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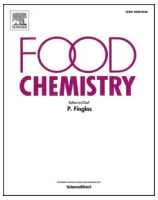

Review

Controlled lipid digestion in the development of functional and personalized foods for a tailored delivery of dietary fats

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ABSTRACT

In recent decades, obesity and its associated health issues have risen dramatically. The COVID-19 pandemic has further exacerbated this trend, underscoring the pressing need for new strategies to manage weight. Functional foods designed to modulate lipid digestion and absorption rates and thereby reduce the assimilation of dietary fats have gained increasing attention in food science as a potentially safer alternative to weight-loss medications. This review provides insights into controlled lipid digestion and customized delivery of fats. The first section introduces basic concepts of lipid digestion and absorption in the human gastrointestinal tract. The second section discusses factors regulating lipid digestion and absorption rates, as well as strategies for modulating lipid assimilation from food. The third section focuses on applications of controlled lipid digestion in developing personalized foods designed for specific consumer groups, with particular emphasis on two target populations: overweight individuals and infants.

1. Introduction

The global rise in obesity has become a critical public health issue, with prevalence nearly tripling since 1975 (Lobstein et al., 2022). The COVID-19 pandemic has further exacerbated this trend, leading to increased mortality and morbidity (Jha et al., 2022). According to the World Health Organization (WHO), over 1 billion people worldwide were classified as obese in 2022 (Boutari & Mantzoros, 2022). Projections from the World Obesity Federation indicate that more than half of the world's population will be overweight or obese by 2035 if no preventive measures are taken. To halt this alarming trend, significant resources and research efforts have been directed toward innovative approaches in food science, focusing on developing optimized formula foods that can reduce dietary lipid intake. Rather than relying on pharmacological approaches to treating obesity (e.g., anti-obesity drugs) (Yongqi Guo et al., 2009), which often come with severe side effects such as an increased occurrence of cancer (reported for lorcaserin-based weight-loss medications), serious cardiovascular

Abbreviations: 2-MG, 2-Monoglyceride; Asp, Aspartic Acid; BMI, Body Mass Index; BSSL, Bile Salt-Stimulated Lipase; CaCl2, Calcium Chloride; CCK, Cholecystokinin; CEH-BSSL, Cholesterol Ester Hydrolase-Bile Salt Stimulated Lipase; CITREM, Citric Acid Esters of Mono- and Diglycerides; CMC, Critical Micellar Concentration; DATEM, Diacetyl Tartaric Acid Ester of Mono- and Diglycerides; DAG, Diacylglycerols; EFSA, European Food Safety Authority; EGCG, Epigallocatechin Gallate; FDA, Food and Drug Administration; FFAs, Free Fatty Acids; GI, Gastrointestinal; GIT, Gastrointestinal Tract; Glu, Glutamic Acid; HDL, High-Density Lipoprotein; HGL, Human Gastric Lipase; HIPE, High Internal Phase Emulsion; HPL, Human Pancreatic Lipase; IL-6, Interleukin-6; LbL, Layer-by-Layer; LLC, Lyotropic Liquid Crystals; NaCl, Sodium Chloride; O/W, Oil-in-Water; PAI-1, Plasminogen Activation Inhibitor-1; PGA, Propylene Glycol Alginate; pI, Isoelectric Point; pKa, Acid Dissociation Constant; PLA2, Pancreatic Phospholipase A2; PLRP1/PLRP2, Pancreatic Lipase-Related Proteins 1/2; PUFA, Polyunsaturated Fatty Acids; PYY, Peptide YY; Ser, Serine; SFA, Saturated Fatty Acids; SLS, Sodium Lauryl Sulfate; TAG, Triglyceride (Triacylglycerol); TNF-α, Tumor Necrosis Factor α; W/O, Water-in-Oil; WHO, World Health Organization; WPI, Whey Protein Isolate; β-LG, Beta-Lactoglobulin.

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events (associated with sibutramine and semaglutide, the active ingredient in Ozempic), or pulmonary hypertension and valvulopathy (linked to fenfluramine) (Bashir and Weaver, 2017; de la Garza et al., 2011; Tchang et al., 2024), there is growing interest in functional foods designed to modulate lipid assimilation by targeting fat digestion or absorption in the gastrointestinal tract. Functional foods can be designed not only to manage weight, but also to tailor lipid intake for specific consumer groups, including infants, pregnant women, athletes, the elderly, and individuals with metabolic conditions, to meet their distinct nutritional needs and address metabolic variations. For instance, personalized food products engineered to enhance lipid assimilation can effectively improve the nutritional status of consumers who would benefit from a high supply of easily digestible lipids, such as infants or patients suffering from diseases that impair lipid digestion and absorption (e.g., lipoprotein lipase deficiency or cystic fibrosis). The processes involved in lipid assimilation are complex and rely on an intricate interplay of events occurring in the mouth, stomach, and small intestine. By targeting different stages of these processes, researchers seek to create tailored dietary interventions capable of optimizing the extent and kinetics of fat digestion/absorption based on the specific nutritional needs of the individual.

Researchers are exploring a wide range of innovative strategies, including the use of advanced emulsion systems with optimized compositions and complex interfacial layers (Borreani et al., 2017; Sarkar et al., 2019; Tzoumaki et al., 2013; Espinal-Ruiz et al., 2014; Y. Tan et al., 2020; R. Zhang et al., 2019), lipid encapsulation and entrapment in hydrogels (Q. Guo et al., 2016, Guo et al., 2017a; X.-M. M. Li et al., 2021; Sarkar et al., 2016; Farooq et al., 2022), stimuli-responsive lipid delivery systems (Frigerio et al., 2024), inducing flocculation, and the incorporation of pancreatic lipase inhibitors (Kumar & Chauhan, 2021; Granato et al., 2020; Hu et al., 2022; Lin et al., 2021; Yang et al., 2022; Y. Zhang et al., 2023; Zhou, Wang, et al., 2021), bile acid chelating agents (Eluppai Asthagiri Kumaraswamy et al., 2024; Guardiola-Márquez et al., 2020; Massa et al., 2022; Singla et al., 2024; Torcello-Gómez et al., 2015), metal cations (Golkar et al., 2018; A.-I. Mulet-Cabero & Wilde, 2021; Pan et al., 2020; Acevedo-Fani & Singh, 2022), amphiphilic lipids (Engstedt et al., 2023; Freire et al., 2022; Manca et al., 2022; Shao et al., 2018), and fat replacers (Joyce et al., 2020; Kishibuchi et al., 2018; O'Connor & O'Brien, 2021; Syan et al., 2024). These advanced food technologies are expected to drive the development of healthier food options that can effectively address the growing concerns related to obesity and metabolic disorders in the near future. Designing such advanced functional foods demands a thorough understanding of the mechanisms governing lipid digestion and absorption, as well as the key factors shaping these processes. It also requires comprehending the kinetics of these processes and recognizing the individual metabolic variations across diverse consumer groups with specific dietary needs.

This review explores the concept of controlled lipid digestion and its significance in developing functional and personalized foods for tailored delivery of dietary fat. The first section provides insight into the mechanisms of lipid digestion and absorption in the human gastrointestinal tract. The second section discusses the key factors influencing lipid assimilation and strategies used to regulate this process. Finally, the third section focuses on the applications of controlled lipid digestion in the development of functional and personalized food formulations, with particular emphasis on two consumer groups: individuals seeking weight management solutions and infants.

2. Lipid digestion and absorption

Dietary fats comprise a complex mixture of lipids, with triglycerides constituting approximately 97 %. Triglycerides, also known as triacylglycerols, are esters formed from glycerol and free fatty acids. Their molecular structure consists of three fatty acid chains bonded to the glycerol backbone, as illustrated in Fig. 1. Triglycerides are typically ingested in large aggregates such as oil droplets or fat crystals. Since lipolytic enzymes (lipases) exert their catalytic function at the oil-water emulsion interface formed between the aqueous environment of the gastrointestinal tract lumen and lipid droplets (McQuilken, 2021a; McQuilken, 2021b), ingested fat needs to be emulsified before enzymatic breakdown can occur. During mastication and digestion, large lipid aggregates are broken down into micro- or nanodroplets, known as mixed micelles. This process enables lipolytic enzymes to access lipid molecules and increases the surface area available for enzymatic degradation. The key enzymes responsible for lipid breakdown are lingual lipases, gastric lipase, and colipase-dependent pancreatic lipase (Golding & Wooster, 2010; Sun et al., 2022). Other enzymes involved in lipid digestion include hepatic lipase, endothelial lipase, lipoprotein

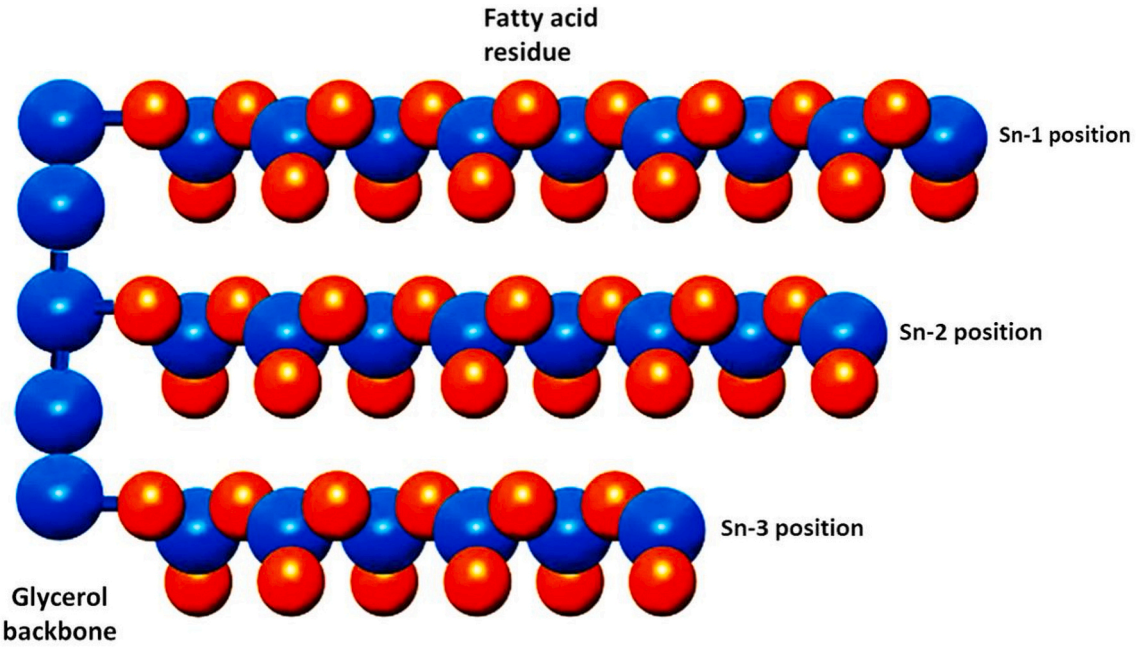

Fig. 1. Triglyceride molecule. Triglyceride molecules are composed of three fatty acid residues attached to the glycerol backbone at one of three positions: sn-1, sn-2, or sn-3.

lipases, bile salt-stimulated lipase (CEH, BSSL), pancreatic lipase-related protein 2 (PLRP2), pancreatic phospholipase A2, and carboxyl ester hydrolase, however, their role in lipid digestion is minor (Kumar & Chauhan, 2021).

The digestion process begins in the mouth, where the food is finely ground by the teeth and mixed with saliva. A small portion of lipids is broken down at this stage due to the action of lingual lipases. Once the food bolus formed in the mouth arrives in the stomach, it undergoes further breakdown by peristalsis and hydrochloric acid, facilitating the release of lipids from food matrices and further emulsification (McClements, 2018). Gastric lipase partially digests dietary triglycerides in the stomach (Golding & Wooster, 2010), however, the majority of lipid digestion takes place in the small intestine, where pancreatic lipase plays a crucial role (Golding & Wooster, 2010; Sun et al., 2022). The next four sections will delve into various stages of lipid assimilation, covering oral, gastric, and intestinal phases of lipid digestion and lipid absorption.

2.1. Oral stage of lipid digestion

During the oral stage of lipid digestion, chewing creates mechanical forces that break down food particles, mix them with saliva, and begin emulsifying lipids. Chewing also stimulates the secretion of lingual lipase by Von Ebner's serous glands found close to the foliate and circumvallate papillae of the tongue (Kulkarni & Mattes, 2014). The catalytic activity of lingual lipase relies on the hydrolysis of ester bonds between the fatty acid and glycerol moieties of dietary triacylglycerols producing monoglycerols, diacylglycerols, and nonesterified fatty acids (Iqbal & Hussain, 2009). Furthermore, lingual lipase aids in emulsifying lipids by coating lipid droplets and preventing them from coalescing. Lingual lipase, similar to other human lipases such as gastric, pancreatic, hepatic, endothelial, and lipoprotein lipases, exhibits serine esterase activity and is classified within the α/β hydrolase superfamily (Kumar & Chauhan, 2021). One key feature shared by enzymes in this family is the presence of the α/β hydrolase fold, a core domain consisting of eight β-sheets interconnected by α-helices (Canaan et al., 1999).

The catalytic function of lipases depends on a nucleophilic serine residue that is part of a catalytic triad (Ser-His-Asp/Glu) and an oxyanion hole formed by NH groups of Gln/Leu residues (Chongyang Wang et al., 2023). The catalytic serine residue is situated within a structural feature known as the nucleophilic elbow. Serine residue is shielded by the extension domain, which includes a mobile "lid" domain and a "cap" domain. This extension domain plays a key role in the enzyme's interaction with the lipid substrates. The lid domain exhibits an amphipathic nature. In the closed (inactive) state, the active site serine remains concealed by the extension domain. In this conformation, the hydrophilic side of the lid is oriented toward the surrounding digestive milieu, while the hydrophobic side is directed inward toward the catalytic site. Upon activation, the lipase undergoes a conformational change where the lid domain is displaced, transitioning the enzyme to an "open" state that allows hydrophobic substrates to access the active site (Canaan et al., 1999). The previously shielded hydrophobic face of the lid becomes exposed, facilitating the binding of the enzyme to the water-oil interface.

Lingual lipase's role in lipid digestion is typically minor in healthy adults, as the bulk of lipid breakdown takes place in the small intestine. However, its significance increases notably in infants, where pancreatic lipase activity is reduced compared to adults (Poquet & Wooster, 2016). In infants, lingual lipase can digest milk fat globules, in contrast to pancreatic lipase. Lingual lipase also assists in breaking down fats in adults with diminished levels of pancreatic lipase due to conditions like pancreatic insufficiency, cystic fibrosis, or alcoholic pancreatitis.

2.2. Gastric stage of lipid digestion

The stomach plays a crucial role in emulsifying dietary lipids, powered by the mechanical forces of peristaltic waves that cause rhythmic contractions approximately three times per minute (Patel & Thavamani, 2023). Both lingual lipase and human gastric lipase (HGL) contribute to the enzymatic breakdown of lipids in the stomach, however, this stage of lipid digestion relies primarily on the catalytic activity of HGL. Gastric lipase is secreted by the chief cells located in the fundic part of the stomach (Miled, 2000). Its secretion is stimulated by the gastrointestinal hormone gastrin, and other signals such as stomach motion, cholinergic stimuli, and meals. This enzyme hydrolyzes approximately 10–30 % of dietary triglycerides.

HGL is a 50 kDa globular protein made up of 379 amino acids (Maldonado-Valderrama et al., 2011; Sams et al., 2016). Structurally, HGL comprises a core globular domain, with α/β hydrolase fold, which contains eight β-sheets connected by α-helices, and a lid domain composed of 58 amino acids (residues 210–267), articulated around two α-helices (Canaan et al., 1999). The lid domain covering the active site contains a hydrophobic region composed of 29 amino acids (residues 215–244) involved in the binding of substrate.

Similar to lingual lipase, the catalytic activity of HGL relies on a hydrolytic activity of a serine residue in the classical catalytic triad (Ser 153-His 353-Asp 324), as well as an oxyanion hole that involves the NH groups of Gln 154 and Leu 67. During hydrolysis, HGL exhibits stereopreference for the ester bonds at either the sn-1 or sn-3 position in triglyceride molecules (Rogalska et al., 1990). Apart from triglycerides gastric lipase can also hydrolyze diglycerides, monoglycerides, mono- and di-esters of polyethylene glycols, but cannot break down phospholipids or cholesterol esters (Sams et al., 2016). As the lipid hydrolysis progresses, the catalytic action of HGL gradually diminishes due to the accumulation of lipolysis products. Free fatty acids, accumulating at the oil-water interface, and a decrease in gastric pH below optimal values limit the hydrolysis rate. Inhibitory concentrations of free fatty acids (2–5 mmol/L) are typically reached after 1 h of gastric digestion (Armand et al., 1999; Lairon, 2009).

Gastric lipase displays unique properties to the point of being considered an extremophile enzyme. It is highly resistant to the acidic conditions of the stomach, resisting pH values between 1.0 and 7.0, with optimal activity occurring at pH 5.0–5.4. After meal consumption, the pH of the stomach contents typically falls within a range of 5.5 to 7.0, depending on the meal's composition. Following this, gastric acid secretion leads to a decrease in pH. Gastric emptying also plays a role in lowering pH by removing the contents of the stomach and reducing their buffering effects. Approximately 1 h after a meal, intragastric pH levels are usually between 4 and 5 (Müller & Petry, 2006). The acidic conditions of gastric juice facilitate the binding of gastric lipase to the oil-water interface, which is a rate-limiting factor of hydrolysis, and enhance the enzymatic activity of HGL (Sams et al., 2016). Once the stomach contents move into the duodenum, where the pH is higher, gastric lipase can continue its hydrolytic action (Sams et al., 2016).

A peculiarity of gastric lipase lies also in its resistance to physiological concentrations of bile salts, which inhibit most other lipases by competing for access to the substrate molecules at the oil-water interface. Gastric lipase behaves like a surfactant, being able to adsorb to the oil-water interface independently, likely due to its amphiphilic nature (Sams et al., 2016). Gastric lipase shows also resistance against the proteolytic activity of pepsin. This property is related to the HGL molecular structure, which lacks specific cleavage sites for pepsin.

By emulsifying lipids and altering the composition of the oil-water interface, the gastric phase of lipid digestion not only helps to assimilate dietary lipids but also facilitates the subsequent digestion stage, carried out by pancreatic lipase in the small intestine (Golding & Wooster, 2010). Additionally, the release of free fatty acids stimulates cholecystokinin (CCK) receptors in the duodenum, which control gastric emptying rate and stimulate secretion of pancreatic lipase and bile. The importance of preduodenal lipid digestion is evident in individuals with pancreatic deficiency who suffer from low bicarbonate and pancreatic lipase secretion. For these individuals, lipid digestion depends solely on

gastric lipase. Studies in individuals suffering from severe exocrine pancreatic insufficiency have demonstrated that HGL alone can achieve around 30 % of lipid digestion (Layer & Keller, 2005). Gastric lipase plays also a particularly important role in lipid digestion in infants who still have immature gastrointestinal tracts. In infants, pancreatic lipase secretion is insufficient to meet physiological requirements with gastric lipase being the main enzyme responsible for the breakdown of triglycerides (Ko et al., 2020).

2.3. Intestinal stage of lipid digestion

Dietary triglycerides that have not been digested by HGL, accounting for 70–90 % of the ingested lipids (Kumar & Chauhan, 2021; Maldonado-Valderrama et al., 2011) enter the small intestine, where colipase-dependent human pancreatic lipase (HPL) and bile salts play pivotal roles (Golding & Wooster, 2010; Sun et al., 2022). The lipid molecules leaving the stomach and entering the duodenum induce the secretion of cholecystokinin (CCK), a hormone that stimulates the gallbladder to release bile (di Gregorio et al., 2021). Partially digested lipids are mixed with bile and pancreatic juice containing a range of lipases, including HPL, pancreatic lipase-related protein 2 (PLRP2), carboxyl ester hydrolase bile salt-stimulated lipase (CEH-BSSL), and pancreatic phospholipase A2 (PLA2) that can collectively break down all dietary fats into free fatty acids, glycerol, cholesterol, and glycerophosphocholine. Among those enzymes, HPL plays a predominant role in the digestion of dietary fats.

Bile salts play an equally vital role in lipid digestion. They are amphipathic, water-soluble, steroidal biosurfactants synthesized in the liver from cholesterol (Di Ciaula et al., 2017; Shansky & Bespyatykh, 2022). Their amphipathic properties allow them to effectively adsorb to the water-oil interface and emulsify the lipids by reducing the surface tension of formed oil droplets. The reduced surface tension at the water-lipid interface also prevents the interfacial denaturation of the lipases. Emulsification leads to the formation of mixed micelles, which are polymerized from 2 to 12 bile acid units. Moreover, bile salts remove other molecules, such as proteins and emulsifiers from the oil-water interface (Maldonado-Valderrama et al., 2011). The displacement of these molecules from the interface exposes the lipid droplet surface allowing the lipase to be adsorbed.

HPL is secreted by the acinar cell of the pancreas (Kumar & Chauhan, 2021), the functional unit of the exocrine pancreas responsible for the synthesis, storage, and secretion of enzymes. Unlike most pancreatic enzymes, which are synthesized as inactive precursors (zymogens), pancreatic lipase is synthesized in the active form and delivered from the pancreas to the small intestine by the pancreatic duct. HPL has a broad pH activity range, from 4.5 to 7.0, with an optimum activity at a pH close to neutral (6.5). Pancreatic lipase exhibits a remarkable increase in catalytic activity when presented with lipid-water interfaces, a phenomenon known as interfacial activation. Before the enzyme can bind its substrate at the catalytic site, it must first associate with the surface of the substrate emulsion. This interaction is facilitated by the presence of two distinct domains within the enzyme molecule: one responsible for interfacial binding and the other for catalytic function. The globular N-terminal domain, which contains an α/β hydrolase fold surrounding a central β-sheet core (Fig. 2), is responsible for the catalytic activity of the enzyme, while the C-terminal domain, composed of β-sheet structures, is involved in interactions with lipids and the HPL cofactor, colipase.

The catalytic site of pancreatic lipase is a classic catalytic triad (Ser152-His263-Asp176). While chemically analogous to the catalytic triad in serine proteases, the structural configuration is different. The catalytic site of pancreatic lipase is shielded by a mobile domain composed of surface hydrophobic loops: a β9 loop (the lid) and the β5 loop (F. I. Khan et al., 2017). The lid is anchored to the enzyme core by a disulfide bridge between two cysteine residues (Cys237-Cys261). The β5 loop presents a large accessible apolar surface area estimated at approximately 877 Å2 located on the same side of the enzyme molecule as the hydrophobic loops adjacent to the active site. These hydrophobic loops remain in a closed position within the aqueous environment, rendering the catalytic site inaccessible to the surrounding environment and hindering the enzyme's catalytic activity.

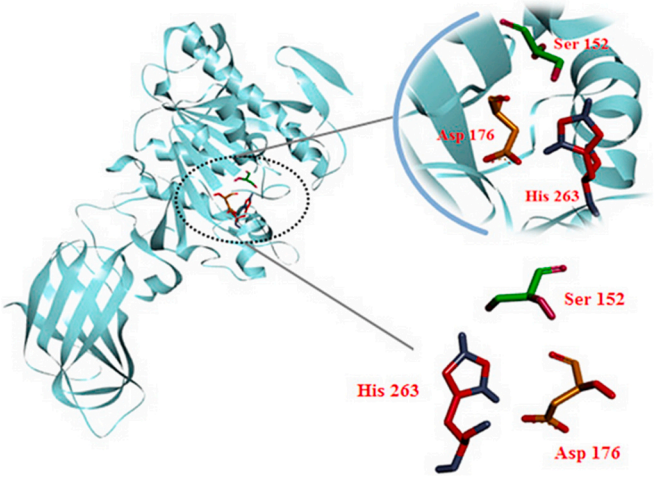

Fig. 2. Three-dimensional structure of human pancreatic lipase molecule. The active site and the catalytic triad (Ser152-Asp176-His263) are highlighted in the magnified view. Reproduced with permission from Nguyen, P.T.V., Huynh, H.A., van Truong, D., Tran, T.D., and Vo, C.V.T. (2020). Exploring aurone derivatives as potential human pancreatic lipase inhibitors through molecular docking and molecular dynamics simulations. Molecules, 25, (20): 4657. doi: https://doi.org/10.3390/MOLECULES25204657. Copyright © 2020 by the authors. Licensee MDPI, Basel, Switzerland.

The interfacial activation mechanism of HPL is more complex than that of lingual or gastric lipase. This complexity arises from the presence of bile salts in the intestinal environment, which hinders the enzyme's ability to bind to the lipid-water interface. Although bile salts enhance the overall efficiency of lipid digestion by increasing the surface area of the emulsion interface available for lipase adsorption, (Golding & Wooster, 2010; Moghimipour et al., 2015; Sun et al., 2022), when alone they actually hinder the adsorption of lipase to triglycerides by covering the interface. HPL can function effectively only in the presence of a small protein cofactor, colipase, which then facilitates the enzyme's binding to the lipid-water interface coated with bile salts. Colipase is a 10 kDa non-enzymatic protein. Procolipase, the inactive precursor form (zymogen) of colipase is produced and released by the pancreatic acinar cells. The conversion of procolipase into the active colipase is a crucial step in regulating pancreatic lipase activity. The zymogen form needs to undergo proteolytic cleavage by other pancreatic enzymes, such as trypsin, which removes the N-terminal pro-peptide and exposes the mature colipase domain (Donato-Capel et al., 2014). The activation of procolipase into the functional colipase is influenced by pH, the presence of bile salts, and the activities of other proteolytic enzymes in the gastrointestinal tract (Brownlee et al., 2010). These factors represent potential targets for regulating the rate of fat breakdown by enzymes.

The conversion of procolipase into colipase allows it to bind to and stabilize pancreatic lipase. The formation of the colipase-pancreatic lipase complex (Fig. 3) is essential for the enzyme to effectively catalyze the hydrolysis of dietary triglycerides. A hydrophobic loop β5', located in the non-catalytic C-terminal domain of HPL (residues 405–414) between two strands β5 and β6, is essential for the enzyme's interaction with the colipase. The lipase-binding domain of the colipase contains hydrophobic sites called hydrophobic fingers. The tips of these hydrophobic fingers bind to the hydrophobic surface of the β5 loop in the C-terminal domain of the enzyme through two salt bridges formed with Asp390 and Lys400 residues. After colipase is bound, the hydrophobic surface of the β5 loop remains uncovered and interacts with an open lid (the β9 loop), causing a pivot movement of the lid and C-

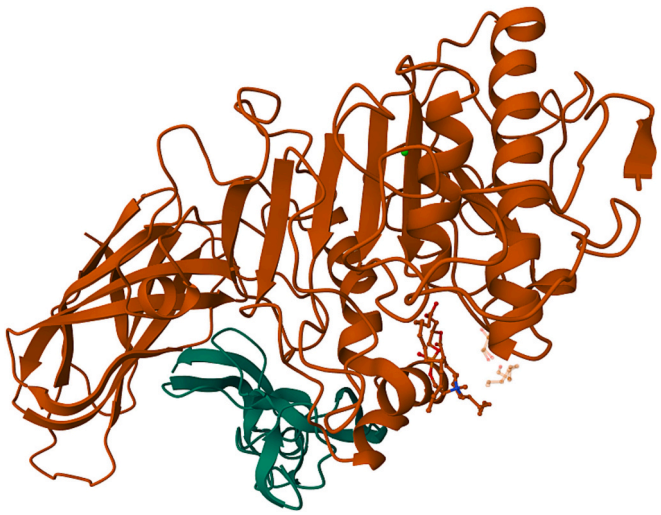

Fig. 3. Three-dimensional structure of the human pancreatic lipase in the open form (orange) and procolipase (green) complex. The amino acid residues that constitute the catalytic triad of human pancreatic lipase are shown in blue (Ser152 residue) and light orange (Asp176 and His263 residues). Source: Protein Data Bank: https://www.rcsb.org/. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

terminal domain. This interaction stabilizes the lid domain in the open position and exposes a large hydrophobic patch around the catalytic triad that can align with the water-oil interface (E. Mateos-Diaz et al., 2017). This increases the hydrophobicity of the catalytic site and facilitates its proximity to the lipid-water interface, significantly improving the affinity of HPL to lipids (Golding & Wooster, 2010; Van Tilbeurgh et al., 1993). It is worth mentioning that colipase is unable to induce the opening of the HPL lid domain on its own. To trigger the conformational rearrangement that leads to the opening of the lid, the presence of both lipid substrate and bile salts is necessary. However, colipase can enhance the proportion of the open enzyme conformation when bile salts are present (Belle et al., 2007).

Colipase features three hydrophobic loops, stabilized by disulfide bonds, positioned at the opposite side of its lipase-binding domain that serve as anchors promoting the adsorption of lipase onto triglyceride molecules. These loops engage with the oil-water interface without altering the conformation of the enzyme. During the adsorption of the enzyme to the oil-water interface, the serine residue of the catalytic site is involved in the recognition of the lipid micelle surface (Kumar & Chauhan, 2021). The binding of HPL molecules to the oil-water interface triggers conformational changes in the enzyme, exposing the catalytic site and enabling substrate docking within the active site. This process also leads to enzyme acetylation, resulting in the formation of a Michaelis-Menten adsorption complex. Consequently, the enzyme acquires the catalytic activity necessary for lipid hydrolysis. Bound colipase reduces the activation energy of the hydrolysis reaction and prevents HPL inhibition by phosphatidylcholine (Kumar & Chauhan, 2021). Pancreatic lipase hydrolyzes dietary triglycerides at sn-1 and sn-3 positions to fatty acids and 2-monoglycerides (Golding & Wooster, 2010), which can be further degraded into glycerol and free fatty acids (Fig. 4).

As lipolysis progresses, fatty acids and monoglycerides accumulate at the emulsion interface, displacing HGL and HPL. The accumulation of degradation products at the interface inhibits the hydrolysis rate. Bile salts and, to a lesser extent, phospholipids remove lipid digestion products that accumulate at the interface by increasing their solubility in the aqueous phase and forming mixed micelles. These micelles are primarily comprised of bile acids and lesser amounts of fatty acids, 2-monoglyceride molecules, phospholipids, and free cholesterol (Ko et al., 2020), along with unilamellar phospholipid vesicles (Golding & Wooster, 2010). Formation of the micelles drives the lipolysis reaction and is necessary for the transport of lipids from the duodenal lumen across the intestinal water layer to the brush border of the epithelial cells lining the duodenum (enterocytes), where absorption occurs (Ko et al., 2020; Łozińska & Jungnickel, 2021; Macierzanka et al., 2019; McClements, 2018). Lipolysis then progresses to enzymatic reactions on hydrolysis products with higher polarity such as monoacylglycerols and phospholipids. The enzymes involved in lipolysis steps after triglyceride and diacylglycerol hydrolysis are carried out by lipases with high affinity for substrates dispersed in water or forming mixed micelles. Other pancreatic lipolytic enzymes include pancreatic phospholipase A2 (PLA2), pancreatic lipase-related proteins 1 and 2 (PLRP1 and PLRP2), and carboxyl ester hydrolase bile salt-stimulated lipase (CEH-BSSL). For more detailed information on these enzymes, readers are encouraged to refer to the relevant literature, e.g., excellent papers by S. A. Khan & Ilies, 2023; Cohn et al., 2010; Cohen, 2008; Ko et al., 2020; Mansbach, 2004; Eydoux et al., 2008; Kirby et al., 2002; or Hui & Howles, 2002.

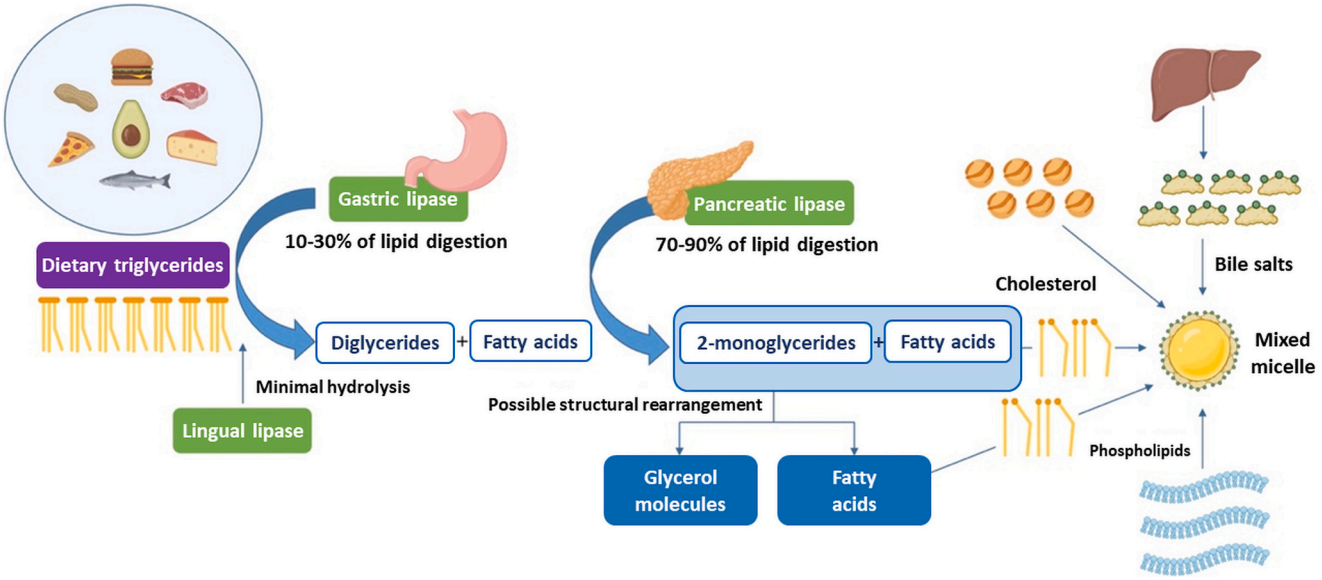

Fig. 4. Scheme of triglyceride digestion by lingual, gastric, and pancreatic lipases.

2.4. Absorption of lipid digestion products

About 90 % of lipid absorption occurs in the small intestine, while the other 10 % takes place in the stomach and the large intestine (McQuilken, 2021a, 2021b). When lipid digestion is complete, the digestion products (fatty acids and monoglycerides or glycerol) solubilized by bile salts form mixed micelles and are transported to the enterocytes. In enterocytes, the fatty acids and monoglycerides/glycerol are re-esterified to triglycerides in the smooth endoplasmic reticulum (Cartwright et al., 2000). Triglycerides and cholesterol esters are not soluble in plasma. To be distributed throughout the body and delivered to tissues, they need to be assembled into lipoprotein particles. These particles consist of a central lipid core primarily composed of triglycerides but also esterified cholesterol and phospholipids, and a coating made up of phospholipids, free cholesterol, and apolipoproteins (Rahmany & Jialal, 2023). There are four main types of lipoprotein particles: chylomicrons, very low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein, with chylomicrons playing a pivotal role in transporting lipids throughout the body.

The assembly of chylomicrons starts with the synthesis and initial lipidation of apolipoprotein B (apo B) in the rough endoplasmic reticulum, involving microsomal triglyceride transfer protein (Wetterau et al., 1997). The resulting pre-chylomicron particles then undergo further enlargement by adding triglycerides and cholesteryl esters in the smooth endoplasmic reticulum before being transported to the *cis*-face of the Golgi apparatus (Mansbach & Nevin, 1998). In the Golgi apparatus, triglyceride, cholesteryl esters, and apolipoproteins apo A-IV, apo C-III, and apo A-I are incorporated into the lipid core of the particles forming mature chylomicrons. One to several chylomicrons are loaded into secretory vesicles and bud from the *trans*-face of the Golgi apparatus. Since the secretory vesicles are too large to diffuse across the basolateral membrane of enterocytes, they are expelled from the cells by exocytosis. They migrate to basolateral regions of enterocytes where they merge with the plasma membrane and release the chylomicrons into lymphatic vessels located in intestinal villi (intestine lacteals). Due to the proximity of lymphatic vessels to the basolateral side of the enterocytes, chylomicrons initially enter intestinal lymph before being transferred to the bloodstream. Lymphatic fluid flowing over the basolateral side of the enterocytes collects the secreted chylomicrons. From there, the chylomicrons are transported through intestinal lymph to eventually reach systemic circulation via the thoracic duct that empties into the right subclavian vein (Ko et al., 2020; McQuilken, 2021b).

3. Controlled lipid digestion

As mentioned before, over the last four decades, there has been a significant increase in the prevalence of obesity and obesity-related diseases such as coronary heart disease, hypertension, diabetes, and various types of cancer (Kloock et al., 2023). A high intake of saturated fats is one of the main risk factors for developing these conditions (Mun et al., 2015). Therefore, minimizing fat intake from food has become a key target for mitigating the health risks associated with excessive fat consumption. One approach to achieving this goal involves controlled lipid digestion.

Research in this field has focused on developing innovative functional foods that can modulate the digestion and absorption of lipids in the human gastrointestinal tract. Numerous studies have investigated the use of emulsifiers, bile salt chelating agents, and pancreatic lipase inhibitors to control the breakdown of triglycerides into absorbable products. Unique formulation methods have also been explored to modify the extent and rate of lipid assimilation within specific areas of the digestive system. These methods involve creating diffusion barriers that impede the release of lipids from food matrices or hinder access of digestive enzymes, bile salts, and other factors involved in this process to the lipids. This can be achieved, for example, through the deposition of thick interfacial layers on lipid droplets or the encapsulation of lipids in gel matrices.

Reducing the fat content in food remains a challenge, as lipids largely contribute to the flavor, palatability, and texture of the product (Frøst & Janhøj, 2007). Reducing the fat content frequently changes the original taste to a degree where it may no longer be appealing to consumers. A promising alternative to reducing fat content in food is to develop functional dietary products that could control lipid digestion while still meeting customer expectations. Two main aspects need to be considered when designing dietary products for controlled lipid digestion (Wilson et al., 1997). The first aspect involves the design of the product's composition and physicochemical properties to achieve the desired digestion rate within the digestive tract. The second aspect involves tailoring the extent of dietary fat assimilation to the nutritional needs of the target consumer group and accounting for the specific attributes of lipid digestion in this particular group, which may differ due to variations in metabolism and physiology.

Lipid digestion and absorption are highly complex processes that involve multiple steps, including the breakdown of the food matrix, release of fat from the matrix, dispersion of lipids into droplets, digestion of the formed emulsion, absorption of digestion products by enterocytes, secretion into the lymph and transfer to the bloodstream (Golding & Wooster, 2010; Ko et al., 2020; McQuilken, 2021b). Consequently, the regulation of lipid assimilation can be approached from various angles. These include modifying the structure and composition of the food matrix, tailoring the oil phase composition to influence the size and stability of oil droplets formed during food transit through the gastrointestinal tract, engineering the composition and structure of the interfacial layer, and many others. This section offers a detailed discussion of the factors that regulate lipid digestion and absorption, along with strategies for modifying their rate.

3.1. Factors influencing lipid digestion and absorption

Adult humans typically consume 20–120 g of lipids per day, consisting mostly of triglycerides (~97 %), a small percentage of phospholipids, approximately 1 % of cholesterol, and less than 1 % of lipid-soluble compounds such as fat-soluble vitamins, phytosterols, and carotenoids. Triglycerides in the human diet come from fats derived from animal-based products (e.g., milk, eggs, the adipose tissue and intramuscular fat of pigs, cattle, poultry, and lamb, etc.), and oils derived from fruits (e.g., palm oil and olive oil), seeds (e.g., corn, rapeseed, and soybean), and marine sources like fish (Mu & Høy, 2004). Phospholipids are also a significant part of the human diet with an average daily consumption of 5 g. Phospholipids can be found in cellular membranes of both plant and animal tissues, as well as in lipoproteins in egg yolk. Cholesterol is present in animal cell membranes and egg yolk while phytosterols are commonly found in plant cell membranes.

Dietary triglycerides are a complex mixture of fatty acid esters that can vary in chain length, positioning, and saturation degree of fatty acid substituents. As a result, triglycerides can vary greatly in terms of physical state, rheological properties, and susceptibility to enzymatic degradation (R. Zhang et al., 2015). Triglycerides can occur in food in different forms such as oil droplets or solid fat crystals dispersed within the food matrix, emulsions like milk and cream, liquid oils such as vegetable and fish oils, solid fats such as butter and palm oil, and lipoproteins (i.e., lipid-protein complexes that serve to improve the solubility of lipids (Cho et al., 2022)) found e.g., in egg yolk. The formation of lipid droplets is a critical stage in fat digestion, as it provides a surface for enzyme adsorption. Much of the fat in the modern diet is derived from processed foods, where it is already emulsified, similar to fat in breast milk, which is naturally emulsified in the endoplasmic reticulum and secreted through the cell membrane of alveolar cells. However, highly emulsified lipids are a relatively recent development in human dietary evolution. In the past, a significant proportion of dietary fat was consumed in an unemulsified form, such as the visceral fat from meat and natural oils in fruits and seeds. This may contribute to higher obesity

rates in consumers following modern eating patterns, where a significant portion of the fat in the adult diet is derived from processed foods (Adams & White, 2015).

Predicting lipid digestion rate necessitates the consideration of all these factors, as well as the rate of emulsification in the gastrointestinal tract, the size of formed droplets, the presence of substances influencing interface structure or stability, such as bile salts, proteins, and phospholipids, and the available surface area for lipase adsorption (Reis et al., 2010).

3.1.1. Composition, physical state, and structure of food matrix

The digestion of lipids is significantly influenced by the properties of the food matrix, including its physical state, structure, and composition (Clemente et al., 2003; A. I. Mulet-Cabero et al., 2017). The structure of the food matrix denotes the arrangement and spatial organization of its components, and profoundly affects both the digestion and absorption of fat, as it regulates oral processing (Ferriday et al., 2016; J. Li et al., 2011), the accessibility of digestive enzymes to lipids, their subsequent digestion (Berton et al., 2012; Singh & Gallier, 2017), and digesta transit through the gastrointestinal tract (S. E. E. Berry et al., 2008; Vors et al., 2013).

Triglycerides found in food can be solid, semi-solid, or liquid. The lipid digestion rate is determined by the physical state of lipids at body temperature, which, in turn, is governed by triglyceride composition and molecular structure. If the melting point of the lipids exceeds 37 °C, the fat crystals will remain solid during lipolysis. In this case, the extent and rate of digestion are closely linked to the microstructure of the dispersed fat. As solid fats transit through the digestive tract, they are dispersed into small fat crystals surrounded by liquid oil (Acevedo-Fani & Singh, 2022; Q. Guo et al., 2017b). The release of lipids from oil droplets containing solid fat crystals is hindered due to the entrapment of liquid lipids within the solid crystal network, limited movement of the droplets, and reduced interfacial area accessible to digestive enzymes. Furthermore, the limited mobility of lipid molecules impairs the enzymes' ability to access and hydrolyze the bonds within the lipid molecules. Consequently, solid lipids exhibit the slowest digestion rate compared to liquid oils and semi-solid fats (Lamothe et al., 2017; Wan et al., 2022). Delayed lipolysis of solid lipids contributes to lower free fatty acid levels in the serum after meals and prolonged satiety (Dias et al., 2019).

There is an inverse correlation between lipid digestion rate and fat crystal size, with emulsions containing larger crystals exhibiting lower digestion rates (Jiao et al., 2019). However, crystals exceeding a certain size threshold (3–5 μm) may puncture the surface of oil droplets, thereby exposing the lipids to lipases and accelerating lipolysis (Q. Guo et al., 2019). The rate of lipid digestion is also influenced by the polymorphism of fat crystals, particularly the content of β polymorph. β polymorph is the most stable fat crystal form showing the densest crystal structure and the highest melting point. With an increase in the content of β polymorphs, the rate of lipolysis decreases. However, no clear relationship has been established between the digestion rate and the quantity of β polymorph fat crystals within oil droplets (Jiao et al., 2019).

Assessment of digestion patterns and postprandial lipid responses to test foods with identical nutrient compositions but different physical states, using dynamic in vitro models, revealed that solid food exhibited phase separation during gastric digestion and a reduced release of fatty acids during intestinal digestion compared to liquid and semi-solid foods. In postprandial feeding experiments, solid food caused a lower increase in serum triglycerides than liquid food and induced greater feelings of fullness and satisfaction (Dias et al., 2019).

Furthermore, emerging research suggests that the food matrix structure may influence the bioavailability of lipids. Studies on postprandial lipemia after consumption of nuts in different forms, including whole and ground nuts, homogenized or reconstituted, revealed that whole nuts result in lower postprandial lipemia compared to reconstituted meals or nut oil, indicating the significance of food structure in the immediate lipemic response to a meal (S. E. E. Berry et al., 2008; Berryman et al., 2013). Moreover, emulsions with smaller fat globules undergo quicker lipolysis due to their larger surface area, which facilitates greater enzyme contact compared to emulsions with larger globules of the same oil volume (Michalski et al., 2013). As research in this area continues to grow, it is also becoming increasingly clear that emulsions stable under acidic conditions result in slower gastric emptying compared to acid-unstable ones (Marciani et al., 2008).

In addition to the physical properties of the food matrix, the interaction between lipids and other macronutrients in the food plays a significant role in the digestion process. It is crucial to explore not only the individual components of the food matrix but also their interactions and synergistic effects on lipid digestion. For example, products containing whey protein exhibit higher solubility in the stomach environment and degrade more readily than those containing casein, leading to a faster release of dietary fats (Boirie et al., 1997).

3.1.2. Molecular structure of dietary fats

One of the key factors affecting the susceptibility of dietary triglycerides to enzymatic degradation is their molecular structure. The rate of lipid digestion and absorption is strongly related to the type of fatty acid substituents, including their chain length, degree of saturation, and position within the molecule (Mu & Høy, 2004). Carefully selecting the type of triglycerides or modifying their molecular structure enables the formulation of dietary products with desired rates of lipid digestion. Understanding how these properties affect lipid metabolism is crucial for the design of functional foods that can tailor fat digestion rates to achieve specific health benefits.

Based on the chain length, the fatty acids can be categorized into long-chain (composed of 16, 18, or 20 carbon atoms), medium-chain (composed of 6–12 carbon atoms), and short-chain (composed of 2–5 carbon atoms). The rate of lipid digestion increases with decreasing length of the fatty acid chains (Bengu Öztürk et al., 2015). For example, coconut oil exhibits a considerably higher rate of lipid digestion compared to fish oil, flaxseed oil, and sunflower oil, all of which contain long-chain fatty acid residues (Bengu Öztürk et al., 2015; Burcu Öztürk et al., 2016). This difference results from limited access of lipase at the interface to long-chain triglyceride molecules (Day et al., 2010; Devraj et al., 2013; J. Zhang et al., 2011). In addition, long-chain fatty acids can form insoluble micelles with bile salts, Ca^{2+}, or Mg^{2+} ions around the oil droplets and precipitate in the intestines, which may adversely affect their bioavailability (Golding & Wooster, 2010). Medium and short-chain fatty acids have a higher affinity to water which facilitates rapid crossover into the aqueous phase (Sek et al., 2002). However, in the presence of high concentrations of bile salts, the length of fatty acid residues appears not to affect the triglyceride digestion rate (Acevedo-Fani & Singh, 2022; Q. Guo et al., 2017b).

Another key factor that significantly influences lipid digestion rate is the location of fatty acid residues within the triglyceride molecule. These residues can be attached to the glycerol backbone at one of three positions: sn-1, sn-2, or sn-3 (Fig. 1). Kinetic mathematical models indicate that the rate of fatty acid hydrolysis at positions sn-1 and sn-3 is 2 to 3 times higher than at position sn-2 (Infantes-Garcia et al., 2020; Nagata et al., 2003; Y. Wang et al., 2022). Lipids containing medium-chain fatty acid residues located at sn-1 and sn-3 positions are easier to digest because such positioning imposes less steric hindrance on lipase adsorption and facilitates faster hydrolysis of ester bonds. Therefore, the lipid digestion rate can be regulated by modifying the positions of fatty acid residues in triglycerol molecules, for example, through an interesterification reaction, which allows for the rearrangement of the fatty acids within the triglycerol molecule (Acquistapace et al., 2019; Yiwen Guo et al., 2022). This reorganization changes the physical characteristics of fat, such as the melting point and texture, and can add specific functionalities offering a wider range of applications. The use of interesterified fats has increased in recent years as part of ongoing reformulation efforts by food producers to reduce the

levels of saturated and *trans* fatty acids in hydrogenated oils (S. E. Berry et al., 2019).

The rate of lipolysis is also directly related to the level of lipid saturation. Generally, fats rich in saturated fatty acids, like coconut oil, are digested more rapidly compared to those containing monounsaturated fatty acids, such as sunflower oil, which, in turn, exhibit a higher digestion rate than those comprising polyunsaturated fatty acids like flaxseed oil (Zhou, Zheng, & McClements, 2021). This can be attributed to the ability of unsaturated fatty acids to form micelles more quickly, translating to faster absorption by enterocytes (J. Maljaars et al., 2009). Consuming lipids abundant in unsaturated fatty acids triggers the ileal brake mechanism (elaborated on in greater detail in the section "Personalized foods for overweight consumers") and stimulates the secretion of cholecystokinin (CCK) in the gut, resulting in an earlier onset and enhanced feeling of satiety.

3.1.3. Emulsion droplet size

Food emulsions can exist in a variety of structural forms, ranging from highly stable and homogenized emulsions found in milk, to partially coalesced structures in ripened cheeses and ice cream, flocculated structures in cream cheese, and phase-separated systems in dressings and vinaigrettes (Golding & Wooster, 2010). One of the key factors affecting the kinetics of lipid digestion is the size and stability of droplets in the emulsion formed after lipids are released from the food matrix. The rate of lipid digestion relies heavily on the specific surface area of the oil-water interface. A larger surface area provides more sites for the adsorption of bile salts, lipase, and colipase, thereby accelerating lipid degradation. Consequently, fat degradation rate correlates negatively with lipid droplet size – smaller droplets exhibit a larger specific area translating to an increased lipolysis rate and thus are digested more rapidly than larger droplets (McClements & Li, 2010).

The effect of emulsion droplet size on lipid digestion has been extensively investigated in vivo and in vitro. Recent studies have consistently shown an inverse relationship between droplet size and the rate of small intestinal lipid digestion. Armand et al. compared the digestion rates of coarse and fine lipid emulsions, containing droplets of identical composition measuring 10.0 μm and 0.7 μm in diameter, respectively (Armand et al., 1999). The concentration of free fatty acids in gastric contents after 30 min of digestion was approximately three times higher for fine droplets than for coarse droplets (7.5 mmol/L vs. 2.2 mmol/L, respectively). The fine emulsion exhibited also significantly greater lipolysis compared to the coarse emulsion. Specifically, lipolysis reached 73.3 % in the duodenum for the fine emulsion, whereas it was only 46.3 % for the coarse emulsion. Furthermore, consumption of the fine emulsion led to a delayed triacylglycerol peak in plasma (3 h 56 min vs. 2 h 50 min for the coarse emulsion), which can have important implications for metabolic health. This delayed triacylglycerol peak suggests a slower absorption and more gradual release of fatty acids into the bloodstream, potentially resulting in improved glycemic control and reduced risk of metabolic disorders like obesity and type 2 diabetes.

In another study, Salvia-Trujillo et al. investigated the digestion rates of carotenoid-enriched oil-in-water emulsions with varying droplet sizes: small (0.72 μm), medium (1.9 μm), and large (15.1 μm) under simulated gastrointestinal conditions (Salvia-Trujillo et al., 2017). They found that emulsions with smaller droplet sizes exhibited faster lipolysis, micelle formation, and enhanced carotenoid bioaccessibility. Furthermore, the sub-micron emulsion demonstrated a higher conversion of monoacylglycerols to free fatty acids, resulting in a greater concentration of FFAs within the mixed micelles. Carotenoid incorporation into the mixed micelles was also accelerated, resulting in a higher final level for the small droplet emulsion and a bioaccessibility of approximately 70 %.

It is worth noting that the inverse relationship between lipid droplet size and digestion rate applies only to emulsion droplets above a certain threshold. In the case of nanoemulsions comprising nanosized droplets with diameters <100 nm (Kupikowska-Stobba & Kasprzak, 2021), this correlation no longer applies. Surprisingly, nanoemulsions exhibit a lower lipid digestion rate than conventional emulsions. Salvia-Trujillo et al. (Salvia-Trujillo et al., 2019) explored the differences in the kinetics of in vitro lipid digestion between conventional emulsions (droplet diameter 0.484–0.897 μm) and nanoemulsions (droplet diameter 0.279–0.226 μm) produced by increasing the concentration of a non-ionic surfactant Tween 80 in the system (surfactant-to-oil ratios were 0.1 and 2.0, respectively). The nanoemulsions prepared at a high surfactant-to-oil ratio exhibited substantial inhibition of lipid hydrolysis under simulated gastrointestinal conditions, likely attributable to the hindered lipase adsorption at the oil-water interface. This study highlights the potential of incorporating nanoemulsions into emulsion-based food systems as a means to modulate lipid digestion. Formulating emulsion-based foods with appropriate nanoemulsion characteristics could provide opportunities to design functional foods for tailored lipid delivery.

The size of emulsion droplets also plays a role in regulating the gastric emptying rate, thereby impacting the duration of satiety. Compared to coarse emulsions, fine emulsions exhibit significantly lower gastric emptying rates (i.e., the rate at which gastric contents pass from the stomach to the duodenum). Slow emptying of the stomach extends satiety through a negative feedback mechanism (Golding & Wooster, 2010) triggered by the secretion of cholecystokinin (CCK) and peptide YY (PYY), which inhibit gastric acid secretion and gastric emptying (P. W. J. Maljaars et al., 2012; Steingoetter et al., 2017, Steingoetter et al., 2019). The relationship between gastric emptying rate and emulsion droplet size is influenced not only by the droplet size itself but also by the degree of uniformity and the potential for phase separation within the system. In emulsions prone to phase separation in the stomach, such as acid-unstable emulsions, a significant portion of the oil within the meal initially floats on top of the stomach contents, away from the pylorus (Marciani et al., 2008). The aqueous phase is emptied first (before the floating oil layer), minimizing hormonal feedback to slow gastric emptying. Consequently, the phase-separated systems initially induce increased cholecystokinin secretion and faster gastric emptying compared to the homogenously dispersed emulsified systems. However, as the lipids begin to empty, the hormonal feedback increases, slowing the emptying rate. Conversely, the homogeneously dispersed lipid droplets in the gastric-stable emulsions are immediately released from the stomach and constantly delivered to the small intestine, triggering consistent hormonal feedback. Within 1 h after the meal, the gastric volume for the stable emulsions is nearly double that for the unstable emulsions (Marciani et al., 2008). Given that gastric volume is a crucial determinant of appetite, this accelerated gastric emptying can substantially affect the subsequent sensation of satiety and food consumption. Wickham and colleagues investigated the effects of emulsion stability in the gastric environment on gastric emptying, feelings of fullness, and hunger. They examined two emulsions – one stabilized with the sorbitan ester Span 80, which remained stable under acidic gastric conditions, and another stabilized with polysorbate Tween 60, which was unstable in the gastric environment. They found that the Span 80-stabilized emulsion rapidly disintegrated and separated in the gastric environment, leading to faster lipid digestion compared to the Tween 60-stabilized emulsion (Marciani et al., 2008). Importantly, the acid-stable emulsion slowed gastric emptying, which increased feelings of fullness and decreased hunger and appetite. These findings demonstrate the feasibility of delaying gastric emptying and enhancing satiety by stabilizing the intragastric distribution of emulsions.

The inverse correlation between droplet size and the rate of lipolysis has been confirmed in numerous in vitro studies, leading to the development of kinetic mathematical models that predict emulsion digestion rates based on droplet size (Infantes-Garcia et al., 2020). Such predictive models can be invaluable in designing personalized foods with customized lipid digestion rates tailored to the dietary needs of specific consumer groups. For example, to create dietary products aimed at reducing calorie intake in overweight consumers, the composition of the

lipid phase is adjusted so that upon release from the food matrix in the digestive tract, they form slowly digestible, coarse emulsions that delay lipid digestion. Such dietary products can offer an attractive alternative to reduced fat and fat-free products, whose original taste may be heavily altered due to reduced lipid content and may not be acceptable to some consumers. Products designed to suppress lipid digestion and absorption would enable consumers to maintain a healthy diet without compromising the sensory qualities of food.

Another important consideration when developing foods for targeted lipid delivery is the dynamic changes in lipid droplet size as they travel through the gastrointestinal tract. Upon ingestion, the emulsion adjusts to body temperature and experiences significant changes in pH and ionic composition. The emulsion also interacts with digestive enzymes and encounters shear forces, such as between the oral mucosa and teeth, or due to gastric contractions and gastrointestinal peristalsis. The ultimate size of droplets reaching the small intestine differs considerably from the initial ingested size due to flocculation, coalescence, disruption, and digestion (McClements et al., 2008; Singh et al., 2009). For example, Armand et al. compared the behavior of coarse emulsion droplets stabilized with egg lecithin (10 μm diameter) and fine emulsion droplets (0.7 μm diameter) with the same composition in a study involving human participants who consumed a meal containing the fat emulsion, with the stomach contents later aspirated (Armand et al., 1999). They found that coarse emulsion droplets maintained their size after ingestion, while fine emulsion droplets rearranged in the stomach to form larger droplets. The smaller emulsion droplets may have aggregated in the stomach due to proteolysis of the adsorbed egg lecithin, leading to an increase in droplet size. Consequently, controlling the physical stability of lipid droplets in the gastrointestinal tract is crucial for regulating the digestion rate by modulating the available surface area. This is a key factor in designing functional foods, as the behavior of lipid droplets in the GIT significantly affects fat metabolism and, ultimately, the absorption of dietary fats.

3.1.4. Bile salt concentration

The concentration of bile salts is a crucial factor in the development of foods for tailored fat delivery, as it directly affects the emulsification process and the rate of digestion, thereby determining the efficiency of lipid absorption in the small intestine. At low concentrations, below the critical micellar concentration (CMC, 1–2 mM), bile salts activate the hydrolysis of emulsified triglycerides by gastric and pancreatic lipases. This is achieved by decreasing the surface tension and preventing the interfacial denaturation of the lipases (A. Salhi et al., 2021). In the absence of bile salts, the high surface tension at the oil-water interface causes irreversible deactivation of the enzymes. However, the stabilizing effect of bile salts on pancreatic lipase is observed only at low concentrations, with maximum activity seen at 0.5 mM for a conjugated bile salt, sodium taurodeoxycholate (Müller & Petry, 2006).

Conversely, at concentrations above the CMC, bile salts start to inhibit pancreatic lipase activity due to the desorption of the enzyme from the interface and adsorption inhibition. At supramicellar levels (above the CMC), bile salts can also induce conformational changes in lipase molecules, causing the opening of the lid domain in solution before the enzyme adsorbs to the interface (Belle et al., 2007). The inhibitory effect of bile salts on HPL can be counteracted by the formation of a complex between the enzyme and colipase. Simultaneously, bile salts maintain the continuity of lipolysis by removing reaction products from the oil-water interface through micellar solubilization. In contrast to pancreatic lipase, gastric lipase is not inhibited by concentrations of bile salts above the CMC and can effectively penetrate the lipid-water interface without the need for a cofactor (Müller & Petry, 2006), owing to its higher tensioactivity, even in the presence of phospholipids (Bénarouche et al., 2017). For other lipolytic enzymes acting on more polar lipids such as phospholipids, galactolipids, and monoacylglycerides, bile salts play a crucial role in dispersing these substrates in the aqueous phase in the form of mixed micelles. The bile salt to substrate molar ratio is critical for the activities of lipases including HPLRP2, CEH-BSSL, and PLA2 (Eduardo Mateos-Diaz et al., 2018).

3.1.5. Ionic strength and pH

The ionic strength and pH are crucial factors that influence the stability of emulsions and the solubility of bile salts, both of which are critical for the processes of lipid digestion and absorption. Modulating these parameters allows food product developers to effectively control lipid behavior and optimize the absorption of dietary fats. The variations in gastric and duodenal pH during digestion as well as the acidity of the meal affect the rate of lipid emulsification in the GIT and the activity of lipase. Following the consumption of a meal, the pH of the gastric contents typically ranges between 5.5 and 7.0, depending on the composition of the ingested food. Subsequently, as gastric acid is secreted, it dilutes the contents of the stomach, resulting in a decrease in pH. Additionally, gastric emptying contributes to this acidity by removing meal components from the stomach and reducing their buffering effects. The intragastric pH value is typically found within a range of 4 to 5 at half gastric emptying time (approximately 1 h after the meal) in healthy volunteers, corresponding to optimal pH conditions for HGL activity (Müller & Petry, 2006).

Duodenal pH variations are less pronounced with values generally falling within a narrower range of 5 to 7 and giving an average value of around 6.25 among healthy volunteers – also corresponding to optimal conditions for HPL activity. The optimal activity pH for HPLRP2 and CEH-BSSL varies depending on the substrate being hydrolyzed, typically falling within the neutral to slightly alkaline range (Eydoux et al., 2007). However, both enzymes exhibit peak activity on cholesterol esters at pH 6 (Amal Salhi et al., 2020).

Changes in pH during food transit through the GIT strongly affect the ionization of lipid surface groups and the density of lipid droplet surface charge (Sukhorukov et al., 2001). Variations in pH affect electrostatic repulsion, steric interactions, and van der Waals forces between lipid droplets, influencing the rate of lipid emulsification and droplet behavior in different regions of the gastrointestinal tract. This effect is especially pronounced in food emulsions stabilized with ionic emulsifiers. Modifying the pH of the food matrix containing oil droplets or fat crystals allows for the control of interfacial layer thickness and integrity, as well as the adsorption of ionizable molecules onto the lipid droplets (Sukhorukov et al., 2001). For example, anionic pectin would not bind to anionic β-lactoglobulin-stabilized lipid droplets under neutral pH conditions, i.e., above the isoelectric point (pI) of β-lactoglobulin, because of the electrostatic repulsion between the polysaccharide molecules and the negatively charged β-lactoglobulin on the droplet surface (D. Guzey et al., 2004). However, it will adsorb to them at lower pH levels, around 3 (below the pI of β-lactoglobulin), when the polysaccharide molecules and the protein-coated droplets carry opposite charges. Incorporating pectins or other polyanions, such as alginate, carrageenan, or xanthan gum, into food products containing positively charged emulsifiers can help shield lipids from digestion in the acidic environment of the stomach. Once the lipids reach the duodenum, the polyanions dissociate from the droplets under neutral pH, exposing lipids to the hydrolytic action of lipases. Protein-based emulsifiers are especially effective in controlling lipid droplet charge under changing pH values. Protein emulsifiers have a positive charge below their isoelectric point (pI), while they carry a negative charge above their pI. As different proteins have different isoelectric points, choosing a protein emulsifier with suitable electrical properties allows for the optimization of the lipid emulsification and digestion rates in different regions of the GIT through the regulation of repulsive forces between droplets (Demet Guzey & McClements, 2006).

The ionic strength of the digestive juices and the food matrix affects the surface charge of lipid droplets, thereby influencing the magnitude of both intramolecular and intermolecular electrostatic interactions among the droplets, including the repulsive forces that prevent their coalescence. These interactions, in turn, play a role in shaping the

structure and thickness of the interfacial layer (McClements, 2004b). Increasing the ionic strength of the continuous phase lowers repulsion between droplets due to the accumulation of counter-ions around their surfaces, promoting droplet flocculation or coalescence (Metaxas et al., 2021). This effect is influenced by both counter-ion concentration and valency; multivalent ions such as Ca^{2+}, Fe^{2+}, and Fe^{3+} have a more pronounced effect on the electrostatic interactions between lipid droplets compared to monovalent ions like Na^{+}, Cl^{-}, and K^{+} (Kupikowska-Stobba et al., 2024). The addition of anionic or cationic polyelectrolytes containing weakly acidic or basic ionizable groups into foods can also effectively alter droplet surface charge (Guzey & McClements, 2006). Incorporating anionic polyelectrolytes (e.g., carrageenan, alginate) into the food matrix introduces negatively charged groups like sulfate, or carboxylate, with *pKa* values around 1–2 and 4–5, respectively, while adding cationic polyelectrolytes (e.g., chitosan) introduces positively charged groups such as amine with *pKa* values around 6.3–6.5 (Kupikowska-Stobba & Lewińska, 2020; Y. Tan et al., 2020).

3.1.6. Emulsifier type and concentration

Foods often contain lipids in the form of emulsions, with fine droplets dispersed throughout a continuous aqueous phase. Lipid components contribute to the sensory attributes of the food, such as taste, texture, and flavor, thereby enhancing the overall quality of the product. The nature and concentration of emulsifying agents used to stabilize lipid droplets within food products are crucial factors that need to be considered when designing functional and personalized foods. The choice of emulsifier directly affects the size and stability of lipid droplets, as well as the rate at which bile salts displace these emulsifiers. This, in turn, influences the efficiency of lipid digestion and absorption in the gastrointestinal tract. By selecting the appropriate type and concentration of an emulsifier, developers can design functional foods that modulate the rate and extent of fat assimilation from food.

Most emulsions incorporated in food are thermodynamically unstable and exist in a state of chemical non-equilibrium (Kupikowska-Stobba et al., 2024). Over time, these systems undergo phase separation (McClements, 2007) through various destabilization mechanisms such as creaming, sedimentation, flocculation, coalescence, and Ostwald ripening (Kupikowska-Stobba & Kasprzak, 2021). In addition to instabilities that develop over time, food emulsions can also separate when subjected to external forces, such as those generated during mixing, shaking, spreading, pumping, homogenizing, or chewing in the mouth. These activities expose emulsions to a broad range of shear forces, with shear rates ranging from approximately 10^{-6} to 10^{3} s^{-1}, increasing the incidence of collisions between droplets (Ghosh & Rousseau, 2010).

Emulsion breakdown in foods can be effectively prevented or delayed using surface active agents, known as surfactants or emulsifiers. Emulsifiers stabilize emulsions by adsorbing onto the surface of lipid droplets creating a physical barrier between them (Tadros, 2014), thereby minimizing destabilization processes (Kupikowska-Stobba & Kasprzak, 2021). The ability of emulsifiers (except for Pickering emulsifiers) to stabilize droplets stems from their amphiphilic nature. These molecules have both hydrophilic (the head) and hydrophobic (the tail) regions. In oil-in-water (O/W) emulsions (standard emulsions), where oil droplets are dispersed in an aqueous phase, emulsifiers envelop the oil droplets with their hydrophobic tails inserted into the droplets and hydrophilic heads oriented outward toward the continuous phase. The specific mechanisms by which different emulsifiers mitigate destabilization processes in foods vary depending on their structure (Wilde, 2019). These mechanisms have been comprehensively discussed in recent publications by Tadros (Tadros, 2014) and Wilde (Wilde, 2019). Interested readers are encouraged to refer to those works for more information.

The emulsifiers commonly used to stabilize emulsion-based food products, such as mayonnaise, butter, margarine, low-calorie spreads, peanut butter, chocolate, milk, cream, etc. (Jones & Brass, 1991), can be divided into low molecular weight emulsifiers (McClements, 2004a; Whitehurst, 2004), such as sodium lauryl sulfate (SLS), diacetyl tartaric acid ester of mono- and diglycerides (DATEM), citric acid esters of mono- and diglycerides (CITREM), sodium stearoyl lactylate, monoacylglycerols, and phospholipids (e.g., lecithin), and macromolecular emulsifiers, such as polysorbates (e.g., Tweens), proteins (caseins, β-lactoglobulin, and soy), fatty acid esters (e.g., sorbitan fatty acid esters such as Spans 20, 40, 60 and 80), block-copolymers (gum arabic, and sugar beet pectin) (Mahendran et al., 2008), and solid particles, known also as Pickering particles (silica, starch granules, chitosan particles or gelatin particles) (Niu et al., 2019; Niu, Chen, et al., 2022a; Niu, Hou, et al., 2022; Posocco et al., 2016; Tan et al., 2014; Wilde, 2019).

Numerous studies have explored the effect of emulsifier type on lipid digestion rate. Reis and co-workers discovered that lipid digestion was slower for droplets coated with monoglycerides compared to those coated with proteins or phospholipids (Reis et al., 2010). Mun et al. (Mun et al., 2015) confirmed these findings using a simulated gastrointestinal tract model that consisted of oral (pH = 6.8), gastric (pH = 2.5), and intestinal phases (pH = 7.0) (Mun et al., 2015). Their study demonstrated that the resistance of lipid droplets to digestion varied depending on the type of emulsifier used, with the following order of resistance: non-ionic surfactants (e.g., Tween 20, monoglycerides) > phospholipids (e.g., lecithin) > proteins (e.g., caseinate or whey protein isolate).

The reduced resistance of protein-stabilized emulsions to digestion, compared to those stabilized by non-ionic emulsifiers and phospholipids, can be attributed to the aggregation of protein emulsifier molecules that can occur as the emulsion passes through the gastrointestinal tract. During the transition from the oral to the gastric stage, protein-stabilized emulsions undergo phase separation due to the low pH and ionic strength of the gastric environment (Mun et al., 2015). As the pH approaches the protein's isoelectric point, the reduction in electrostatic repulsion between lipid droplets causes proteins to become less soluble, promoting increased aggregation, flocculation, and coalescence of lipid droplets (Ladjal-Ettoumi et al., 2016; Li et al., 2016). Additionally, as the pH decreases, the protein-stabilized emulsions transform into a cationic form, leading to conformational changes in the protein molecules adsorbed to the lipid droplets. The aggregation of the droplets results in a reduced surface area-to-volume ratio, which limits the access of lipolytic enzymes to the lipid substrate and hinders lipid digestion. In contrast, non-ionic emulsifiers and phospholipids form more stable interfacial layers that can withstand the pH changes encountered along the gastrointestinal tract.

Protein emulsifiers typically create thicker interfacial layers around lipid droplets. However, in the acidic gastric environment, emulsions stabilized by proteins tend to be less stable than those stabilized by low molecular weight emulsifiers, which form thinner interfacial layers. The lower resistance of protein-stabilized emulsions to digestion can be partly explained by the enzymatic breakdown of protein emulsifiers in the stomach. Protein adsorption to the oil droplet surface induces the unfolding of the protein molecules, making them more susceptible to hydrolysis by the proteases present in the gastric fluids. The proteolytic action of pepsin on the adsorbed proteins reduces the droplet charge and removes steric repulsion barriers, leading to destabilization of the interface, further aggregation, and coalescence of the emulsion droplets. Sarkar et al. (Sarkar et al., 2009) provided additional empirical support for the described mechanism by examining the gastric digestibility of an oil-in-water emulsion stabilized by the globular protein β-lactoglobulin. Initially, this emulsion was a stable anionic system at pH 7, but upon exposure to simulated gastric fluid, it experienced a reversal of surface charge and extensive droplet flocculation, along with some degree of coalescence. This change was primarily attributed to the hydrolysis of the β-lactoglobulin at the interfacial layer by pepsin.

Conversely, emulsions with adsorbed layers composed of low molecular weight emulsifiers, such as phospholipids or monoacylglycerols, exhibit greater resistance to the acidic conditions of the stomach environment. As these emulsions transition from the oral to the gastric

phase, the droplet aggregates formed during the oral stage tend to dissociate in the gastric environment due to decreased attraction between the droplets (Mun et al., 2015). Furthermore, low molecular weight surfactants are not prone to proteolysis in the stomach, allowing them to sustain their stabilizing effects. As a result, low molecular weight emulsifiers are generally more effective in protecting lipid droplets from aggregation under gastric conditions compared to protein emulsifiers.

These studies emphasize that choosing the right emulsifier to coat lipid droplets can significantly impact the rate of lipid digestion. However, it is important to note that the interfacial composition of lipid droplets may change significantly during gastrointestinal transit due to digestion and competitive adsorption of surface-active compounds like bile salts, phospholipids, diacylglycerols, monoacylglycerols and free fatty acids produced during the hydrolysis (Ivanova et al., 1990; Liang et al., 2018; Sarkar et al., 2009). As a result, the characteristics of the droplets in the small intestine may differ substantially from the initially ingested emulsion. The final composition of the adsorbed layer on an emulsion droplet is dependent on the concentrations and surface activities of the various components present in the digestive environment. However, our understanding of the diverse surface-active molecules, the kinetics of interfacial material exchange, and how these exchanges influence emulsion stability is currently limited.

On the other hand, some studies suggest that the emulsifier type does not have a significant impact on lipid digestion rate. McClements et al. conducted a study using oil-in-water emulsions with similar droplet sizes and concentrations, stabilized by different emulsifiers: non-ionic surfactants, phospholipids, and proteins. The release profiles of free fatty acids were similar across emulsions, indicating that the emulsifier type did not strongly affect the overall rate and extent of lipid digestion. Additionally, cross-linking the protein layer in protein-stabilized emulsions did not significantly impact lipid digestion, further suggesting that the emulsifier type may not be a major determinant of lipid digestibility.

The variation in results across different studies may be due to differences in the specifics of the in vitro methodologies employed, such as the initial physicochemical properties of the lipid droplets (droplet size and concentration, oil type), the composition and ionic strength of the simulated intestinal fluid (bile salts, lipase, and mineral concentrations), and other experimental parameters. While the findings suggest that emulsifier selection can modulate lipid digestion, the outcome depends on the specific conditions of the in vitro digestion model, as well as the surface activity and interfacial properties of the emulsifier and its ability to inhibit bile salt and lipase adsorption. Further research is needed to establish robust in vitro-in vivo correlations that would enable the development of standardized in vitro tests for evaluating formulations aimed at modulating lipid digestion.

As the food industry evolves, the choice of emulsifiers has become increasingly important in responding to consumer preferences for healthier and more natural ingredients. Although synthetic emulsifiers like Tweens and Spans create highly stable emulsions (Tadros, 2014), this shift is driving the industry to explore natural alternatives that can effectively replace synthetic options while aligning with clean-label and sustainability trends. The most commonly used natural emulsifiers in food formulations, valued for their effective emulsifying properties, include proteins like egg whites and soy, natural block-copolymers like gum arabic or sugar beet pectin, phospholipids like lecithin, and plant-derived saponins.

In addition to the type of emulsifier used to stabilize the emulsion, its concentration has been found to significantly impact the rate of lipid digestion. Typically, higher emulsifier concentrations lead to a reduction in oil droplet size and produce more stable emulsions, which are associated with higher digestion rates (Muhamad et al., 2016). However, for certain stabilizers such as gelatin particles used in Pickering emulsions, increased emulsifier concentrations can actually reduce emulsion stability, leading to delayed digestion. Tan et al. found that increasing the concentration of gelatin particles created a thicker interfacial layer around oil droplets, which counteracted the positive effect of smaller droplet sizes and contributed to reduced emulsion stability (Tan et al., 2014). Moreover, there is a critical concentration limit for emulsifiers, known as “over-emulsification”, beyond which emulsion stability begins to decline. This occurs when an excessive amount of emulsifier creates an imbalance at the droplet interface, leading to destabilization (Demet Guzey & McClements, 2006). At concentrations above this threshold, the excess emulsifier molecules accumulating at the interface repulse each other disrupting the interfacial film.

3.1.7. Calcium concentration

Calcium ions play an important role in lipid digestion by acting as cofactors for pancreatic lipase and facilitating the precipitation of free fatty acids that accumulate at the lipid-water interface during lipolysis. By adjusting calcium levels in functional foods, fat digestion can be modulated, potentially lowering lipid uptake and enhancing fat excretion.

Calcium ions are integral to the 3D structure of pancreatic lipase, where they help maintain the enzyme’s stability and reduce electrostatic repulsion between the enzyme and the charged lipid-water interface (A. Salhi et al., 2021). Additionally, calcium ions and free fatty acids may generate soaps, potentially impacting the kinetics of lipolysis by removing free fatty acids from the lipid-water interface. These soaps can be insoluble, which can reduce fat absorption in the intestine. Compounds binding Ca^{2+} ions such as polyelectrolytes may be used to inhibit the transfer of lipid digestion products from the interface, limiting access and inhibiting the catalytic activity of lipase.

Calcium ions are also vital for the catalytic function of secretory phospholipase A2 (sPLA2-IB), where they interact with the phosphate group of the phospholipid substrate and stabilize the negative charge in the oxyanion hole (N. J. Liu et al., 2016). Both substrate binding and catalysis depend on Ca^{2+} ions, which are coordinated within a bipyramidal coordination geometry. In addition to two other coordinating ligands, one water molecule coordinated to the Ca^{2+} ion in the axial region is displaced by the sn-3 phosphate group of the substrate. When bound to the enzyme, this water molecule undergoes deprotonation, producing a hydroxyl ion that subsequently attacks the sn-2 ester carbonyl group. This leads to the formation of a tetrahedral intermediate during the deacylation reaction. The breakdown of this tetrahedral intermediate is a rate-limiting step of this enzymatic reaction. Calcium ions not only facilitate the enzyme-substrate interaction but also play a role in sPLA2’s interaction with lipid aggregates (Rajakannan et al., 2002). By condensing the polar head groups of negatively charged phospholipids, calcium ions help organize the substrate molecules, optimizing their accessibility to the enzyme (Sovago et al., 2007). Controlling calcium levels and interactions with Ca^{2+}-binding compounds opens up potential strategies for dietary interventions targeting fat metabolism.

3.2. Strategies for regulating lipid digestion and absorption

3.2.1. Adjusting the composition, thickness, and structure of the interfacial layer

When designing emulsion-based foods for customized lipid delivery, selecting the optimal emulsifier type and concentration is essential for achieving the desired lipid digestion kinetics. The emulsifier choice and its concentration significantly influence the size of lipid droplets formed in the gastrointestinal tract, as well as their stability against flocculation and coalescence (S. Li et al., 2022; Wooster et al., 2014). The same oil stabilized by various emulsifiers may exhibit very different digestion kinetics (Niu, Chen, et al., 2022a, 2022b; Sarkar et al., 2017; R. Zhang et al., 2015). For example, linseed oil emulsion stabilized by low molecular weight anionic surfactants such as cetyltrimethylammonium bromide (CTAB) or Citrem have been shown to undergo severe coalescence in the gastric juice, which greatly reduced the contact area

between oil droplets and both bile salts and the lipase and led to diminished digestion rate. Linseed oil emulsions stabilized by protein stabilizers like gelatin and sodium caseinate underwent flocculation and partial coalescence while those stabilized with gum arabic effectively resisted both processes and maintained excellent stability in gastric juice. These also exhibited greater resistance to environmental stresses such as pH and temperature changes compared to emulsions stabilized with proteins or low molecular weight surfactants (Kontogiorgos, 2019; Lamothe et al., 2020; Wu et al., 2016).

Resistance of lipid emulsions to highly variable conditions of the digestive tract may also be improved by replacing digestible emulsifiers, such as lecithin, or milk-derived proteins like casein (Borreani et al., 2017) with non-digestible emulsifiers including sugar beet pectin, chitosan, microcrystalline chitin, microcrystalline cellulose, resistant starch (granular starch or retrograded starch), silica particles, etc. (Tzoumaki et al., 2013). Interfacial layers made of non-digestible emulsifiers can form thick viscoelastic films at the oil-water interfaces that are not susceptible to degradation by digestive enzymes including pepsin, trypsin, and amylase and can retain their structural integrity in gastrointestinal fluids for extended periods (Borreani et al., 2017; Sarkar et al., 2019; Tzoumaki et al., 2013). Among non-digestible emulsifiers, cationic polysaccharides such as chitin or chitosan (a cationic polysaccharide derived from chitin) have proven particularly valuable due to their ability to bind negatively charged bile salts, anionic free fatty acids, lipase, and colipase molecules (Espinal-Ruiz et al., 2014; Y. Tan et al., 2020; R. Zhang et al., 2019). These polysaccharides can inhibit lipid digestion in two main ways. First, they can form a protective coating around negatively charged oil droplets. This coating binds bile salts, lipase, and colipase, trapping them at the interface. This coating prevents the displacement of surfactant molecules at the oil-water interface (Espinal-Ruiz et al., 2014; Y. Tan et al., 2020; R. Zhang et al., 2019). Second, chitin or chitosan can promote the flocculation or aggregation of lipid droplets (Y. Tan et al., 2020). Both mechanisms limit lipase access to the lipids, thus inhibiting their breakdown (Mun et al., 2006). Additionally, chitosan's ability to bind anionic free fatty acids and bile salts may alter the composition and availability of the mixed micelles, potentially affecting their absorption (Qin et al., 2016).

The digestion rate of lipids in emulsion-based foods can be reduced by depositing thicker interfacial layers on the surfaces of oil droplets. These layers act as protective barriers, limiting the access of lipolytic enzymes and bile salts to the emulsion interface. Oil droplets with thicker surfactant layers are digested more slowly than those with thinner coatings. McClements and Li (McClements & Li, 2010) compared the digestion rates of corn oil-in-water nanoemulsions stabilized by β-lactoglobulin with droplet sizes of 60 nm against conventional emulsions with 200 nm droplets. They found that the digestion rate was slower in the nanoemulsion compared to the conventional emulsion. This disparity stemmed from variations in the thickness and structure of the interfacial layer surrounding the lipid droplets. In the conventional emulsion, the droplets were coated by a thin monolayer of spherical protein molecules. In the nanoemulsion, the droplets were covered by a substantially thicker layer of aggregated protein molecules as a result of droplet shrinkage during their preparation by solvent evaporation. This thick interfacial layer effectively hindered bile salts from displacing protein molecules from the interface, impeding lipid digestion. It has been also found that the composition and thickness of the interfacial layer adjoining the phase boundary could exert a comparable influence on lipid digestion rate as emulsion droplet size (McClements & Li, 2010).

Another strategy for generating thicker interfacial layers on oil droplets involves the electrostatic deposition of multilayer adsorption films via layer-by-layer (LbL) assembly of oppositely charged polyelectrolytes (Kupikowska-Stobba & Lewińska, 2020; Niu et al., 2023). This method enables control over lipid digestion rates by adjusting the number and thickness of the assembled layers. The stability of polyelectrolyte multilayers deposited using the electrostatic technique is highly sensitive to the pH and ionic strength of the solution surrounding the oil droplets, which poses a significant limitation to this approach. As the lipid emulsion travels from the mouth to the stomach and then to the small intestine, the pH of the digestive fluids changes significantly: from 5.0 to 7.0 in the mouth, dropping to 1.5–3.0 in the stomach, and rising to 6.0–7.5 in the small intestine (Mao & Miao, 2015). Therefore, with the progress of digestion, the changes in the digestive juice pH may lead to the destabilization and dissociation of the polyelectrolyte multilayer. The polyelectrolytes dissociated from the emulsion droplets can complex Ca^{2+} ions present in the digestive juice. Calcium ions serve a vital role in lipid digestion, acting as cofactors for pancreatic lipase and aiding in the precipitation of free fatty acids that accumulate on the surface of oil droplets in the course of lipolysis. Complexation of Ca^{2+} ions by polyelectrolyte molecules may inhibit the timely transfer of lipid digestion products from the interface, limiting access and catalytic activity of lipase. Dissociated polyelectrolytes may also increase viscosity around oil droplets which can further hinder migration and adsorption of bile salts and lipase to the interface. While these inhibitory effects on lipid digestion may be advantageous for preventing or managing obesity, they could also potentially hinder the assimilation of essential fatty acids, beneficial lipids, lipid-soluble vitamins, and other lipid-soluble compounds necessary for optimal health.

The limitations of polyelectrolyte films have prompted research into the development of alternative types of interfacial layers. Promising results have been achieved with polysaccharide-protein interfaces, particularly those based on covalent peptide-polysaccharide conjugates produced by the Maillard reaction. This reaction leads to the formation of strong, irreversible bonds between the carbonyl groups of polysaccharide molecules and the amino groups of protein molecules (Yang, Cui, Gong, Guo, et al., 2015; Yang, Cui, Gong, Miller, et al., 2015). The protein moiety is adsorbed at the oil-water interface, while the polysaccharide moiety extends into the continuous phase. Interfacial layers made of covalent conjugates are much more stable under the harsh environment of the digestive tract than non-covalent complexes formed through electrostatic, hydrophilic, or hydrophobic interactions. This significantly reduces their susceptibility to destabilization during the transit of oil droplets through the GIT (Niu et al., 2023; Sun et al., 2022).

Another approach to modulating the digestion rate of lipids involves the use of Pickering emulsions. These emulsions utilize solid particles adsorbed at the oil-water interface to stabilize the droplets. These emulsions tend to show lower lipid digestion rates than emulsions stabilized with conventional surfactants due to the higher adsorption energy of solid particles to the interface. Hence, displacing these particles by bile salts requires more energy, making Pickering emulsions less prone to coalescence and reducing their digestion rate (Nikbakht Nasrabadi et al., 2020; Zhao et al., 2021). The key limitation of the interfacial layers formed by solid particles is the frequent occurrence of gaps between the particles, which can expose the oil phase to lipolysis. The strategies developed to overcome this issue include using anisotropic or polydisperse particles instead of conventional, monodisperse spherical particles. Polydisperse particles have a superior ability to fill small or irregular gaps, thus the interfacial layers composed of them are much less susceptible to discontinuities. To further enhance the stability of interfacial layers in Pickering emulsions, solid particles deposited on the interface can be sintered or fused into a compact layer by heating (Sarkar et al., 2019). These studies underscore the significance of the nature, structure, and thickness of the interfacial layer, as these parameters can substantially impact the rate and degree of lipid digestion.

In summary, the development of emulsion-based foods for tailored lipid delivery requires understanding various factors, including emulsifier type and interfacial stability. The choice of emulsifying agents significantly influences the stability of the water-lipid interface within the gastrointestinal tract. Non-digestible emulsifiers, covalent peptide-polysaccharide conjugates, and Pickering particles can create robust interfacial layers that control lipid digestion kinetics by hindering the adsorption of lipolytic enzymes and bile salts. Furthermore, the deposition of thick multilayer adsorption films, such as those formed through

layer-by-layer technique, enables control over lipid digestion rates by allowing the tailoring of the number and thickness of the assembled layers.

3.2.2. Reducing interface surface area through flocculation

Another approach to slowing lipid digestion involves limiting the specific surface area of lipid droplets by promoting their aggregation into larger clusters through flocculation (Wang, Xu, et al., 2019). Flocculation is the process whereby emulsion droplets aggregate into larger clusters, or flocs, without coalescing (Shen et al., 2019; L. Wang et al., 2012). By reducing the specific surface area of the interface, flocculation decreases the number of sites available for the adsorption of bile salts, lipase, and colipase.

Flocculation induction has been extensively studied as a strategy for reducing the digestion rate of protein-stabilized emulsions (McClements, 2004a). Flocculation of these emulsions can be induced by proteolytic enzymes, such as pepsin, or through acidification (e.g., in the stomach) (Kenmogne-Domguia et al., 2012; Sarkar et al., 2009; Sandra et al., 2008). As the initially stable emulsion passes through its isoelectric point, it can become flocculated. In this flocculated state, the emulsions are prone to coalescence due to proteolysis of the interfacial layer (Golding & Wooster, 2010). The degree to which this process reduces the emulsion digestion rate depends on the type of protein used as an emulsifier. For instance, emulsions stabilized by β-conglycinin, a major component of soy protein, exhibit a higher degree of flocculation in gastric juice than emulsions stabilized by soy protein isolate, soy lipophilic protein, or glycinin (Zhong et al., 2021). Conversely, to accelerate lipid digestion, stabilizers that prevent flocculation can be utilized. Lecithin, a common ingredient in infant formulas, is an example of an emulsifier that prevents the flocculation of lipid droplets in the digestive tract (Zhu et al., 2021).

Reducing the interface surface area through flocculation may present certain challenges. Flocculation can alter the texture and stability of the emulsion, potentially affecting the mouthfeel and appearance of the product. Such changes could influence consumer acceptance and pose obstacles to market adoption. Additionally, achieving precise control over the degree of flocculation is often difficult, resulting in variability in the final product. In some instances, flocculation may not adequately reduce the surface area of lipid droplets, leading to uneven floc/droplet size distribution and potential issues, which can negatively impact digestion, absorption, and ultimately the nutritional profile of the product.

In conclusion, flocculation is an effective method to slow down lipid digestion by reducing the specific surface area available for the adsorption of bile salts and lipases. This technique has been studied extensively, particularly in protein-stabilized emulsions, where the type of protein stabilizer significantly impacts flocculation rates. While flocculation can help manage lipid digestion rates, it may also alter the texture and appearance of food products, potentially affecting consumer acceptance. Careful formulation is essential to ensure that flocculation does not hinder the absorption of essential nutrients, such as lipid-soluble vitamins and fatty acids.

3.2.3. Encapsulation of lipid droplets in gel matrices

The physicochemical properties of the continuous phase surrounding oil droplets significantly influence lipid digestion kinetics. One pivotal characteristic that affects the emulsion digestion process is the viscosity of the continuous phase. In general, high-viscosity continuous phases tend to obstruct the diffusion and adsorption of bile salts and lipase to the oil-water interface, as well as mixing and mass transfer during lipolysis, thus delaying digestion (Ni et al., 2021). To reduce the lipid digestion rate, the viscosity of the continuous phase can be increased by adding highly viscous stabilizers such as xanthan gum (Sun et al., 2018) or soybean polysaccharides (Udomrati et al., 2020). Soybean polysaccharides can increase the overall viscosity of the continuous phase, particularly around the lipid droplets. Due to their surface-active properties, they can also adsorb to the oil-water interface, forming a protective coating that restricts the access of digestive enzymes to the lipid phase, further slowing down the digestion process. Xanthan gum reduces the rate of lipid digestion through a different mechanism. Although it is a non-surface-active polysaccharide, its high molecular weight allows it to significantly increase the viscosity of the aqueous phase, even at low concentrations. This increased viscosity helps prevent the sedimentation or floating of droplets and particles. As the concentration of xanthan gum increases, the viscosity of the system is further enhanced, improving its stabilizing capacity.

An alternative approach to delaying lipid digestion involves entrapping oil droplets within a hydrogel matrix, such as gelatin or indigestible fiber gels, which serve as a protective barrier against lipolysis. This entrapment enhances the stability and provides a controlled release of lipids, leading to improved shelf-life of the emulsion. Emulsion entrapment within hydrogels is particularly beneficial for products like dairy items (e.g., ice cream, yogurt, cheese) and processed meats (Geremias-Andrade et al., 2016), where maintaining emulsion integrity is essential. The gel matrix serves as a protective barrier against lipolysis by preventing lipases from accessing their substrates (Q. Guo et al., 2014a, 2014b). Altering the viscosity of a meal by incorporating alginate can also slow gastric emptying, which can lead to an increased sensation of fullness and reduced postprandial glycemia in individuals with diabetes (Hoad et al., 2004; Torsdottir et al., 1991).

The protection of emulsions against digestion largely depends on the mechanical properties and digestibility of the gel matrix. It has been shown that firmer gels provide greater protection against lipid digestion than softer gels, due to their denser network of polymer molecules and lower disintegration rate, which more effectively block digestive enzymes from accessing the oil droplets (Q. Guo et al., 2016, Guo et al., 2017a). Fig. 5 illustrates the differences in digestion rates for canola oil-in-water emulsions entrapped in firm and soft whey protein isolate (WPI) gels, produced at varying NaCl and $CaCl_2$ concentrations. When considering the chemical composition of gel matrices for encapsulating lipids, proteins are typically not the optimal choice, as they are susceptible to enzymatic breakdown by digestive proteases. In contrast, gels composed of indigestible dietary fibers will maintain their structural integrity within the small intestine, providing an effective barrier to lipid digestion. The resistance of the gel matrix to digestion can be enhanced by incorporating salts (such as NaCl and $CaCl_2$) (Q. Guo et al., 2017a), microgel particles (like whey protein microgel particles) (X.-M. M. Li et al., 2021; Sarkar et al., 2016), or cross-linking polymer molecules to form an interconnected three-dimensional network (Farooq et al., 2022).

A promising strategy for enhancing the stability and functionality of emulsions is encapsulating lipid droplets within hydrogel microcarriers such as microbeads and microcapsules (Kupikowska-Stobba & Lewińska, 2020). One of the most commonly used polymers for encapsulating emulsions is alginate, a natural polysaccharide derived from brown seaweed. Studies have shown that encapsulating emulsions in alginate microbeads effectively prevents lipid decomposition in gastric juice and delays lipolysis in the proximal small intestine (Corstens et al., 2017; Zhang, Zhang, & McClements, 2016). By delaying lipolysis, these microbeads can deliver undigested lipid droplets to the distal small intestine, where lipolysis takes place (Corstens et al., 2017, 2018). Such microbeads may effectively induce ileal brake inhibiting digestion, reducing appetite, and increasing satiety (P. W. J. Maljaars et al., 2008; Zhang, Chen, et al., 2016). Emulsions are usually encapsulated within alginate microbeads through the ionic gelation method, a simple, fast, and cost-effective technique that involves cross-linking alginate with divalent cations like calcium ions (Lewińska et al., 2017). This method allows for the formation of hydrogel beads under mild conditions, preserving the delicate nature of the emulsion during the encapsulation process, and ensuring the encapsulated components retain their integrity, properties, and desired functionality.

The degree of lipid protection against digestion can be further

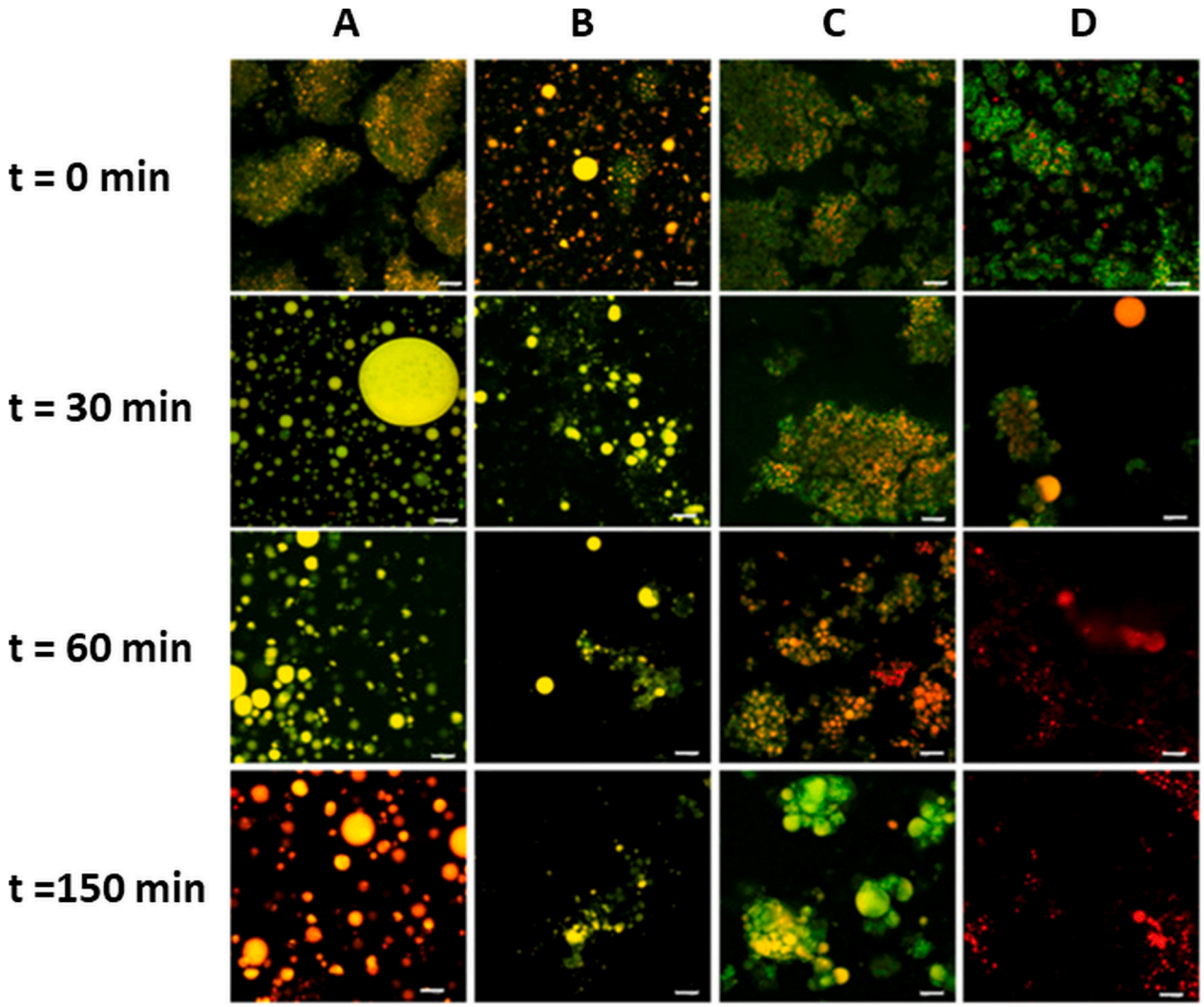

Fig. 5. Confocal scanning microscopy images of canola oil oil-in-water emulsions stabilized and gelled with whey protein isolate (WPI) at different concentrations of NaCl and $CaCl_2$. Emulsions were prepared by high-pressure homogenization and entrapped in soft WPI gels (A and B) gelled at lower salt concentrations (7 mM + 25 mM $CaCl_2$, and 70 mM + 25 mM $CaCl_2$, respectively), or in firm gels (C and D) fabricated using higher salt concentrations (200 mM NaCl +25 mM $CaCl_2$, or 200 mM NaCl +25 mM $CaCl_2$, respectively). The gelled emulsions were then subjected to intestinal digestion over 0, 30, 90, and 150 min. Gels depicted in columns A and C underwent 60 min of digestion in gastric juice before intestinal digestion. Gels depicted in columns B and D underwent 240 min of gastric digestion before intestinal digestion. Adapted with permission from Q. Guo et al., 2017a, Food Hydrocolloids published by Taylor & Francis, 2017. Copyright © 2017 Taylor & Francis.

enhanced by encapsulating lipids in core/shell microcapsules, such as alginate/pectin microcapsules (Norcino et al., 2022). In core/shell microcapsules, the hydrogel matrix is surrounded by a natural or synthetic polymer shell (Kupikowska-Stobba et al., 2014; Lewińska et al., 2017; Morales et al., 2017; Przytulska et al., 2015). This arrangement provides an additional barrier against the diffusion of bile salts and proteins (Kupikowska-Stobba et al., 2021) including digestive enzymes and co-factors, increasing the resistance of encapsulated lipids to digestion. Recently, indigestible calcium alginate beads covalently cross-linked by oxidized polyphenols, including chlorogenic acid, tannic acid, caffeic acid, and catechin have been investigated as carriers for camellia oil emulsions (Farooq et al., 2022). Cross-linking the alginate molecules was shown to significantly slow down the disintegration of the beads under gastric conditions, delaying the release and hydrolysis of encapsulated lipids.

Hydrogel microbeads and microcapsules carrying an oil cargo can be used to deliver bioactive compounds such as fat-soluble vitamins (Martins et al., 2017;), proteins (Kupikowska-Stobba et al., 2021), essential oils (Yun et al., 2021), and antioxidants (Norcino et al., 2022). Encapsulation not only increases the stability of lipids and protects sensitive bioactive compounds, but also allows for the controlled release of flavors or nutrients. Furthermore, it facilitates the incorporation of these ingredients into various food and beverage products by masking undesirable tastes and aromas. However, the process also has some limitations that need to be considered in its application. One of the constraints of lipid droplet encapsulation is the potential alteration of the emulsion sensory properties such as texture, mouthfeel, and taste release. While encapsulating additive lipid droplets (e.g., omega-3 oil) can be an effective strategy for protecting them against oxidative stress or controlling their digestion rate, when a product contains a major oil fraction, the gel matrix surrounding the primary oil phase could significantly alter its overall sensory experience. Since the oil often plays a crucial role in the product's sensory properties, this approach is generally not recommended in such cases. Additionally, the compatibility of lipid droplet encapsulation with other ingredients and formulation components needs to be carefully evaluated. Furthermore, certain ingredients may interact unfavorably with the gel, leading to issues such as phase separation or compromised emulsion stability. Despite these challenges, lipid encapsulation is a promising strategy for modulating lipid digestion and bioavailability in functional food products.

3.2.4. Incorporating cations in the continuous phase

As previously mentioned, the composition and concentration of ions in the continuous phase play a crucial role in emulsion stability, consequently affecting the rate of lipid digestion. The impact of ions on the lipid digestion rate is complex. Metal cations such as Na^{+}, K^{+}, Ca^{2+}, and Mg^{2+} ions can shield the negative surface charges on oil droplets, effectively reducing the electrostatic repulsion between them. This increased interaction heightens the risk of emulsion destabilization, which can significantly reduce the rate of lipid digestion (Golkar et al., 2018; A.-I. Mulet-Cabero & Wilde, 2021; Pan et al., 2020). Conversely, lipid digestion is accelerated by the presence of Ca^{2+} or Mg^{2+} ions in the digestive juices, which aids in the formation of mixed micelles with free fatty acids and facilitates the removal of digestion products from the water-oil interface. Incorporating these ions into the aqueous phase may accelerate the overall lipid digestion process (Acevedo-Fani & Singh, 2022). However, the stimulatory effect of Ca^{2+} and Mg^{2+} on lipolysis might be diminished if the formulation contains anionic emulsifiers, as these emulsifiers can readily bind to these ions. Therefore, to maintain their stimulatory effect, Ca^{2+} and Mg^{2} ions should not be combined with anionic stabilizers in the same formulation. Additionally, calcium ions significantly impede the transport and absorption of saturated long-chain free fatty acids by forming insoluble complexes (soap precipitates) with these fatty acids (Astrup et al., 2010; Ayala-Bribiesca et al., 2017; Golding & Wooster, 2010; Guéguen & Pointillart, 2008). These insoluble compounds can significantly reduce the bioavailability of fatty acids, which may be of significant interest for the development of foods for controlled delivery of dietary fats.

3.2.5. Pancreatic lipase inhibitors

Pancreatic lipase inhibitors offer an effective strategy for modulating the digestion and absorption of dietary fats. By inhibiting the catalytic activity of pancreatic lipase, they can slow down lipid hydrolysis, potentially reducing calorie absorption and promoting a greater sense of satiety. This approach can be leveraged in the development of functional foods that may aid in weight management. Currently investigated pancreatic lipase inhibitors can be divided into two main categories: chemically synthesized and natural (Cardullo et al., 2021). Chemically synthesized pancreatic lipase inhibitors include β-lactone derivatives, alkylphosphonate derivatives, carbonyl derivatives, triacylglyceride derivatives, and heterocyclic compounds (Kumar & Chauhan, 2021). These synthetic inhibitors often have more adverse side effects and worse safety profiles compared to natural alternatives. The only synthetic pancreatic lipase inhibitor approved by the FDA for treating obesity is orlistat, which is a synthetic derivative of the naturally occurring compound lipstatin. Lipstatin is produced by the bacterium *Streptomyces toxytricini* and interferes with lipid digestion by binding to the active site of lipase and altering its conformation, thereby inhibiting its catalytic activity. Orlistat remains bound to lipase and is excreted along with the enzyme, without causing long-term effects on the body. However, orlistat usage frequently leads to adverse side effects such as fecal urgency, fecal incontinence, steatorrhea, oily spotting, bloating, diarrhea, abdominal pain, and anal fissures (de la Garza et al., 2011).

To mitigate the potential adverse effects associated with synthetic lipase inhibitors, researchers have explored natural compounds as safer alternatives. Natural lipase inhibitors are derived from plants, fungi, bacteria, and algae, and include flavonoids, carotenoids, polyphenols, terpenoids, alkaloids, phytosterols, saponins, soy proteins, protamine, ovalbumin, and chitosan (Granato et al., 2020; Hu et al., 2022; Lin et al., 2021; Yang et al., 2022; Y. Zhang et al., 2023; Zhou, Wang, et al., 2021; Acevedo-Fani & Singh, 2022; Bajes et al., 2020; Birari & Bhutani, 2007; Dąbrowski et al., 2024; Podsędek et al., 2014). The inhibitory effects of these compounds on pancreatic lipase activity have been widely studied.

For example, Du et al. (Du et al., 2018) found that astaxanthin derived from *Phaffia rhodozyma* reduced pancreatic lipase activity in a non-competitive manner within a tested range of 0–70 μg/mL. At a dose of 40–50 μg/mL, astaxanthin exhibited an inhibitory effect equivalent to 0.6 μg/mL of orlistat, indicating that it alters the secondary conformation of lipase. Similarly, Matsumoto et al. demonstrated significant inhibition of lipase activity in the gastrointestinal tract and suppressed lipid absorption model by two marine carotenoids, fucoxanthin and fucoxanthinol (Matsumoto et al., 2010). In a rat study, the total triglycerides released into the lymph 4 h after ingestion were markedly lower in the carotenoid-fed groups compared to controls. An in vitro triolein digestion experiment also demonstrated dose-dependent inhibition of pancreatic lipase by fucoxanthin and fucoxanthinol, with approximately 50 % inhibition at 500 μg/mL concentrations. A double-blind, placebo-controlled study investigating the effect of fucoxanthin in overweight Japanese adults showed that relative parameters of body condition were significantly improved in the fucoxanthin-treated groups compared to a placebo group (Hitoe & Shimoda, 2017). Additionally, an extract from the freshwater alga *Oedogonium intermedium*, rich in neoxanthin, exhibited pancreatic lipase inhibitory activity with IC50 values around 4 mg/mL for the crude extract and 1 mg/mL for the saponified lipid extract (N. Wang et al., 2018).

Studies indicate that the lipase inhibition mechanism relies on the blockage of the catalytic site's entrance channel, involving key amino acid residues such as Ser152, Asp176, and His2638. Through *in-silico* molecular docking analysis, Ahmed et al. identified ten plant-derived compounds with potent inhibitory effects on pancreatic lipase (Ahmed et al., 2018). These compounds included kushenol K (a flavonoid from *Sophora flavescens*), rosmarinic acid (a phenolic ester found in plants such as *Perilla frutescens* and *Salvia* species), reserpic acid (a yohimban alkaloid from *Rauvolfia vomitoria*), munjistin (a 1,3-dihydroxyanthraquinone-2-carboxylic acid from *Rubia* species), and several other flavonoids, lignans, and anthraquinones. The docking scores (used to predict their binding affinity to the lipase) for these inhibitors, ranged from −12.03 to −13.78 kcal/mol, and were higher than that of orlistat, suggesting their potential as more effective and targeted lipase inhibitors.

To summarize, while chemically synthesized inhibitors like orlistat are effective, they can cause significant side effects. In contrast, numerous plant-derived molecules with potent inhibitory effects on pancreatic lipase have been identified, presenting a safer alternative. Studies have shown that compounds like astaxanthin and marine carotenoids effectively reduce lipase activity and lipid absorption, demonstrating effects comparable to orlistat.

3.2.6. Bile salt chelating agents

Given the various side effects associated with pancreatic lipase inhibitors, researchers have shifted their focus toward developing regulators of lipid digestion that target bile salts instead of pancreatic lipase (T.-T. Liu et al., 2020). When added to emulsion-based foods, these agents decrease the extent and rate of lipid digestion and absorption by chelating bile salts. By binding to bile salts, these compounds can also alter the release of lipids from food, allowing for more controlled delivery of dietary fats.

Bile salt chelating agents are cationic compounds that form stable complexes with negatively charged bile salt molecules in the small intestine. This process sequesters bile salts, preventing their adsorption to oil droplets, the displacement of emulsifier molecules from the interface, and the subsequent reabsorption of the bile salts (Ramírez-Pérez et al., 2017; Tangso et al., 2014). Reducing the bile acid pool stimulates increased bile acid synthesis, which competes with cholesterol production in the liver and contributes to the lowering of serum cholesterol levels. Among potential bile salt chelators, chitosan has emerged as an attractive candidate due to its cationic nature under physiological conditions, which enables it to bind negatively charged bile salt molecules through electrostatic interactions (Zhou et al., 2006). Its high binding affinity makes chitosan one of the most effective chelators, particularly for managing hypercholesterolemia (J. Liu et al., 2008). The chelating efficacy of chitosan is strongly influenced by its physicochemical properties, such as molecular weight and degree of deacetylation (Ruiz &

Corrales, 2017). Smaller chitosan particles exhibit an enhanced ability to bind and sequester cholesterol. Chitosans with a higher degree of deacetylation and higher molecular weight more effectively reduce total cholesterol and low-density lipoprotein cholesterol levels, while also increasing high-density lipoprotein cholesterol levels, though not all of these differences were found to be statistically significant.

In addition, dietary fibers like pectin (Guardiola-Márquez et al., 2020; Massa et al., 2022), β-glucan (Eluppai Asthagiri Kumaraswamy et al., 2024; Singla et al., 2024), and cellulose esters (Torcello-Gómez et al., 2015) can chelate bile salts through hydrogen bonding and hydrophobic interactions. By forming gel-like structures, these fibers sequester bile salts and fats, contributing to cholesterol reduction. Additionally, dietary fibers offer benefits such as promoting satiety, supporting digestion, and enhancing overall gut health. Among dietary fibers, β-glucan found in oat is recognized as the most effective at lowering cholesterol, with a potency comparable to chitosan (Massa et al., 2022). Pectin is considered moderately effective, having been demonstrated to lower cholesterol levels and improve gastrointestinal health, although its bile salt-binding capacity is weaker compared to β-glucan. Cellulose esters are less effective than chitosan or β-glucan at complexing with bile salts and reducing lipid digestion rate. It is important to note that, in large amounts, dietary fibers can also cause side effects like bloating, flatulence, or reduced nutrient absorption.

Proteins, such as soy proteins, and polyphenols (Bellesi & Pilosof, 2021; Eran Nagar et al., 2023) have also proven effective in inhibiting lipid digestion by interacting with bile salts (di Gregorio et al., 2021; Gunness et al., 2016; Lopez-Pena et al., 2019; Macierzanka et al., 2019; Pigliacelli et al., 2019; Torcello-Gómez et al., 2015). Polyphenols, for example, EGCG (epigallocatechin gallate) and oolongtheanins, found in green and oolong teas, inhibit lipid digestion by creating a hydrophobic environment that adsorbs bile acids, thereby reducing the micellar solubility and absorption of lipids like phosphatidylcholine and cholesterol (Naumann et al., 2020). However, proteins and polyphenols generally exhibit weaker bile salt chelating properties than chitosan (Y. Liu et al., 2023; Tveter et al., 2023).

The inhibitory potency of polyphenols is highly dependent on their concentration. Due to their relatively low bioavailability (Eran Nagar et al., 2023), higher doses are often required to achieve significant effects. Recently, polyphenol-dietary fiber conjugates have gained attention as they may offer prolonged bioactivity compared to isolated polyphenols, potentially enhancing their inhibitory effects (Fernandes, Mateus, & de Freitas, 2023). These conjugates can be created through carbodiimide-mediated coupling, free-radical-induced processes, or enzyme-facilitated polyphenol-polysaccharide conjugation methods. Using these approaches, phenolic acids such as caffeic, ferulic, coumaric, gallic, and vanillic acids can be covalently bonded to various polysaccharides, including chitosan (Chatterjee et al., 2015), pectin (Chun Wang et al., 2020), and starch (Wen et al., 2016).

Since bile salt chelating agents are typically large polymer molecules, they are not absorbed into the bloodstream from the digestive tract, preventing systemic effects. Instead, they are excreted almost entirely in the feces, along with bound bile salts. This augmented fecal excretion of bile salts stimulates the liver to synthesize more bile acids from cholesterol. Consequently, this process leads to a reduction in serum cholesterol levels, particularly in low-density lipoprotein (LDL), commonly referred to as “bad cholesterol”. Consequently, bile salt chelating agents are used in treating hypercholesterolemia to lower cholesterol levels. While generally safe due to their lack of systemic absorption, some bile salt chelators may cause gastrointestinal side effects such as diarrhea, constipation, flatulence, and bloating. Additionally, they may interfere with the absorption of fat-soluble vitamins and certain oral medications.

In summary, bile salt chelating agents are being explored as alternatives to pancreatic lipase inhibitors for regulating lipid digestion, as the latter can cause undesirable side effects. These cationic compounds form stable complexes with bile salts in the small intestine, reducing lipid digestion and absorption to allow for more controlled delivery of dietary fats. Chitosan has shown particular potential as a bile salt chelator, owing to its high binding affinity and ability to effectively manage hypercholesterolemia by lowering serum cholesterol levels. Other dietary fibers, such as β-glucan and pectin, also demonstrate bile salt-chelating properties that reduce cholesterol levels while supporting gut health.

3.2.7. Amphiphilic lipids

In recent years, there has been growing interest in using amphiphilic lipids to develop novel functional foods (Freire & Salentinig, 2024). Amphiphilic lipids have a unique molecular structure containing both hydrophilic and hydrophobic moieties, allowing them to self-assemble into various structures, such as vesicles, micelles, microemulsions, and liquid crystalline structures (Glatter & Salentinig, 2020). Their amphiphilic nature allows them to accumulate at water-oil interfaces and form structural barriers that hinder digestive enzymes from accessing dietary fats, thereby modulating lipid metabolism (Porter et al., 2007; Porter et al., 2008). For example, phospholipids like lecithin, commonly used to stabilize emulsions in food products, can inhibit lipase activity by forming physical barriers that limit enzyme access to triglycerides (Sadu Singh et al., 2020). Additionally, amphiphilic lipids can influence the action of bile salts, which are crucial for lipid emulsification and absorption in the small intestine (Salentinig, 2019).

Amphiphilic lipids can form lyotropic liquid crystals (LLCs), which play a key role in lipid digestion and absorption. Food-related amphiphilic lipids capable of forming LLCs include glycerol monooleate (GMO), long-chain fatty acids such as oleic acid, and omega-3 polyunsaturated monoacylglycerols (Engstedt et al., 2023; Freire et al., 2022; Manca et al., 2022; Shao et al., 2018). LLCs are self-assembled supramolecular structures that form when amphiphilic molecules, such as lipids or surfactants, are mixed with a solvent (usually water). LLCs exhibit distinctive properties, such as extensive lipid-water interfacial area and exceptionally low surface tensions, which enable the spontaneous formation of nanostructures (Salentinig, 2019). The molecular arrangement of LLCs is determined by the concentration of amphiphiles in the solvent. The system can transition between different phases, known as “mesophases”, depending on amphiphile concentration, temperature, and pH. The most common mesophases include micelles, hexagonal phases, and lamellar phases. Micelles are spherical aggregates of amphiphilic molecules in which the hydrophobic tails are buried inside while the hydrophilic heads face outward, interacting with the solvent. The hexagonal phase is a highly ordered structure where cylindrical aggregates of amphiphiles are arranged in a hexagonal pattern (Yaghmur et al., 2019), while the lamellar phase is a layered structure where alternating layers of water and lipid molecules form a sandwich-like arrangement (Salentinig et al., 2011). For example, at pH 8.6, oleic acid forms multilamellar vesicles, shifting to nanostructured emulsions at pH < 8.0 and oil droplets at pH < 6.5 (Manca et al., 2022). These structural changes alter the interfacial tension and induce self-propelling particle motion.

Due to their ordered lipid-water interfacial areas and in situ formation during emulsion digestion, LLCs may enhance the solubilization of poorly water-soluble compounds and modulate their interactions with intestinal cell membranes. Additionally, they could facilitate lipid digestion under low bile salt conditions, as seen in patients with digestive disorders or preterm infants (Freire et al., 2023; Salentinig, 2019). In experiments simulating the digestion of oil-in-water emulsions without bile salts, LLCs have been shown to form a lipid-water interface that partially compensated for limited lipase access to lipids. Although the precise role of LLCs during digestion is not yet fully understood, it is hypothesized that these structures may assist in solubilizing hydrophobic lipids in the absence of bile salts or when bile salts are scarce.

LLCs have been also shown to facilitate lipid absorption by maintaining lipid-water interfaces (Salentinig et al., 2013). These structures may act as reservoirs, storing lipids until sufficient bile salts are

available to convert them into absorbable mixed micelles. These mixed micelles are then absorbed through the intestinal mucosa. Some LLCs exhibit muco-adhesive properties, adhering to the gastrointestinal lining to further support nutrient absorption (Salentinig et al., 2013). The structure of LLCs can be modulated by altering pH and bile salt concentration or adding compounds like vitamin E to the oil phase (Freire et al., 2023). Tailoring of the structures formed during digestion presents a novel approach to controlling lipid digestion kinetics and nutrient bioavailability. Such systems can be used to facilitate the gradual release of fats, promoting more consistent nutrient absorption over time. This approach may be particularly beneficial for individuals who need a steady intake of lipids, such as athletes or patients with malabsorption disorders. Furthermore, incorporating amphiphilic lipids into structured lipid systems can modify the physical properties of fats within food matrices. This technology holds significant potential for developing personalized foods for infants, who need specific types of lipids for optimal growth and development.

Amphiphilic lipids are widely used in encapsulation technologies to enhance the stability and bioavailability of fat-soluble bioactives such as omega-3 fatty acids, carotenoids, and phytochemical antioxidants like curcumin (Rakotoarisoa et al., 2019). Among the various encapsulation systems for tailored lipid delivery, lipid nanoparticles show exceptional potential for the controlled release of lipophilic cargos. These nanoparticles exist in several forms, including nano-emulsions, cubosomes, and solid or gel-like lipid nanoparticles (Hou et al., 2020; Schachner-Nedherer et al., 2023; Seo et al., 2023; Tenchov et al., 2021; Yang et al., 2024). Rakotoarisoa et al. (Rakotoarisoa et al., 2019) utilized spongosome and cubosome lipid nanoparticles to *co*-encapsulate curcumin and fish oil rich in omega-3 polyunsaturated fatty acids. Since curcumin is water-insoluble and requires carriers to improve its bioavailability, and omega-3 fatty acids are prone to oxidation, encapsulating them in lipid nanoparticles can not only improve their stability but also enhance their absorption in the gastrointestinal tract and overall bioavailability.

An interesting system for encapsulation of β-carotene was proposed by Tan et al. (H. Tan et al., 2014). They produced stable oil-in-water Pickering high internal phase emulsions (HIPEs) using gelatin particles as emulsifiers, designed for use as nutraceutical carriers. The gelatin particles were irreversibly adsorbed at the oil-water interface, preventing droplet coalescence and stabilizing the emulsion. Notably, stable Pickering HIPEs were formed with minimal emulsifier concentrations at pH values far from the isoelectric point of the gelatin. Increasing the concentration of gelatin particles led to more solid-like Pickering HIPEs. This system allowed for controlled release of the encapsulated β-carotene, with the release rate easily adjustable by modifying the concentration of gelatin particles in the formulation.

High-internal-phase emulsions have been also successfully used for co-encapsulation of hydrophilic and hydrophobic cargos, such as probiotic bacteria suspensions and curcumin (Su et al., 2021), or anthocyanin and β-carotene (Lee et al., 2019). For example, Su et al. developed a high-internal-phase emulsion-based delivery system to co-encapsulate probiotic bacteria *Lactobacillus rhamnosus GG* and curcumin (Su et al., 2021). Composite hydrogel particles composed of β-lactoglobulin and propylene glycol alginate (PGA) served as particulate emulsifiers to facilitate the formation of stable HIPEs across a wide range of emulsifier concentrations (0.1 to 2.0 wt%). The oil droplet interface consisted of β-lactoglobulin nanoparticles and a PGA network, which collectively contributed to the gel-like behavior of the HIPEs. HIPEs with high particle loadings exhibited remarkable resistance to pasteurization, exhibiting no significant flocculation or coalescence. Importantly, the HIPE formulation effectively protected the probiotic bacteria and curcumin from degradation during processing, retaining up to 7.91 log CFU cm^{-3} of viable *Lactobacillus rhamnosus GG* and 93.0 % of curcumin after pasteurization. Furthermore, the HIPEs effectively delayed the release of curcumin and improved the bacteria viability under simulated gastrointestinal conditions.

Lee et al. (Lee et al., 2019) proposed an innovative system for co-encapsulating hydrophilic anthocyanin and hydrophobic β-carotene using gel-in-gel water-in-oil high internal phase emulsions (HIPEs). These HIPEs exhibited excellent stability due to structuring both phases of the emulsion using interfacial and biphasic network stabilization. Unlike oil-in-water HIPEs, water-in-oil HIPEs are generally unstable and challenging to produce without high surfactant concentrations. Lee's approach addresses these challenges by using hydrogels dispersed in oleogels and inducing the spontaneous formation of Pickering crystals and biphasic networks. The system employed biodegradable glycerol monooleate – a glycerol fatty ester that can solidify to form fat crystals – providing spontaneous interfacial Pickering stabilization of the water-in-oil emulsion. To further enhance emulsion stability and viscoelastic rheological properties, natural structuring agents, including carrageenan and beeswax, were incorporated into both the internal aqueous phase and external oil phase. This led to the formation of HIPEs with a carrageenan hydrogel in the internal water phase and a beeswax-containing oleogel in the external oil phase. These HIPEs showed strong resistance to gastrointestinal conditions and provided a controlled release of the co-encapsulated anthocyanin and β-carotene.

To summarize, the unique self-assembled structures formed by amphiphilic lipids, such as vesicles and micelles, can be used to regulate lipid digestion by forming barriers against digestive enzymes and bile salts. Those that form lyotropic liquid crystals can enhance fat solubilization and absorption, particularly under conditions where bile salt levels are low. Additionally, these lipids are utilized in encapsulation technologies to improve the stability and bioavailability of fat-soluble bioactives, such as omega-3 fatty acids and carotenoids, allowing for controlled nutrient delivery. Integrating amphiphilic lipids into functional foods offers innovative solutions for optimizing lipid metabolism and enhancing nutrient absorption, particularly for specific populations, including infants and individuals with malabsorption issues.

3.2.8. *Stimuli-responsive lipid delivery systems*

One of the most exciting advancements in the development of functional foods for tailored fat delivery is "smart" stimuli-responsive lipid delivery systems. These systems are designed to respond to specific physiological triggers, such as changes in pH or the presence of certain digestive enzymes, ensuring the targeted delivery of fats and fat-soluble nutrients to the specific regions within the gastrointestinal tract. These controlled-release platforms can be used to enhance nutrient bioavailability, absorption, and metabolic efficiency.

Emulsion-based systems have emerged as a particularly versatile platform for stimuli-responsive lipid delivery. By utilizing appropriate emulsifiers and stabilizers, these systems can be engineered to withstand the harsh conditions of the stomach, protecting their cargo, and then rapidly disintegrate in the more alkaline environment of the small intestine, facilitating nutrient absorption. These systems exploit natural variations in pH and ionic composition along the gastrointestinal tract, which can significantly alter the structure of the oil-water interface, leading to structural transitions. For example, Frigerio et al. demonstrated that increasing the pH of a triolein/water system from 6.5 to 9.0 led to the formation of multilamellar interfacial layers in the presence of TRIS buffer (Frigerio et al., 2024). The authors attributed this phenomenon to the hydrolysis of triolein, which released oleic acid that subsequently interacted with the TRIS buffer.

Other examples of pH-sensitive lipid delivery platforms include nanostructured emulsions and fatty acid self-assemblies, which can undergo structural rearrangements in response to specific pH conditions within the gastrointestinal tract. Freire et al. (Freire et al., 2022) explored pH-induced structural transformations in oleic acid–triolein–water emulsions. They found that higher pH values triggered the deprotonation of carboxyl headgroups, converting neutral headgroups into negatively charged species. This alteration in molecular polarity increased electrostatic repulsion between the deprotonated headgroups, triggering structural changes in the self-assembled system, including a

transition from lamellar to micellar nanostructures (Freire et al., 2022). Such transformations arise from the interplay between the charged headgroups and hydrophobic tails, which can adopt different packing arrangements depending on pH.

Another category of stimuli-responsive platforms comprises pH-sensitive polymer carriers, which release encapsulated fats when exposed to the acidic environment of the stomach or the slightly alkaline conditions of the small intestine. These carriers are primarily used to transport labile lipids, such as hydrophobic vitamins, carotenoids, and drugs (Kupikowska-Stobba et al., 2021; Kupikowska-Stobba & Lewińska, 2020), through the harsh gastric environment to the small intestine, ensuring more efficient absorption and preventing their premature digestion (McClements & Li, 2010). These lipid delivery systems can also improve lipid digestion under compromised digestive conditions, such as those seen in preterm infants and individuals with exocrine pancreatic insufficiency or chronic pancreatitis (Lowe, 2018). For instance, pH-sensitive functional food structures loaded with pancreatic lipase could be designed to transport the enzyme through the stomach to the small intestine, where it can exert its lipolytic activity. Recently, Zhang et al. proposed a targeted pancreatic lipase delivery system using pH-responsive hydrogel alginate beads (Zhang, Zhang, & McClements, 2016).

Enzymatically triggered release systems are another innovative approach under investigation. Lipid-based nanoparticles, engineered with lipase-sensitive amphiphilic coatings, can release their contents only in the presence of lipase enzymes. This technology can facilitate the targeted delivery of genes (Akkuş-Dağdeviren et al., 2023), drugs Iversen et al., 2024; Mohammed et al., 2023; Tang et al., 2022) and bioactives, such as coenzyme Q10 (Pastor-Maldonado et al., 2020) and fat-soluble vitamins (A, D, E, and K), to optimize their absorption at specific points along the digestive tract or in other areas of the body, such as adipose tissue (Hou et al., 2020).

In summary, stimuli-responsive lipid delivery systems represent a significant advancement in functional foods for tailored fat delivery. These systems are designed to react to specific physiological triggers, including pH changes and the presence of digestive enzymes. Emulsion-based systems, stabilized with appropriate emulsifiers, can withstand stomach conditions and rapidly disintegrate in the small intestine, facilitating nutrient absorption through structural transitions triggered by pH variations. pH-sensitive polymer carriers and enzymatically-triggered release systems can be used to further optimize nutrient delivery by ensuring that labile lipids and bioactives are released under optimal conditions for absorption, which is particularly beneficial for individuals with malabsorption disorders.

The factors influencing lipid digestion and absorption rates, as well as the strategies for tailoring dietary lipid delivery, discussed in the preceding sections, are summarized in Fig. 6. The next section will focus on developing functional food products with lipid release profiles tailored to specific consumer groups.

4. Personalized foods

Personalized dietary products have gained increasing attention in recent years due to the growing demand for individualized nutrition (Han et al., 2020; Luo et al., 2019). This demand has been driven by several factors, including increased consumer awareness of the link between diet and health, and a desire for more convenient and effective ways to achieve personal health goals. Different consumer groups, such as infants, pregnant women, athletes, the elderly, overweight individuals, or patients suffering from a disease causing poor lipid digestion and absorption (e.g., lipoprotein lipase deficiency or cystic fibrosis), have distinct dietary requirements for fats. One of the key goals of controlled lipid digestion is to develop personalized foods that address the differences in human metabolism between specific consumer groups. This section introduces to the readers the specifics of the lipid digestion and absorption processes in two target consumer groups: infants, who require a high supply of easily digestible lipids, and overweight consumers, who may benefit from slowly digestible lipids. It also outlines current strategies to optimize lipid intake for those groups.

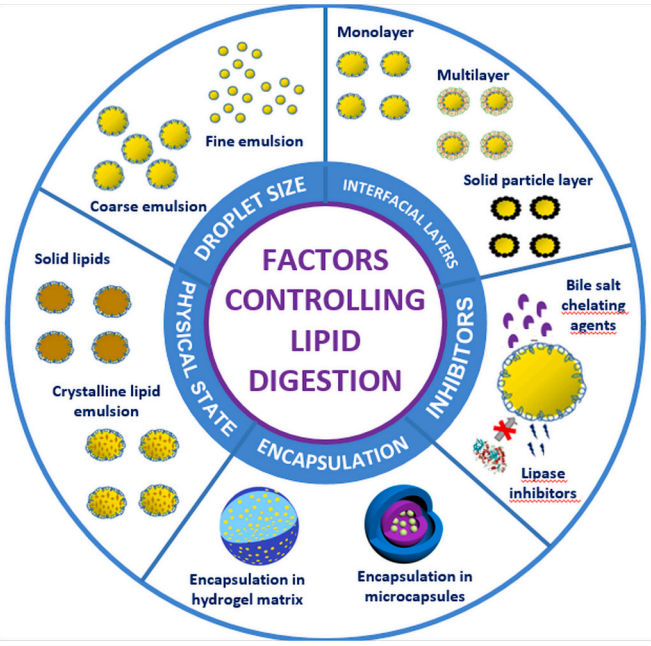

Fig. 6. Key factors regulating lipid digestion: emulsion droplet size; type and thickness of interfacial layer; physical state of lipids; encapsulation of lipids in hydrogel matrices, microbeads, or core/shell microcapsules; presence of inhibitors: bile salt chelating agents or lipase inhibitors.

4.1. Personalized foods for overweight consumers

Overweight and obese consumers are a key target group for food products that modulate lipid digestion rates. According to the WHO, obesity is characterized by a BMI exceeding 30 kg/m^2 and is primarily marked by increased fat accumulation in adipose tissue, both subcutaneous and visceral (intra-abdominal adipose tissue surrounding internal organs), leading to an expanded waist circumference (McCarthy, 2010). Over time, obesity can contribute to the development of insulin resistance, type 2 diabetes, cardiovascular disease, obstructive sleep apnea, asthma, nonalcoholic fatty liver disease, osteoarthritis as well as various types of cancer (Yongqi Guo et al., 2009; Tchang et al., 2024). Pathogenesis of these diseases has been linked to increased secretion of inflammatory cytokines by adipocytes, including interleukin-6 (IL-6), plasminogen activation inhibitor-1 (PAI-1), tumor necrosis factor α (TNF-α), and resistin, resulting in a chronic state of inflammation (Schmidt & Duncan, 2003; Tchang et al., 2024). The Global Burden of Disease Report indicates that obesity is the fourth leading risk factor for death, with over 4.7 million adults dying each year as a result of this condition (Stanaway et al., 2018).

To counteract the dramatic increases in the prevalence of obesity and overweight, researchers have directed their efforts toward developing foods that can restrict the digestion and absorption of dietary fats. One approach involves substituting the lipids present in the food with edible materials that provide little or no calories, known as fat replacers (Joyce et al., 2020; Kishibuchi et al., 2018). Fat replacers are compounds that resemble natural fats in terms of flavor and texture but provide fewer calories. They can be categorized into two groups: fat substitutes and fat mimetics.

Fat substitutes, such as salatrim, olestra, and caprenin, are food ingredients designed to mimic the chemical structure and physicochemical properties of conventional dietary fats (Lipp & Anklam, 1998; Peters et al., 1997). They are typically either indigestible or provide fewer

calories per gram compared to regular fats. These substitutes can be either chemically synthesized or derived from natural fats through enzymatic modification of the triglyceride structure via transesterification or interesterification (Ognean et al., 2006). Such modifications can confer new beneficial properties to fats, such as improved resistance to high temperatures used for cooking or frying. By modifying their molecular structure, lipids can also be engineered to be indigestible in the human gastrointestinal tract. For example, the olestra fat substitute is created by esterifying sucrose molecules with multiple fatty acids, which results in a more bulky molecular structure. Another fat substitute, salatrim, is composed of a glycerol backbone with a combination of short- and long-chain fatty acid constituents, where the presence of short-chain fatty acids decreases the overall digestibility (Syan et al., 2024).

In contrast to fat substitutes, fat mimetics have a different chemical structure from dietary fats but exhibit similar physical and sensory characteristics such as viscosity, mouthfeel, and texture (O'Connor & O'Brien, 2021). They are typically protein- or carbohydrate-based. Protein-based fat mimetics are derived from egg white or milk proteins (Aryana & Haque, 2001; Khalil, 1998; Yashini et al., 2019). Protein-based fat replacers produced by microparticulation of egg white or milk whey protein are available commercially under the names Finesse™, Simplesse™, and Dairy-Lo™. Carbohydrate-based fat replacers are the most commonly used class of fat replacers. They are obtained from plant sources such as algae (Joyce et al., 2020; Kishibuchi et al., 2018) or corn and starchy foods (e.g., grains or cereals) by grounding into fine particles, and include dextrins, modified dietary fibers, gelatin, cellulose, and gums (Belluco et al., 2022; Colla et al., 2018; Slavin & Green, 2007). Their high ability to swell in water gives them a fat-like texture. It has been shown that the addition of fat replacers based on extracts from algae such as *Spirulina platensis* can significantly inhibit pancreatic lipase activity, leading to reduced lipid digestion and decreased postprandial levels of triglyceride in the blood, which in turn contributes to suppressed hunger and food intake (Joyce et al., 2020; Kishibuchi et al., 2018). Commercially available carbohydrate-based fat replacers include products such as Methocel™, Avicel™, and Solka-Floc® (Zeece, 2020). Although fat replacers can provide a similar texture and mouthfeel as natural fats, they may also affect the digestion process, leading to reduced absorption of fat-soluble vitamins and potential adverse side effects such as abdominal pain, cramps, and diarrhea.

These limitations have prompted further research into modifying the food's structure to reduce fat content without altering product composition. One of the structuring strategies aimed at reducing lipid content in emulsion-based foods involves replacing conventional emulsions with double water-oil-water (w/o/w) emulsions (Cofrades et al., 2013; Keršienė et al., 2020; Klojdová & Stathopoulos, 2022; Lobato-Calleros et al., 2009; Burcu Öztürk et al., 2016). This type of emulsion consists of small water droplets suspended in larger oil droplets dispersed in an aqueous continuous phase. Replacing the fat phase with double emulsion introduces an additional water component (internal water phase i.e., small water droplets dispersed within the larger oil droplets), which allows for reduced overall fat content and caloric load while maintaining the same total external surface area of the oil droplets. This approach preserves the contact area between the oil phase and taste buds, making it difficult for consumers to notice any difference between full-fat products and those with double w/o/w emulsions (Klojdová et al., 2019). Moreover, products containing double emulsions can be used to encapsulate delicate water-soluble bioactive compounds in the internal water phase, protecting them from the low pH of the stomach during digestion.

Another approach to reducing calorie intake involves activating the ileal brake, a mechanism that regulates food intake, satiety, and glycemic control. The ileal brake is a primary negative feedback mechanism that controls the rate of food passage through the digestive tract (P. W. J. Maljaars et al., 2008; Shin et al., 2013). It utilizes the distal small intestine's (ileum) sensitivity to nutrients to regulate the rates of gastric emptying (the movement of stomach contents to the small intestine) and intestinal transit. Koopmans and Sclafani's groundbreaking 1982 study established the first model of the ileal brake mechanism, demonstrating its potential to effectively reduce food intake and promote weight loss in rats (Koopmans et al., 1982). Subsequent studies have confirmed that activating the ileal brake delays gastric emptying and modulates intestinal motility, reducing intestinal transit rate when undigested nutrients or unabsorbed free fatty acids are present in the ileum (P. W. J. Maljaars et al., 2008). This process decreases lipid digestion and absorption while prolonging satiety (Martín et al., 2005; Welch et al., 1988). The ileal brake can be induced by consuming foods rich in polar lipids (such as oats), and slowly digestible polysaccharides like starch. The presence of undigested nutrients in the ileum stimulates the secretion of cholecystokinin (CCK) and peptide YY (PYY), which inhibit gastric acid secretion, reduce food intake, and increase satiety, as depicted in Fig. 7 (Chegeni et al., 2022; Lindberg Yilmaz et al., 2021).

One of the strategies to improve the nutritional profile of food products is to partially replace saturated fatty acids (SFA) with unsaturated fatty acids, particularly polyunsaturated fatty acids (Vasilopoulou et al., 2020). High intake of SFAs is associated with elevated levels of low-density lipoprotein (LDL) cholesterol, a well-established risk factor for cardiovascular disease and atherosclerosis (Ference et al., 2017; Peters et al., 2016). *trans*-Fatty acids, which are produced industrially by the partial hydrogenation of vegetable and fish oils, have also been shown to negatively affect cholesterol levels and increase the risk of cardiovascular disease. According to a Cochrane systematic review involving nearly 60,000 participants across 15 randomized controlled trials, reducing SFA intake significantly decreased the risk of cardiovascular events by up to 17 %. An even greater (27 %) reduction in cardiovascular events was observed when SFAs were replaced with unsaturated *cis*-fatty acids, particularly polyunsaturated fatty acids (PUFAs) (Hooper et al., 2020). Replacing SFAs with unsaturated fatty acids has also been found to improve endothelial function, reduce inflammation, and decrease platelet activity (Stanner et al., 2018).

Another dietary strategy for promoting cardiovascular health and supporting weight loss involves incorporating plant-derived stanols and phytosterols into food. Stanols and phytosterols are lipophilic compounds, naturally found in fruits, vegetables, seeds, nuts, and cereals, that maintain proper permeability and fluidity of cell membranes (Moreau et al., 2018). Common examples include campestanol, campesterol, stigmasterol, sitosterol, sitostanol, and stanol (Alkhalaf et al., 2019; Putnik et al., 2018; Vu et al., 2019; Wang, Lin, et al., 2019). Structurally similar to cholesterol, stanols and phytosterols interfere with cholesterol's hydrolysis catalyzed by animal lipases and cholesterol esterases resulting in its inhibition. They also compete with cholesterol during solubilization by bile salts and the formation of mixed micelles, leading to cocrystallization with cholesterol and the generation of insoluble mixed crystals (Trautwein et al., 2003). This competition reduces cholesterol absorption from the gastrointestinal tract and increases its excretion in the feces (Danesi et al., 2016; Yi et al., 2016). Reduced intestinal absorption of cholesterol contributes to significantly lower plasma levels of total cholesterol and LDL cholesterol, which are almost always elevated in obese patients (Mc Auley, 2020). Foods enriched with stanols and phytosterols may improve the metabolic health of obese individuals and support their efforts to achieve long-term weight loss.

In conclusion, overweight and obese consumers are a key target for food products aimed at modulating lipid digestion and absorption. To address obesity, researchers are developing foods that limit the assimilation of dietary fats, incorporating fat replacers that mimic the sensory qualities of traditional fats without the associated calories. Emerging strategies involving double emulsions and activation of the ileal brake are also being explored to reduce caloric intake and enhance satiety. Other approaches include replacing saturated fatty acids with healthier unsaturated fats and incorporating plant-derived stanols and

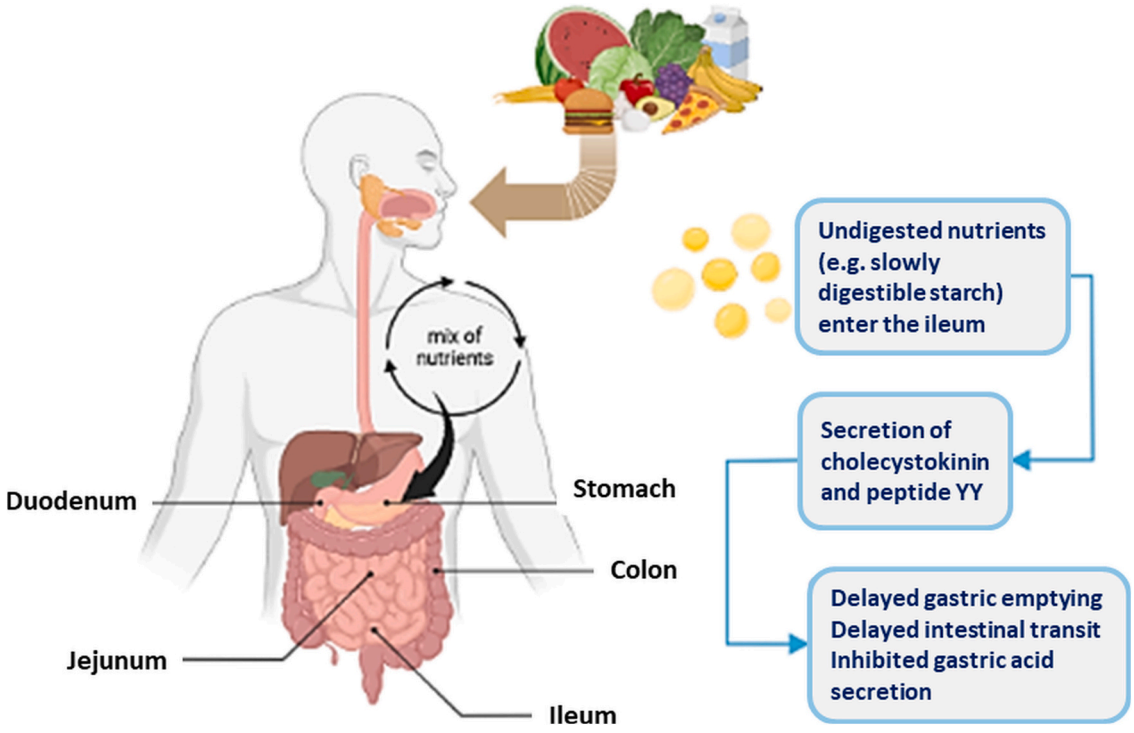

Fig. 7. The principle of ileal break. Undigested nutrients (e.g., slowly digestible starch) entering the ileum stimulate secretion of cholecystokinin (CCK) and peptide YY (PYY), which activate the ileal break feedback mechanism, leading to delayed gastric emptying and intestinal transit. These changes contribute to inhibited gastric acid secretion, reduced food intake, and enhanced feeling of satiety.

phytosterols to lower cholesterol absorption, thereby improving metabolic health and supporting weight loss in obese individuals.

4.2. *Personalized dietary products for infants*

The effort to address rising obesity rates has accelerated advancements in tailored lipid delivery, spurring research into personalized foods for other consumer groups, such as infants, who require easily digestible lipids. The process of lipid digestion has been extensively studied in adults but remains largely unexplored in infants. A key difference between adults and infants is that infants have lower levels of pancreatic lipase, other gastrointestinal enzymes, and bile salts (Hamosh, 1996). These differences can contribute to digestive issues such as bloating, abdominal pain, diarrhea, regurgitation, and reflux. Preterm infants may face additional challenges due to their immature digestive systems, including feeding intolerance, maldigestion, and an elevated risk of necrotizing enterocolitis (Arévalo Sureda et al., 2021). Exocrine pancreatic function typically matures by about one month of age for both premature and full-term infants (Lebenthal & Lee, 1980). During the immediate postnatal period, the insufficient activity of the digestive system is typically compensated by enzymes provided in breast milk, such as amylase, lipase, and esterase (Alemi et al., 1981).

In adults, pancreatic lipase plays the primary role in lipid digestion. However, in infants, gastric lipase, bile-salt stimulated lipase (BSSL) secreted in mothers' breastmilk, and pancreatic lipase-related protein 2 (HPLRP2) play crucial roles in the luminal lipid digestion (Lindquist & Hernell, 2010). Lipid digestion in infants begins with lingual lipase, secreted by the serous glands located in the posterior region of the tongue (Bernbäck et al., 1987; Fredrikzon et al., 1982). Present at birth, lingual lipase has been detected in the gastric contents of preterm infants as early as the 34th gestational week. The enzyme is resistant to acid inactivation and its activity in the gastric contents increases following a meal. Lingual lipase plays a vital role in the early stages of lipid digestion by hydrolyzing dietary triglycerides into diglycerides and free fatty acids. In the stomach, gastric lipase acts on the sn-3 position of triacylglycerols, hydrolyzing some of them to 1,2-diacylglycerols and free fatty acids (van Aken et al., 2011). Gastric lipase can be found in the fundic mucosa of the human fetus as early as the 11th week of gestation, indicating that it may be active in preterm infants (Sarles et al., 1992). In preterm neonates with low or absent pancreatic lipase activity and bile salt deficiencies, lingual and gastric lipases assume their roles, with intragastric lipolysis accounting for the majority of lipid digestion (Hamosh et al., 1981). The digestion process continues in the small intestine, where bile-salt stimulated lipase and pancreatic lipase-related protein 2 (HPLRP2) further hydrolyze triacylglycerols and 1,2-diacylglycerols into 2-monoacylglycerols and free fatty acids (Lindquist & Hernell, 2010).

Given the unique physiological characteristics of the gastrointestinal tract in children, particularly in neonates and young infants, there is growing interest in predictive in vitro models that account for differences in fluid volume, pH, bile salt concentration, enzyme activities, gastric emptying, and intestinal transit time in the pediatric population. Since pancreatic lipase is underdeveloped in this population and lipid digestion relies heavily on gastric lipase, neonatal in vitro models must simulate both gastric and intestinal conditions. In 2016, Kamstrup et al. proposed an in vitro model that used the pH-stat lipolysis setup, which incorporated simulated gastric and intestinal media specific to the neonatal population (Kamstrup et al., 2017). Klitgaard et al. further refined this model by incorporating a physiologically relevant gastric pH drop and continuous transfer of gastric contents to mimic gastric emptying (Klitgaard et al., 2017). However, these neonatal digestion models have the same limitations as other gastric digestion models, as they rely on rabbit gastric lipase rather than the human enzyme.

Recent studies have combined in vitro lipolysis with in vitro permeation, either across human colonic Caco-2 cell monolayers or artificial bio-mimetic barriers (Mackie et al., 2020). Keemink et al. proposed an advanced, physiologically relevant two-compartment in vitro setup that allows lipid digestion and absorption to occur simultaneously (Keemink et al., 2019). This system includes an upper compartment (luminal), where lipid digestion occurs, and a lower,

receiving compartment (serosal) to simulate intestinal lipid absorption. The two chambers are separated by a Caco-2 cell monolayer, commonly used as an absorptive membrane model to predict intestinal lipid absorption. Although some combined lipolysis-permeation models correlate well with in vivo data, they remain relatively complex and require further validation to ensure kinetics. Continued research on in vitro models for neonatal and pediatric populations is crucial to advancing personalized nutrition tailored to the unique needs of these sensitive groups.

Dietary lipids are extremely important for proper infant development. They are the main energy source in the infant diet providing more than half of calorie intake. Lipids are indispensable for the development of the nervous system, proper maturation of the gastrointestinal system, the absorption of lipid-soluble vitamins, lipoprotein metabolism, and other physiological processes (Uauy & Castillo, 2003). Therefore, ensuring sufficient lipid intake is one of the key aspects of infant nutrition (Poquet & Wooster, 2016). Human milk is considered optimal for infant nutrition as it supports gut maturation and strengthens an infant's innate immunity (Delplanque et al., 2015; Lee et al., 2018; Spitsberg, 2005). When unavailable, infant milk formula becomes an alternative source of nutrients (Manson & Weaver, 1997).

Typically, infant formulas are oil-in-water emulsions designed to closely resemble the lipid profile of breast milk (Luo et al., 2020). While cow's milk has historically been the primary fat source in formula (Koletzko, 2016), recent research suggests that other animal milk, such as yak milk, may be a superior source of lipids for infants. In vitro studies on infant gastrointestinal digestion have shown that fat globules from yak milk were digested more efficiently than those from cow milk (Luo et al., 2020). The more effective digestion of yak milk fat was attributed to a superior composition of yak milk fat. The advantageous lipid profile compensated for larger fat globule size in yak milk, resulting in an improved overall digestion rate.

Enhancing lipid digestion in infant formulas can also be achieved by reducing fat globule size via high-pressure homogenization (Rodarte et al., 2018). Milk homogenization typically involves passing milk through a small orifice at high pressures up to 400 MPa (Escobar et al., 2011). This process disperses milk fat globules, reducing their size to approximately 1.0–3.5 μm (Massoud et al., 2016). The reduction in fat globule size increases the surface area available for enzyme adsorption, thus enhancing lipid digestion in the formula (Berton et al., 2012; Singh & Gallier, 2017).

The lipid digestion rate in a formula can be further improved by using emulsifiers that increase the electrostatic attraction between lipid interfaces and gastric lipase. Incorporating protein emulsifiers, such as milk whey and casein, soy lecithin or functionalized soy lecithin containing unsaturated phospholipids, including such as phosphatidylcholine, phosphatidylinositol, and phosphatidylethanolamine, can expedite lipid digestion by modifying the surface charge of lipid droplets (Scholfield, 1981). Among phospholipid-enriched formulas, those containing negatively charged phospholipids like phosphatidylserine exhibit the highest lipid digestion rates due to improved electrostatic attraction with gastric lipase (Bourlieu et al., 2016).

An important consideration in designing infant formulas is recreating the liquid crystalline phases that form during the in vivo digestion of human breast milk (Bourlieu & Michalski, 2015). These naturally occurring liquid crystalline structures play a crucial role in the efficient digestion and absorption of breast milk lipids. They are formed during intestinal lipid digestion even in the absence of bile salts due to complex structural transitions within oil droplets from emulsions to complex mesophases like inverse micellar and hexagonal phases. Similar liquid crystalline phases are seen in bovine and goat milk. The structure of mesophases formed during milk digestion is influenced by the milk composition, resulting in unique mesophase profiles specific to each milk type.

Numerous studies have explored the relationship between the lipid composition of various mammalian milks and milk-like systems and the structural properties of the mesophases formed during their digestion (Pham et al., 2020). Comparative studies have shown that human milk, with its higher content of unsaturated fatty acids, forms more compressible monolayers than bovine milk (Bourlieu & Michalski, 2015). These structural differences enable greater penetration by gastric lipase, enhancing lipid digestion efficiency. An improved understanding of the liquid crystalline phases in human milk has driven the development of infant formulas that replicate these structures. For instance, bovine-derived and goat-derived milk formulas have been engineered to form similar LLC mesophases (Mulet-Cabero et al., 2019). Replicating the behavior of liquid crystalline phases in infant formulas can enhance lipid bioavailability and support optimal growth and development in infants, particularly those with conditions that hinder fat absorption.

In summary, infants have a unique digestive physiology due to lower pancreatic lipase activity and bile salt levels. Current research aims to enhance lipid assimilation from milk by developing optimized formulas with smaller fat globules and incorporating protein emulsifiers, such as milk whey and phospholipids, to strengthen electrostatic interactions at the lipid interface and support faster digestion. Furthermore, efforts are being made to replicate the liquid crystalline phases found in human milk to improve lipid bioavailability in formulas. Ongoing research into predictive in vitro models, considering factors like fluid volume, pH, enzyme activity, and gastric emptying, seeks to deepen our understanding of infant lipid digestion and optimize formula design for their developmental needs.

5. Challenges and future directions for tailored delivery of dietary fats

Despite the growing importance of personalized foods designed for tailored dietary fat delivery, several challenges remain before these products can reach a broad consumer base. Given the complex nature of lipid digestion, further research is essential to understand the metabolism, distribution, and elimination of functional food ingredients, such as pancreatic lipase inhibitors, bile salt chelators, and fat replacers, especially with regard to their long-term safety and potential adverse effects on other metabolic pathways. Although many new products have undergone preliminary in vitro and animal testing, a full assessment of their safety profiles and potential health benefits requires human clinical trials (Frestedt, 2017) and comprehensive evaluations by regulatory bodies like the FDA and European Food Safety Authority (EFSA) (Lenssen et al., 2018).

From a technological standpoint, primary challenges in manufacturing functional foods for customized lipid delivery include managing lipid oxidation, especially in products enriched with polyunsaturated fatty acids like omega-3 s, and preventing the degradation of sensitive bioactive compounds added to the oil phase, such as fat-soluble vitamins, antioxidants, and proteins. Additionally, some strategies to regulate lipid assimilation may noticeably alter the texture and sensory qualities of functional foods, potentially impacting consumer acceptance (Jiménez-Martín et al., 2016; Lorenzo et al., 2016). Addressing these obstacles requires further research on innovative food structuring techniques (Rogers, 2009), oxidative stabilization methods for products prone to lipid oxidation (Chen et al., 2017; Espinosa et al., 2015; Kaushik et al., 2015; Qiu et al., 2017) and encapsulation strategies to protect labile lipids and bioactives within hydrogel matrices or carriers such as polymer microspheres, core-shell microcapsules, lipid nanoparticles, or smart stimuli-responsive delivery systems (Jiménez-Martín et al., 2016; Lorenzo et al., 2016).

Another important area for future research in controlled lipid digestion is the development of personalized foods for patients with conditions that impair lipid digestion and absorption, such as lipoprotein lipase deficiency, a genetic metabolic disorder (Donato-Capel et al., 2014). Individuals with this condition suffer from severely reduced levels of lipoprotein lipase that leads to increased plasma triglyceride levels and accumulation of lipid droplets (chylomicrons) in the

circulation and tissues. This can result in damage to the brain, liver, spleen, and bone marrow. The disease typically manifests in childhood with symptoms like abdominal pain, enlargement of the liver and spleen (hepatosplenomegaly), recurrent inflammation of the pancreas (pancreatitis), and eruptive cutaneous lesions (xanthomas) (Patil & Gupta, 2021). Patients are typically advised to follow a strict low-fat diet, limiting fat intake to $\leq$20 g per day while closely monitoring plasma triglyceride levels (Brahm & Hegele, 2015; Stroes et al., 2017). Since there are currently no pharmaceutical treatments for lipoprotein lipase deficiency (Aljouda et al., 2023), developing foods that aid lipid digestion could offer significant benefits for this group.

Future directions in developing foods for tailored fat delivery must also consider that most in vitro models simulate the gastrointestinal conditions of a healthy adult's digestive system. To gain a more realistic understanding of how specific lipid characteristics influence digestion and absorption in target populations such as infants, the elderly, or people with particular health conditions, further development of specialized in vitro digestion models is necessary. Ideally, when simulating the complex physiological and physicochemical events in the human gastrointestinal tract following lipid consumption, in vitro models should realistically replicate each stage of the digestive process with appropriate pH, enzymatic conditions, transit times, mixing, etc. Additionally, these models should incorporate factors like resident microbiota, immune system responses, feedback mechanisms, hormonal controls, intestinal uptake mechanisms, lymphatic transport, and hepatic metabolism to mimic human digestion accurately. However, replicating these complex processes remains technically very challenging.

Currently, there is a growing focus on developing patient-specific models and combined digestion-permeation models. The increasing interest in functional foods for pediatric populations has led to advancements in predictive in vitro models that account for the unique physiological differences in the gastrointestinal tracts of children, particularly neonates and young infants. Although these models require further validation, recent studies on combined in vitro lipolysis and permeation models represent a promising step toward creating predictive digestion models for this demographic. At present, no single in vitro digestion model can fully and consistently predict the in vivo lipid digestion kinetics. However, with the rising interest in personalized nutrition, several patient-specific digestion models are expected to become reliable predictors of lipid behavior in the gastrointestinal tract in the near future.

6. Conclusions

Controlled lipid digestion and the design of functional foods are rapidly evolving fields within food and nutrition science. Lipid digestion is a complex process that involves multiple stages, including breaking down the food matrix, dispersing lipids into droplets, and enzymatic hydrolysis facilitated by bile salts, colipase, and lipases. The kinetics of each of these steps can be influenced by a variety of factors.

Decades of extensive research have identified numerous factors that regulate lipid digestion, including the structure, pH, and ionic strength of the food matrix and digestive milieu; the physical state and composition of dietary fats; the levels of bile salts and calcium level; the size of the lipid droplets; and the characteristics of the interfacial layer, which are determined by the type and concentration of emulsifiers used. Understanding how to manipulate these factors has paved the way for the development of advanced techniques for manufacturing innovative food products with optimized physicochemical properties and compositions. These products can effectively modulate lipid assimilation from the gastrointestinal tract, catering to the diverse dietary needs of various consumer groups.

Further progress has been made with the introduction of methods to deposit protective interfacial layers around lipid droplets and encapsulate emulsions in hydrogel matrices, microbeads, core/shell microcapsules, lipid nanoparticles, and stimuli-responsive delivery platforms. The use of amphiphilic lipids, which can form self-assembling nanostructures offers new opportunities to modulate digestion rate, stabilize fat-soluble nutrients, and enhance the bioavailability of essential fatty acids. These advancements have allowed lipid-containing foods to evolve from conventional products with no control over fat intake into advanced, customized foods with tailored fat digestion rates to meet individual consumer requirements. While much of the rapid advancement in tailored lipid delivery has been driven by the urgent need to address rising obesity rates, it has also spurred research into personalized foods for other consumer groups, such as infants, who require a high supply of easily digestible fats.

The significance of advancements in personalized and functional foods for public health is undeniable. However, several unresolved issues must be tackled before these products can become more widely available to consumers. The intricate nature of lipid digestion requires further research into the metabolism, distribution, and elimination of innovative ingredients found in functional foods, particularly concerning their long-term safety and potential impacts on other metabolic pathways.

The strategies outlined in this review may open potential avenues for developing novel dietary products and personalized nutrition approaches that can effectively control lipid digestion and absorption, leading to improved health outcomes. By equipping researchers and food product formulators with practical knowledge of cutting-edge food formulation techniques, this discussion can drive further advancements in the field, maximize the potential of functional foods across various sectors of the food and nutrition industry, and transform our approach to nutritional interventions for weight management and the prevention of nutrition-related chronic diseases.

CRediT authorship contribution statement

Barbara Kupikowska-Stobba: Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Hui Niu:** Writing – original draft, Conceptualization. **Iveta Klojdová:** Writing – original draft. **Ruben Agregán:** Writing – original draft. **Jose Manuel Lorenzo:** Writing – original draft. **Mirosław Kasprzak:** Writing – original draft, Visualization, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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