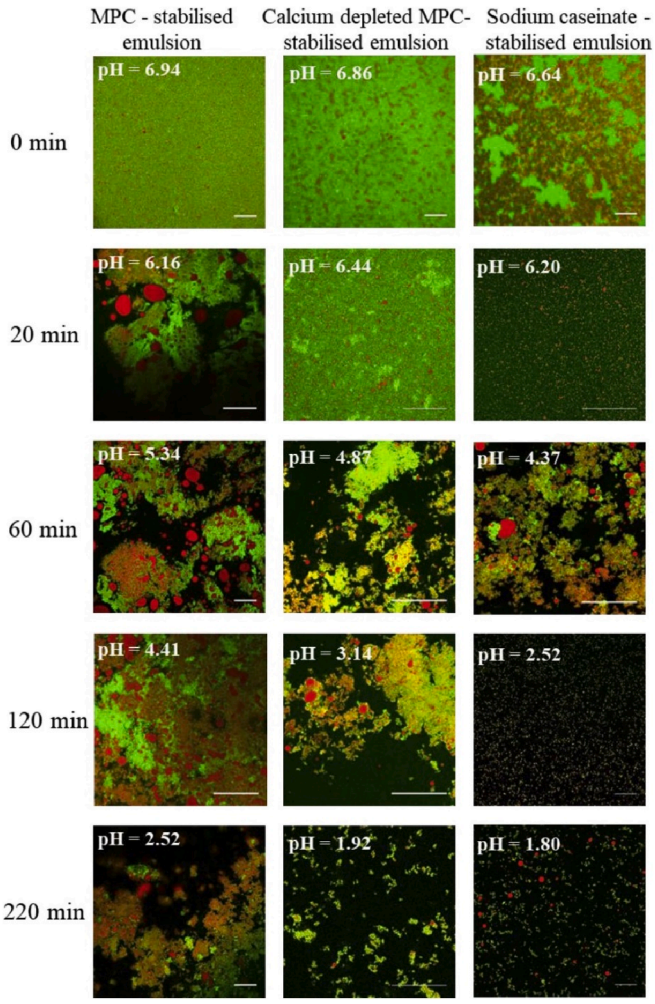

Fig. 4. Confocal microscopy images of digestion residues of emulsions stabilized by different milk protein ingredients in an HGS at different times during gastric digestion. Samples were stained with Nile Red (for oil) and Fast Green (for protein). The scale bar in all images is 50 μm. Reproduced from Wang, Lin, Ye, Han and Singh [72], with permission from Elsevier Inc. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

However, our recent studies [77,78] using the HGS revealed interesting insights into the stability of the fat globules in milk: in the initial stages of gastric digestion, casein micelles coagulated to form a curd and the majority of the milk fat globules became entrapped within the curd. These entrapped globules showed flocculation and coalescence during the later stages of digestion. Surprisingly, the fat globules present in the liquid phase of the chyme were not as extensively coalesced [78]. This observation highlights the role of shear in the HGS in the stability of the fat globules entrapped within the curd, and this effect cannot be easily replicated in static in vitro methods.

Interestingly, an in vivo study in rats [79] has shown that the fat globules increased in size under gastric conditions, possibly because of the action of gastric lipase and shear. Spherical protrusions that were rich in lipolytic products were observed at the surface of the fat globules in the gastric chyme. This was attributed to the accumulation of long-chain fatty acids at the interface, mainly because of their poor solubility in water [79].

Another example of a natural emulsion is the oil bodies present in nuts and oilseeds. These oil bodies are stabilized by a layer of phospholipids and embedded structural proteins, oleosins and caleosins

[11,80]. Stable oil-in-water emulsions can be formed by crushing the nuts/seeds in water and filtering the solution. Gallier and Singh [81] showed that the olesins were mostly hydrolysed by pepsin, resulting in a less negative zeta-potential of the oil bodies. Although some peptides and phospholipids remained at the interface, the oil bodies were flocculated. Walnut oil body dispersions also flocculated under gastric conditions [82] and followed the same pattern as almond oil bodies.

Recently, Wang, et al. [83] studied the in vitro gastric digestion of an almond dispersion (about 3% protein and 7% lipids) using the HGS. It was found that the decrease in pH resulted in flocculation of the oil bodies, and these flocculated oil bodies appeared to be entrapped within the protein aggregates. With further digestion, as the pepsin activity increased (because of the further drop in pH), the aggregated protein network disintegrated, which led to release of the oil bodies and eventually separation of the cream and water phases. The hydrolysis of interfacial proteins at later stages of digestion caused coalescence of the flocculated oil bodies; it appeared that peptides and the remaining phospholipids were not able to stabilize the oil body surface. This phase separation in the HGS dramatically affected the lipid content of the digesta emptied at different times.

3.1.2. Emulsion stability and gastric lipolysis

As the lipolysis reaction is dependent on the accessibility of the oil–water interface by gastric lipase, the droplet interfacial area (which is determined by the droplet size) has a marked influence on the extent of hydrolysis. Armand, et al. [84] showed, in both in vitro model and in vivo human studies, that lipid hydrolysis was faster in emulsions with a smaller average droplet size than in emulsions with a larger average droplet size; depending on the droplet size, the extent of TAG hydrolysis ranged between 5 and 37%. This TAG hydrolysis rate would be expected to decrease when the emulsion droplets undergo flocculation and coalescence, because of a decrease in the available lipid surface area for lipase binding. This phenomenon could also influence the access of gastric lipase to TAG within the lipid core.

However, it is not clear how the extent of gastric lipolysis affects the stability of emulsions. The surface activity of the emulsifier will play a role in determining whether or not the gastric lipase is able to adsorb on to the oil–water interface; the higher is the surface activity of the emulsifier, the lower is the potential for lipase adsorption. If gastric lipase is able to adsorb and penetrate at the interface, it will act on the TAG core, preferentially cleaving at sn3 ester bonds of the TAGs, resulting in NEFAs and DAGs. This lipolysis will lead to the accumulation of protonated NEFAs at the oil−water interface, which will competitively displace the original emulsifier from the interface. It is not clear how this process may impact emulsion stability.

A recent study by Infantes-Garcia, et al. [85] reported the gastric stability and digestion of emulsions stabilized by emulsifiers of different chemical natures [sodium taurodeoxycholate (ionic), soy lecithin (zwitterionic), Tween 80 (non-ionic), soy protein isolate and citrus pectin] in a static in vitro digestion model containing gastric lipase. As expected, the Tween-80-based emulsion was unaffected by the gastric acid environment, whereas the other emulsions showed flocculation and/or coalescence to varying degrees. In the case of the sodium-taurodeoxycholate-based emulsion, early instability in the gastric environment led to a low extent of gastric lipolysis. Interestingly, despite the good stability of the Tween-80-based emulsion, there was a limited extent of lipolysis because this emulsifier almost completely prohibited adsorption of the gastric lipase. The lecithin-based emulsion reached a significant extent of gastric lipid digestion (15%) because of its emulsion stability and an apparent moderate interfacial displacement of gastric lipase. From these results, it can be inferred that the extent of lipolysis in the gastric phase will decrease if emulsions are acid unstable and contain emulsifiers that inhibit the adsorption of gastric lipase. Interestingly, the different extents of gastric lipolysis observed in these systems did not significantly affect the lipolysis kinetics in the in-vitro intestinal phase [86].

3.1.3. Emulsion stability and gastric emptying

Gastric emptying is the process by which food contents leave the stomach and enter the duodenum for further digestion and absorption. This process involves stomach contractions (tonic and peristaltic), retropulsion and emptying. These events create strong shearing forces that facilitate grinding, mixing and re-emulsifying of the food particles with the gastric juices. The emptying starts when the pylorus opens and fluids and food particles smaller that 1–2 mm move from the stomach cavity to the duodenum, while retaining larger particles in the stomach for further processing [87]. In general, liquids empty from the stomach much faster than solids, but the bioregulation of gastric emptying is very complex and depends on several factors, including the volume, caloric content, nutritional content and viscosity of the food, the feedback from intestinal hormones, and the gender and age of the individual, among others [88]. For example, the emptying of low-caloric liquids tends to be very fast initially, followed by a slower late linear phase; however, in high-caloric liquids, a lag phase, which is driven mainly by the interactions between nutrients and small intestinal receptors that control the amount of nutrients entering the duodenum, can occur [88].

Phase separation of liquid foods, such as oil-in-water emulsions, also influences emptying. To date, some clinical trials with human volunteers have reported the gastric digestion dynamics using non-invasive techniques such as magnetic resonance imaging (MRI) and ultrasound for visualizing changes in the emulsion stability and the effect on gastric emptying and metabolic responses.

Cumulative evidence suggests that phase separation of emulsions in the stomach induces a faster gastric emptying because the aqueous phase empties first, which limits activation of the hormonal inhibitory mechanisms [2,89]. In a pilot human clinical study, the gastric behaviour and the effect on gastric emptying of acid-stable (Tween-80-stabilized) and acid-unstable (Span-80-stabilized) emulsions were investigated using echo-planar magnetic resonance. The emulsions had equal lipid contents and similar particle size distributions. Gastric emptying was significantly delayed when participants were fed with acid-stable emulsions compared with acid-unstable emulsions, which was associated with the acid-unstable emulsion being rapidly separated into a lipid layer and an aqueous phase within the stomach [90]. These gastric emptying findings were further confirmed by Marciani, et al. [91], who also demonstrated that an acid-stable emulsion emptied the stomach linearly, whereas an acid-unstable system was emptied exponentially (Fig. 5).

More recent studies indicate that emulsion stability and gastric emptying have a profound effect on postprandial lipaemia. In a study, emulsions designed to undergo different degrees of instability in the stomach (stable, flocculated, partially coalesced and coalesced) were tested in vitro and in vivo. The major factor controlling the rate of lipid digestion in vitro was found to be the droplet surface area available for lipase adsorption, which was governed by emulsion instability. In vivo (humans), the absorption of TAGs was affected only by large changes in the emulsion structure, being more evident in emulsions that showed extensive coalescence during gastric digestion [92]. The crystallinity of the lipid phase of emulsions (liquid versus solid) can also affect gastric emptying and lipid absorption. An MRI study comparing four emulsions (two acid-stable and two acid-unstable) demonstrated that the two acid-stable emulsions exhibited similar steady gastric emptying, a continuous increase in blood TAGs and the lowest hunger rating. For the acid-unstable emulsions (one with liquid lipids and one with solid lipids), the gastric emptying was different from that of the acid-stable emulsions but with some interesting differences in the TAG absorption profiles. Even when the acid-unstable liquid lipid emulsion underwent phase separation in the stomach, the absorption profile of the TAGs was similar to that of the acid-stable emulsions, indicating the strong effect of intragastric re-emulsification. In contrast, the TAG profile of the acid-unstable solid lipid emulsion was significantly lower, compared with those of the other emulsions, which suggests that oil droplets with a solid lipid core were more resistant to re-emulsification in the stomach.

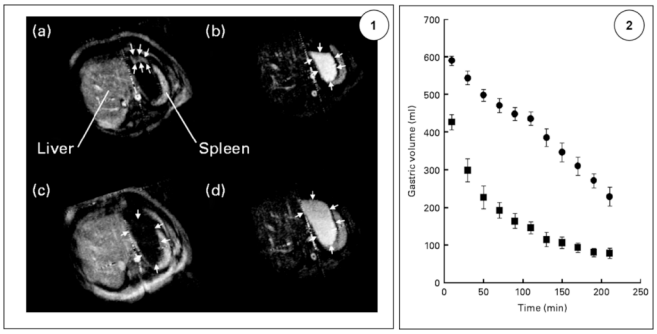

Fig. 5. 1) Echo-planar magnetic resonance images acquired across the body of the stomach of one volunteer at $t = 40$ min after ingestion of the acid-unstable fat emulsion meal (a and b) and the acid-stable fat emulsion meal (c and d). The imaging inversion time in (a) is set to null the bulk water phase of the acid-unstable meal and a fat layer (indicated by the white arrows) can be clearly seen floating on top of the stomach for this meal. In the corresponding image for the acid-stable meal (c) no fat layer is observed and the stomach contents yield a low fat background signal (indicated by the white arrows) that appears to be homogeneous. In (b) the imaging inversion time is set to null the fat layer of the acid-unstable meal. The bulk water phase (indicated by the white arrows) can now be seen very bright. In the corresponding image for the acid-stable meal (d) the bulk water phase, indicated by the white arrows, appears less bright than in (b). 2) Gastric emptying patterns (gastric meal volumes *v.* time) of (●) acid-stable and (■) acid-unstable emulsions as analysed by echo-planar magnetic resonance. The gastric half-emptying time of the acid-unstable emulsion meal was faster than that of the acid-stable emulsion. Adapted from Marciani, Faulks, Wickham, Bush, Pick, Wright, Cox, Fillery-Travis, Gowland and Spiller [91] with permission from Elsevier Inc.

[93]. A second study that compared the effect of these four emulsions on gastrointestinal hormone responses concluded that evenly dispersed, stable, small size emulsions within the stomach led to prolonged gastric distension (and longer grehlin suppression) and accelerated fat sensing (cholecystokinin and peptide YY), triggering more satiation [94].

3.2. Modulation of lipolysis in the small intestine

In the small intestine, the pancreatic lipase–colipase system is responsible for the hydrolysis of the majority of the emulsified lipids. The rate of lipolysis is fundamentally dependent on the accessibility of the cleavage site on the TAGs to the active site of pancreatic lipases. Thus, the available lipid surface area, the composition of the interface, the fatty acid composition and diffusion of the enzymes etc. affect the rate of lipid hydrolysis [36]. In simple emulsion systems, many of these parameters have been shown to influence the kinetics of lipid digestion (often measured as the release of NEFAs) in in vitro digestion systems. The uptake of hydrolysis products into mixed micelles and the subsequent transport of these micelles towards the site of absorption are key intraluminal factors in determining the rate of absorption of fatty acids. Much of this information has been covered extensively in other reviews (2,3,14). Here we highlight a few approaches that have been shown to influence the rate of lipid hydrolysis in emulsions, mainly in in vitro digestion models. These include altering the physical state of the lipid core in the emulsion, designing complex interfaces that reduce the access of lipolytic enzymes to TAGs and the presence of emulsion components that may interact with intestinal lumen secretions, such as bile salts and enzymes.

3.2.1. Physical state of oil in the emulsion

The physical state of the lipids within emulsion droplets (e.g. crystalline, liquid crystalline or liquid) has been shown to have an impact on the rate and the extent of lipid digestion, with emulsions containing a solid fat phase (at body temperature) showing lower digestion rates [95]. Guo, et al. [96] confirmed that the rate of lipid digestion in an in vitro intestinal model decreased exponentially with increasing solid fat content in whey-protein-stabilized emulsions, and that fat crystal polymorphism and crystallite size did not play a significant role in the rate and extent of lipolysis. They suggested that, in emulsions prepared using fully hydrogenated soybean oil (FHSO) or 7.5% FHSO and 2.5% soybean oil (SO), liquid oil was entrapped within the fat crystal network, whereas, in emulsions prepared using 5% FHSO and 5% SO or 2.5% FHSO and 7.5% SO, the fat crystals were embedded in the liquid oil. This difference in the microstructure of the dispersed oil/fat was considered to be an important factor influencing lipid digestion, i.e. the release of liquid oil trapped within the fat crystal network was delayed because of restricted movement of the droplets. The slow digestion of solid fats was ascribed to low accessibility of the ester bonds within the TAG crystals by pancreatic lipase. Another factor in the slow digestion of solid fat (versus liquid oil) could have been due to partial coalescence of the emulsified solid fat, which may have further retarded lipid digestion by decreasing the interfacial area of the oil phase [97]. In contrast, Jiao, et al. [98] reported that the solid fat content of crystalline palm stearin-in-water emulsions stabilized by sodium caseinate did not influence the extent of lipid digestion, but that the lipid digestion was closely related to the fat crystal size and the β polymorph content. The rate of release of NEFAs decreased as the fat crystal size and the content of β polymorphs increased, but there was no obvious relationship between NEFA release and fat crystal quantity or solid fat content. Clearly, further work to understand the fate of different physical states and structures of lipids during digestion is required.

There is also some in vivo evidence to indicate that TAGs in the solid state (e.g. FHSO) have lower bioavailability (in rats) than liquid TAGs (e.g. SO) because of the slow digestion of solid fat [99]. This is consistent with the lower blood TAG levels observed after the consumption of solid fat in human studies [93,97].

Gelation of the oil phase (oleogelation) has been shown to delay in vitro lipid digestion by altering the rigidity of the emulsified oil [100]. For example, recently Guo, et al. [101] used rice bran wax (RBX) as an oleogelator at concentrations of 0, 0.25, 0.5, 1 and 4 wt% in whey protein–soybean oil emulsions. They reported that the release of NEFAs was delayed during intestinal digestion at up to 1 wt% RBX addition, but that a further increase to 4 wt% enhanced the release of NEFAs; this was attributed to emulsion instability resulting from the growth of intra-droplet RBX crystals. Tan, et al. [102] reported that oleogels made from ethylcellulose suppressed an increase in plasma TAGs compared with palm oil or rice bran oil in a randomized, controlled, crossover human trial.

3.2.2. Nature of the oil-water interface

As discussed earlier, certain types of interfacial material can be used to produce gastric-stable emulsions, but it is a real challenge to create interfacial structures that are fully or partly resistant to intestinal conditions. The key objective is to control the kinetics of NEFA formation rather than to block the lipolysis process completely. Thus, an ideal interfacial structure would be expected to slow down the rate of diffusion of lipase and/or bile salts into the lipid core or to partly/fully resist its displacement by bile salts; this approach would still allow complete lipid digestion but over a much longer digestion time.

It is generally agreed that monolayered adsorbed films formed with conventional emulsifiers (low-molecular-weight emulsifiers and amphiphilic biopolymers) have a minor influence on the lipolysis rates in the intestinal environment. However, there are a few exceptions: monolayers of galactolipid digalactosyldiacylglycerol have been shown to reduce the lipolysis rate compared with lecithin from egg yolk because of inhibition of bile salt adsorption via steric hindrance. Poloxamers (e.g. Pluronics) are non-ionic high-molecular-weight brush-like emulsifiers. Emulsions formed with Pluronic F127 were shown to undergo relatively slow lipolysis (≈ 15% degradation over 120 min of intestinal digestion), as this surfactant was not easily displaced from the oil–water interface by bile salts and pancreatic lipase, because of low

interfacial tension, high interfacial coverage and a sterically stabilized interfacial layer [103].

It is logical to assume that more compact, thicker interfacial structures may be more protective against lipolysis, and this can be achieved by building multilayers on top of the first adsorbed layer. A greater number of layers will provide steric hindrance and will increase the distance over which the enzymes and bile salts need to diffuse. A vast amount of information on the in vitro intestinal lipolysis of multilayered emulsion systems has been published, but it is difficult to reach a definitive conclusion because of the broad range of experimental conditions (e.g. enzyme/substrate/bile salt concentrations) used in different studies. It appears that electrostatically adsorbed multilayers (formed at acid pH) readily disintegrate under intestinal conditions and may be suitable only for providing gastric stability. For example, multilayered interfaces formed from whey protein, pectin and chitosan or gelatin and pectin interfaces had the same rate of fatty acid release during in vitro intestinal digestion [62,104].

Emulsions stabilized with protein particles have been shown to undergo slightly slow lipolysis in the intestinal model. For example, interfacial layers that were stabilized by enzymatically modified soy protein particles [105], whey protein microgels [64] or kafirin particles [106] had a reduced degree of lipolysis under in vitro intestinal conditions because the protein-particle-laden interface resisted the displacement of bile salts. However, protein-particle-based interfaces are gradually eroded because of hydrolysis by intestinal proteases, and lipase is generally able to diffuse through the holes in the interface. In contrast, interfaces formed with non-digestible materials, such as chitin particles and nanocrystalline cellulose, can suppress the lipid digestion of oil-in-water emulsions [65]. Another notable approach is to exploit the swelling and recrystallization properties of starch granules at the interface to create a barrier against lipolysis [107]. Oil-in-water emulsions stabilized by starch granules were subjected to heat treatment under different conditions to form a dense layer around the oil droplets that had the ability to prevent lipase transport through the starch barrier layer.

The most successful approach to influencing the lipolysis rate has involved trapping or encapsulation of emulsion droplets into microgels, often consisting of protein and/or polysaccharides [108]. For example, Li, et al. [109] observed, in both in vitro and in vivo models, a significant reduction in the extent of lipolysis and lipid absorption when whey-protein-stabilized oil droplets were trapped within alginate hydrogel beads (d_{43} = 510 μm). Pickering emulsions stabilized by kafirin nanoparticles and then incorporated into a sodium alginate gel (1.5% *w*/w of alginate crosslinked with 1% Ca^{2+}) showed that the rate of lipid digestion was retarded, especially at the early stage of intestinal digestion [110]. Comparison of emulsion-filled alginate beads with carrageenan beads indicated that the carrageenan beads had a relatively fragile structure that was easily disrupted in the intestinal environment, with the release of the encapsulated lipid droplets, whereas the alginate beads had a robust structure that remained relatively intact [111]. Consequently, the rate and extent of lipid digestion decreased in the following order: free lipid droplets > carrageenan beads > alginate beads. Corstens, Berton-Carabin, Elichiry-Ortiz, Hol, Troost, Masclee and Schroen [108] produced stable beads of different sizes (0.55, 0.78 and 1.15 mm) and mesh sizes (ξ = 9.2, 6.4 and 5.4 nm) using ionotropic (Ca) gelation of alginate-containing oil-in-water emulsions ($d_{32} \approx 21$ μm). Lipolysis could be controlled through variation of the bead and mesh sizes, resulting in a broad range of release profiles: from 1 to 50% release after 1 h to 20–80% release after 2.5 h.

Overall, the structural rigidity, porosity and tortuosity of the microgel matrix encapsulating the emulsion droplets determine the rate of diffusion of lipase and bile salts to the surfaces of oil droplets. In addition, direct interactions between the matrix material and pancreatic lipase or bile salts may play a role in determining the lipolysis rate. Combining the information from various studies, it can be concluded that the hydrolysis of TAGs by pancreatic lipase might be controlled by designing interfaces that are capable of resisting bile salt displacement and lipase diffusion. However, it is worth noting that many of the effects seen in simple in vitro systems may not be seen in vivo in humans. Moreover, most fabricated emulsion systems would be difficult to incorporate into real food systems, as they would be affected by food processing operations and consequent interactions with other food components.

3.2.3. *Interactions of emulsion components with intestinal lumen secretions*

In addition to providing a protective interfacial layer to control the rate of lipid digestion, it is possible to select other components of emulsions that are able to bind to digestive enzymes (such as lipase) and bile salts, thereby reducing their ability to adsorb to the droplet surface and to solubilize and transport the lipid digestion products. Another approach is to increase the viscosity of the intestinal lumen by adding thickening or gelling agents in the continuous phase, which not only will retard the transport of enzymes towards the emulsion droplet but also will slow down diffusion of the resulting digestion products (e.g. mixed micelles) towards the epithelial cell wall for absorption. Some of key interactions of emulsion components within the intestinal lumen, which affect lipid digestion and absorption are depicted in Fig. 6. For example, components that bind pancreatic lipase and slow down the rate of lipolysis, bile salts chelators that reduce their efficacy during lipolysis, and the formation of insoluble soaps between NEFAs and calcium.

3.2.3.1. Pancreatic lipase inhibitors. Certain food-grade compounds are known to bind to pancreatic lipase and inhibit its activity. This field has been extensively researched in the continuing search for effective agents/drugs for obesity and weight management [112–114]. Extracts from hundreds of species of plants, microorganisms, fungi and marine algae are being studied for potential lipase inhibitory activity (see reviews above). In the food context, some lipase inhibitors of plant origin

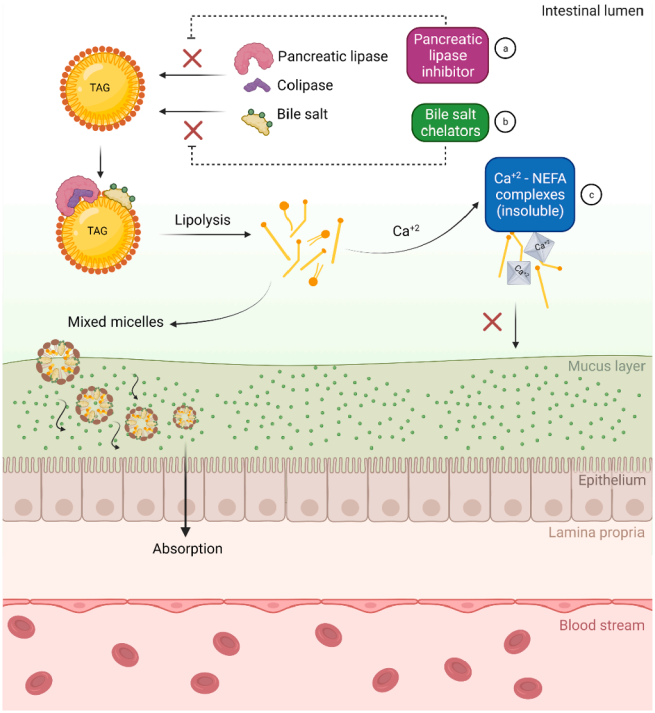

Fig. 6. Interactions of emulsion components with intestinal lumen secretions; lipid digestion kinetics in emulsions can be controlled by a) including components that inhibit pancreatic lipase activity b) the presence of compounds that chelate bile salts, reducing their efficacy and c) adding calcium to form insoluble calcium-fatty acid soaps which are not absorbed. Adapted from "*Helicobacter pylori* infection", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates

are of interest, including soybean proteins [115], protamine [116], ovalbumin and β-lactoglobulin [117]. Other lipase inhibitors from plant origin include basic polysaccharides, especially chitosan oligosaccharides, water-soluble chitosan (46 kDa) and polydextrose when a basic group is introduced [118], phytic acid and other myo-inositol phosphate esters [119]. Many polyphenols, including flavones, flavonols, tannins and chalcones, have been shown to have an inhibitory action on pancreatic lipase [120]. Some examples are proanthocyanidins from edible herbs, such as those from *Cassia mimosoides* [121], and tea catechins, especially (−)-catechin gallate and (−)-gallocatechin gallate [122]. Some of these compounds with lipase inhibitory activities could potentially be incorporated in food emulsions/formulations to develop functional foods for the treatment of obesity and weight control. More research to investigate the feasibility of incorporating these compounds into foods and to define the optimal dose is needed. Their fate during gastrointestinal processing, along with their mechanism of action and possible side or toxic effects, will need to be addressed.

3.2.3.2. Bile acid chelators. Similar to the lipase inhibitors, several food components that can bind to bile acids, reducing their effectiveness in the lipid digestion process, have been identified [123]. For example, cationic chitosan molecules bind anionic bile salts strongly, involving electrostatic interactions between the sulphated head-group of the bile salts [sodium taurocholate (NaTC)] and the ammonium ion in chitosan [124]. Pectin has been shown to reduce the rate and extent of lipid digestion via its binding to bile acids, which reduces the level of surface-active components available to form/stabilize lipid droplets, alters the interfacial composition and solubilizes/transports lipid digestion products [125].

Non-ionic cellulose ethers [methylcellulose (MC), hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC)] have been shown to interact with bile salts [sodium taurodeoxycholate (NaTDC) and NaTC], as revealed by micro-differential scanning calorimetry and rheology under neutral pH conditions [126,127]. A nuclear magnetic resonance study confirmed interactions between a model bile salt (NaTC) and HPMC in simulated intestinal media [128]. Interactions between the bile acid and HPMC molecules appeared to be driven by hydrophobic interactions. Certain food proteins have been shown to interact with bile salts, but no details on molecular mechanisms have been reported. In vitro studies on soy protein isolate and wheat gluten have reported bile acid binding capacities of 17 and 12% respectively under duodenal pH conditions. Acid-soluble lupin protein isolate and corresponding hydrolysates have been shown to bind different bile acids to a greater extent than their soy protein counterparts [129]. Highly hydrophilic and non-ionic biopolymers, such as β-glucan and arabinoxylan, are known to form locally entangled, viscous polymer networks, reducing the mobility and mixing of gastrointestinal components, including bile salts and digestive enzymes [130]. It must be pointed out that, during the digestion process, some of these food polymers are likely to simultaneously interact with many components of the intestinal lumen, including bile salts and enzymes, making it difficult to pinpoint their mechanism of action exactly.

3.2.3.3. Fatty acid and calcium interactions. The calcium content and its ionic state are known to play a crucial role in lipid digestion in oil-in-water emulsions, involving fatty acid-calcium interactions [131]. Several in vitro studies on simple emulsion systems have shown that an increase in the calcium concentration promotes the rate and extent of lipid digestion in the small intestinal phase [132–134]. Soluble calcium salts, such as calcium gluconate, calcium acetate and $CaCl_2$, had greater effects on the rate and extent of NEFA release than did insoluble salts, such as CaO and $CaSO_4$, suggesting that the ionic state of calcium plays a critical role in lipid digestion in emulsions [133]. The sequestering of ionic calcium by ethylenediaminetetraacetic acid, high-methoxyl pectin and alginate has been shown to cause a substantial decrease in the lipid digestion rate [134].

In protein-stabilized emulsions, it is important to consider the effect of added calcium on the state of the emulsion droplets. Ye, Cui, Zhu and Singh [133] showed that the addition of calcium to emulsions stabilized by whey proteins and caseinate induced flocculation and aggregation of the droplets, leading to a decrease in the surface area. This reduction in surface area contributed to a lower lipid digestion rate. Similar effects were observed by Li, et al. [135] in a β-lactoglobulin-stabilized emulsion; high levels of calcium induced extensive flocculation, resulting in reduced lipolysis. The effect of calcium on lipolysis by pancreatic lipase is attributed to calcium complexing with NEFAs produced from the lipolysis of TAGs to form calcium soaps, which are insoluble under intestinal conditions; this process increases the removal of NEFAs from the interface to the aqueous phase in the form of calcium soaps, enhancing the access of substrate to the lipase. Therefore, the addition of calcium increases the rate of lipolysis, but the poor solubility of the calcium–fatty acid soaps could reduce lipid bioaccessibility and absorption [136]. Several human studies have shown that increased dietary calcium intake leads to increased faecal fat excretion, indicating that fatty acid absorption is somehow impaired by calcium [131]. The main mechanism behind the fat excretion is also suggested to be the formation of insoluble calcium–fatty acid soaps that are poorly absorbed [137].

The observations from the above studies indicate that the lipid digestion pathways of model emulsions can be manipulated under intestinal conditions by modifying some of the structural characteristics of emulsions. However, there are relatively few in vivo studies to validate these findings.

4. Food emulsions and postprandial lipaemia

Most human clinical studies have focused on the effects of whole foods or food matrices containing lipids in different states of dispersion. In these studies, it is difficult to distinguish the effect of emulsion droplet structure from the surrounding food matrix effect. These studies indicate that the nature of the food matrix influences the rate and the extent of lipid release during digestion and postprandial lipaemia. For example, the increase in postprandial lipaemia was much lower following the consumption of a meal containing whole almond seed or walnut macroparticles, in which the oil bodies are intact and embedded within the cell matrix, than following the consumption of almond or walnut oil mixed with defatted almond or walnut flour [138,139]. These effects are largely related to the integrity of cell walls and lipid encapsulation in seed particles, which create a physical barrier to access of digestive enzymes.

A clinical trial with type-2 diabetic patients compared three different meals with similar volumes and compositions but with the main source of lipid represented by foods with different physical structures (milk, Mozzarella cheese and butter). Even when there was no difference in the magnitude of postprandial lipaemia among the meals, the increase in TAGs was delayed after consumption of the meal with butter compared with the other two meals, suggesting the food structure plays an important role in the time course of TAG increase in the blood [140]. The authors attributed these differences to the fact that the lipid droplets in cheese and milk are present as small fat globules, whereas the lipid fraction in butter is shown as large aggregates that may require a longer time for hydrolysis [140]. These findings were later confirmed by Drouin-Chartier, et al. [141], who compared the impact of the cheese matrix on postprandial lipaemia through a human clinical intervention trial. Cheddar cheese, cream cheese and butter (as the control) were compared, and the increases in plasma TAGs were determined. Although all products induced similar increases in TAG concentration after 4 h, the TAG response at 2 h caused by cream cheese consumption was greater than that induced by butter and Cheddar cheese consumption.

Similarly, Vors, et al. [142] demonstrated the impact of the physical state of milkfat consumption on postprandial lipaemia in a trial with obese human participants who were fed 40 g of milkfat, either

emulsified (in skim milk) or non-emulsified (milkfat spread), through breakfasts with identical compositions and caloric contents. The emulsified milkfat meal led to earlier and sharper chylomicron and fatty acid peaks in the plasma than the non-emulsified milkfat meal, which indicated that the postprandial metabolic handling of fatty acids can be greatly modified by emulsifying the lipids.

A recent study from our group investigated the impact of food matrix on postprandial lipaemia, comparing three fabricated foods with emulsified lipids (chocolate cookie, chocolate drink and chocolate pudding) and with the same nutrient compositions and energy contents [143]. The digestion behaviours of the test foods were assessed using a dynamic in vitro digestion model, whereas the postprandial lipaemic response was assessed in a human clinical trial with healthy participants. The results showed that the solid food (chocolate cookie) presented phase separation during in vitro gastric digestion, which affected gastric emptying rates of lipids, resulting in a much lower release of lipids to the small intestinal phase, compared with the liquid (chocolate drink) and the semi-solid food (pudding). The cookies also caused a lower increase in plasma TAGs than the chocolate drink and pudding and produced higher fullness and satisfaction. These findings suggested that the form and the structure of a food not only modulate the lipid release and postprandial lipaemia but also control the appetite sensations regardless of the nutrient and energy contents of the food.

5. Conclusions and future directions

During the last decade, significant advances in our understanding of the biophysical and physiological processes involved in lipid digestion have been made. In particular, there is a growing body of knowledge of how different food emulsion systems interact with a range of biochemical and biophysical environments in the GIT. This has led to the possibility of designing emulsions with specific structures and properties that can alter the rate of lipid digestion, transport and absorption. From the available knowledge, it appears that food emulsions can be designed to achieve considerable differences in lipid digestion although, to date, this has almost exclusively been applied to relatively simple model systems and in in vitro digestion models. Much effort has been devoted to altering the interfacial layers of emulsions to modulate lipid digestion, but, because of the high surface activity of bile salts, most of these approaches have shown limited success. Encapsulation of emulsion droplets within hydrogel particles appears to delay lipid digestion, but this approach is likely to have limited application in real foods. The manipulation of the physical state and internal structure of oil droplets by changing the ratio of solid lipid to liquid lipid appears to be a possible strategy to delay lipid digestion, but these systems may result in a portion of the lipid (solid, crystalline fat with a melting point above body temperature) to be completely non-digestible. The physiological consequences of the exposure of these undigested lipids to the large intestine need to be understood before this knowledge can be used in food formulations. Moreover, the incorporation of saturated and restructured lipids into foods would not be desirable from a human health perspective.

In practice, the most feasible strategy to delay lipid digestion is to control the stomach emptying rate of lipids, which is largely affected by interactions of emulsion droplets with the food matrices. Food matrices with different responses to the gastric environment and with different interactions between oil droplets and the food matrix can be designed to influence lipid digestion. In this respect, more systematic studies to characterize the gastric behaviour of different food materials and natural foods in relation to the gastric partitioning and emptying of macronutrients are required. This should be undertaken using more advanced dynamic in vitro methodologies that can accurately monitor the emptying of the gastric components.

As alluded to in this review, large differences have been reported in the data obtained from static in vitro digestion models and dynamic in vitro digestion models and the limited data from in vivo studies. Human in vivo studies are needed to validate these models as well as the different in vitro approaches used in modulating lipid digestion.

It must be noted that the vast majority of foods are multiphase mixed dispersed systems containing many additional components. In these systems, the emulsion is just one of the ingredients and it can participate in forming the structures of more complex products; that is, other components of the food (proteins, polysaccharides) form a matrix in which the emulsion droplets are trapped or with which they interact (e.g. yoghurts, processed cheeses and other gelled systems). There is limited understanding of how emulsion structures that are designed to control lipid digestion behave and interact in these complex systems. One of the future challenges will be to ensure that the digestion characteristics and the design of emulsions are robust and can ultimately be maintained during the processing and storage of complex foods: in other words, to ensure that the emulsion system, a part of the complex mix, has the desired functionality in the body. Alternatively, a more holistic approach could be applied whereby interactions between various components of the complex food system could be manipulated to alter the behaviour of emulsified droplets during digestion.

Ultimately, an understanding of the complexity of lipid digestion processes in connection with food systems will lead to the development of functional foods that have specific lipid digestion profiles (indicated by postprandial lipaemia). These foods will, in turn, have specific physiological responses, providing health benefits (e.g. management of satiety, weight control and prevention of cardiovascular diseases). Further human clinical studies to examine the long-term health benefits associated with delayed or controlled lipid digestion are required.

Credit

AAF: writing – original draft, editing, artwork design. HS: conceptualization, funding acquisition, writing – original draft, writing – review.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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