Advances of plant-based structured food delivery systems on the *in vitro* digestibility of bioactive compounds

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Abstract

Food researchers are currently showing a growing interest in *in vitro* digestibility studies due to their importance for obtaining food products with health benefits and ensuring a balanced nutrient intake. Various bioactive food compounds are sensitive to the digestion process, which results in a lower bioavailability in the gut. The main objective of structured food delivery systems is to promote the controlled release of these compounds at the desired time/place, in addition to protecting them during digestion processes. This review provides an overview of the influence of structured delivery systems on the *in vitro* digestive behaviour. The main delivery systems are summarized, the pros and cons of different structures are outlined, and examples of several studies that optimized the use of these structured systems are provided. In addition, we have reviewed the use of plant-based systems, which have been of interest to food researchers and the food industry because of their health benefits, improved sustainability as well as being an alternative for vegetarian, vegan and consumers suffering from food allergies. In this context, the review provides new insights and comprehensive knowledge regarding the influence of plant-based structured systems on the digestibility of encapsulated compounds and proteins/polysaccharides used in the encapsulation process.

Keywords: gastrointestinal digestion; emulsions; interface; bioaccessibility; bioavailability; encapsulation.

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1. Introduction

The study of bioactive compounds, including phenolic compounds, vitamins, pigments, polyunsaturated fatty acids, proteins and polysaccharides, has become a priority among food researchers and food industries due to their beneficial properties to health (Talbot-Walsh, Kannar, & Selomulya, 2018; Gavahian, et al., 2019; Wu et al., 2019; Sá et al., 2020). Most of these compounds are sensitive to food processes and digestion conditions (mechanical stress, high temperature, acidic or basic medium, presence of salts and enzymes). Moreover, the amount of these compounds available to the organism depends on many factors, such as their molecular and physicochemical properties, their structure and the food matrix composition (Ana, Shrestha, & Sadiq, 2019; McClements, Decker, & Weiss, 2007).

The structured delivery system approach aims the protection of beneficial compounds when in contact with adverse conditions and to promote their controlled release under gastro-intestinal (GI) conditions. These delivery systems have been reported to increase the bioaccessibility (amount of released compound from a matrix for absorption in the circulation) and bioavailability (amount of released and absorbed compound that can be delivered to different parts of the body) of bioactive compounds (Lucas-González, Viuda-Martos, Pérez-Alvarez, & Fernández-López, 2018). Examples of structured delivery systems include conventional, Pickering, double and multilayered emulsions, coacervates, nano- and microgels, micelles and liposomes (Timilsena, Akanbi, Khalid, Adhikari, & Barrow, 2019; Costa et al., 2020; Huang & Zhou, 2019).

Furthermore, the interest in food digestion has increased in previous years since studies are necessary to understand the complex processes that occur in each step of food transformation under gastric and intestinal conditions. Digestion models are applied in order to study the mechanical and enzymatic processes, and they measure the portion of the compounds that is converted into available materials for the organism (McAllister, 2010). The investigation of these different digestibility methods is necessary due to their particular limitations (Dupont et al., 2019), once they take into consideration

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the occurrence and concentration of digestive enzymes, the pH values in gastric and intestinal phases, digestion time and salt concentrations (Lucas-González, Viuda-Martos, Pérez-Alvarez, & Fernández-López, 2018; Marcano et al., 2015; Augustin et al., 2014; Alminger et al., 2014; Minekus et al., 2014).

The behavior of structured food ingredient delivery systems during digestion has gained attention in the research field since different structures and compositions result in different mechanism and kinetics of digestion (Singh, Ye & Ferrua, 2015; Martins et al., 2018; Koutina et al., 2018; Huang & Zhou, 2019; Yang et al., 2019; Costa et al., 2020). To date, the digestibility of encapsulated compounds has been studied for complex coacervates with different combinations of protein and polysaccharides, including cashew gum and gelatin (Oliveira et al., 2020), lactoferrin and sodium alginate (Bastos et al., 2020), whey protein and gum arabic (Zhou et al., 2018), gelatin and gum arabic (Souza et al., 2019), ovalbumin and sodium alginate (Soares et al., 2019). The digestibility of encapsulated compounds was evaluated for other types of structured delivery systems as well, including oil-in-water emulsion (Espert, Salvador, & Sanz, 2019), double water-in-oil-in-water emulsion (Huang & Zhou, 2019), emulsion microgel particles (Torres, Murrray, & Sarkar, 2019), Pickering emulsions (Costa et al., 2020) and nano- delivery systems (Gasa-Falcon, Odriozola-Serrano, Oms-Oliu, & Martín-Belloso, 2020).

In addition to structured delivery systems, *in vitro* digestibility of food ingredients and food matrix has been investigated. Most studies have focused on dairy proteins (Singh & Ye, 2013), food structure and composition (Sun, Acquah, Aluko, & Udenigwe, 2020; Nguyen, Bhandari, Cichero, & Prakash, 2015), or plant-based food (Ogawa et al., 2018). However, to the best of our knowledge, none of them focused on the advantage of plant-based delivery systems on the *in vitro* digestibility of bioactive compounds. Moreover, due to the increase in vegan, vegetarian and allergic consumers, food industries are searching for alternatives in plant-based functional foods. In line with this, the acquisition of proteins and polysaccharides of plant origin and their effect on the digestibility process is of extreme

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importance for the development of innovative food products. In this regard, this review fills an essential gap in the literature.

The aims of this review are (1) to provide an understanding of the current strategies of static and dynamic digestibility studies, (2) critically evaluate the use of plant-based structured food delivery systems on the *in vitro* digestibility of bioactive compounds (encapsulated and encapsulating materials), as well as (3) their advantages and disadvantages.

2. Digestibility study

There are two types of digestion models: *in vivo* and *in vitro*. While *in vivo* models, which include human and animal models, are generally regarded superior in given direct evidence of the efficacy of a treatment, there are often difficult to perform, unsuitable as a model system, expensive or unjustifiable on ethical grounds. In addition, *in vivo* models seldom provide the necessary mechanistic insight into changes in the food structure during GI transit as the output of *in vivo* studies are often blood, stool or urine, whereas the GI lumen is too often considered a black box. In order to understand the physiological response to bioactives, food or food ingredients, a more detailed monitoring of the digestive process is required. Hence, laboratory-based *in vitro* models are widely used to simulate the digestion of food or food ingredients. A large number of samples can be analyzed at the same time, and the conditions can be controlled or adapted, and easily sampled. However, *in vitro* digestion methods need to be performed with caution, and limitations in simulating the complex human GI tract need to be considered when choosing specific digestion methods. Various *in vitro* digestion methods have been developed, classified into (a) static, (b) dynamic and (c) semi-dynamic methods (Dupont, D., & Mackie, A., R., 2015; Lucas-González, Viuda-Martos, Pérez-Alvarez, & Fernández-López, 2018: Mulet-Cabero et al., 2020).

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Static *in vitro* methods are simplified "one pot" methods with a constant food to enzyme/electrolyte ratio at each of the digestive phases namely the oral (mouth), gastric (stomach) and small intestinal phase. According to Hur, Lim, Decker, & McClements (2011), a large variety of somewhat related digestion conditions was being used, which makes the comparison of digestion studies among different research groups challenging, if not meaningless, accurate due to the significant variation of parameters. For this reason, an EU-funded international COST action INFOGEST was created to harmonize and standardize a static *in vitro* digestion method based on available physiological data (Dupont et al., 2011; Minekus et al., 2014), and written in a standardized protocol format that included recommended standard enzyme assays and videos (Brodkorb et al., 2019).

During the oral phase, Simulated Salivary Fluid (SSF) is prepared with the corresponding electrolyte stock solutions, enzymes and separate $CaCl_2$. The oral phase is the beginning of the digestion process and also very important in particular for solid and semi-solid food. It is a simplified procedure compared to the complex mastication mechanism. The particle size of food before and after oral phase is an essential factor influencing gastric and intestinal digestion (Minekus et al., 2014; Engelen et al., 2005; Fontijn-Tekamp et al., 2000). The chewing (teeth) with sufficient salivary lubrication is responsible for breaking down the food into small pieces (Rémond et al., 2007; Li, Yu, Wu, & Chen, 2020). According to the INFOGEST method, the solid food should be minced in SSF to create a paste and salivary amylase is added, if necessary. After that, the food bolus (resulting from the oral phase) is transferred to the gastric phase and the Simulated Gastric Fluid (SGF) is added to it 1:1 (w/w). Pepsin and $CaCl_2$ are added and the pH is adjusted to 3.0. Finally, the process continues with the intestinal phase. Simulated Intestinal Fluid (SIF) is prepared and mixed 1:1 (w/w) with the gastric chyme, the pH is adjusted to 7.0 and the digestive enzymes, bile salts and $CaCl_2$ are added. Figure 1 summarizes the *in vitro* digestion procedure with the oral, gastric and intestinal conditions outlined.

[FIGURE 1]

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With regard to dynamic *in vitro* digestion, different models have been developed in order to simulate the human system as much as possible. These models are composed of single and multi-compartment systems (Dupont & Mackie, 2015). Single compartmental models can be observed in the Dynamic gastric model (DGM), the Human gastric simulator (HGS) and the Gastric digestion simulator (GDS). These models were developed by Kong & Singh (2010) at the Institute of Food Research (Norwich, UK), the University of California, and by Kozu et al. (2014) at Tsukuba University, respectively. The DGM system was developed to imitate the complex processes in the stomach including three features: (1) storage and mixing, (2) shear and turbulent flow, and (3) the calorie-dependent gastric process and stomach emptying (Chessa et al., 2014; Mason et al., 2016). The gastric digestion is simulated in a realistic time-dependent way, which also allows analyzing complex food systems. The time of experiment depends on the type of food matrix, lasting between 25 min and 4.5 h (according to the size and composition). The DGM system has many advantages, including a greater capacity for analyzing food and the process can be followed in real-time (Thuenemann et al., 2015). On the other hand, it is not as efficient for liquid food or matrix with small particles due to the *in vivo* gastric physical forces that cannot be accurately reproduced due to the alignment of body and antrum (Li et al., 2020; Thuenemann et al., 2015). The HGS is a system consisting of a flexible outer vessel, which is also focused on gastric digestion, but if necessary, oral and intestinal phases may be added to the process (Dupont et al., 2019). It is designed to imitate the mechanical conditions of the stomach by using series of rollers that can control the forces that are subjected to food during the gastric process. One of its advantages is to be able to reproduce the mechanical forces observed *in vivo* due to the control of the motor activity (Ferrua & Singh, 2015). In the case of the GDS, gastric peristalsis is imitated and this process can be visualized through its transparent windows (Kozu et al., 2017). Moreover, there is the combination of physical force resulted from simulated peristaltic contractions and the biochemical reactions, which facilitate the breakdown of food particles. The GDS has the advantage

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of controlling the gastric peristaltic movements and the analyses of digestion in real-time; however, it is not possible to simulate the gastric emptying (Li et al., 2020; Kobayashi et al., 2017).

On the other hand, the multi-compartment systems are considered more complete and closer to the real digestion process. TNO's gastrointestinal model (TIM) is one of the most studied dynamic in vitro digestion methodologies. It was developed at TNO Nutrition and Food Research (Netherlands) and is known by its four interconnected multi-compartment gastrointestinal systems, including the stomach, duodenum, jejunum and ileum. The more simplified TinyTIM model consists of on intestinal phase, where as a more recently developed Advanced Gastric Compartment (TIM-agc) includes an improved gastric compartment (Minekus, 2015). Additionally, the simulator of the human intestinal microbial ecosystem (SHIME) is another dynamic *in vitro* digestion method, developed by Molly, Vande Woestyne, and Verstraete (1993). This approach has a multi-compartment system, comprising a five-stage multi-chamber reactor: (1) duodenum/jejunum, (2) ileum, (3) caecum and ascending colon, (4) transverse colon and (5) descending colon.

The recently developed semi-dynamic method is based on the static version of INFOGEST method with some modifications regarding gastric secretions and emptying. Like the static and dynamic methods, this method consists of oral, gastric, and intestinal phases; however, the gastric phase is designed to be dynamic. For this reason, simulated secretions are added gradually, and pH decreases from 7 to 2 according to the buffering capacity of the food and amount of SGF added in the gastric reaction vessel. Emptying, performed manually, is another essential factor considered in this step once the chyme is digested separately in parallel. Nonetheless, the digestion process during oral and intestinal phases remains similar to the static protocol (Mulet-Cabero et al., 2020). This method promotes the assessment of modification in the food structure once it focusses on gradual acidification and gastric emptying. Moreover, the semi-dynamic protocol standardized by Mulet-Cabero et al. (2020) is easy and low cost, using common laboratory equipment, and is applicable for different types of foods.

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3. Digestibility of plant proteins and polysaccharides

As mentioned above, proteins and polysaccharides are the main biopolymers used for the development of structured food ingredient delivery systems. Their digestive behavior has an influence on the digestibility of the delivery systems and on encapsulated bioactive compounds. For this reason, the digestibility of plant proteins and polysaccharides is discussed in this section.

Proteins are known for their functional properties, including emulsifying capacity, water solubility, foaming capacity, biocompatibility and biodegradability, in addition to their use as carrier agents/encapsulating material for the encapsulation of food bioactive compounds (Burgos-Díaz et al., 2016). They are broken down into amino acids when subjected to digestive enzymes. The amino acids profile of the protein is determining their nutritional quality (López et al., 2018). Animal derived proteins such as dairy and meat are known as complete proteins as all essential amino acids are present, whereas plant proteins can be deficient of some essential amino acids (Sá, Moreno, & Carciofi, 2020). Proteins from plant origin have been widely explored due to their low cost, better sustainability and good nutritional properties, besides the expansion of food options for vegan, vegetarian and allergic populations. Some examples of plant proteins used as emulsifiers are pea protein, soy protein, chia protein, lupin protein, quinoa protein and lentil protein (Burgos-Díaz et al., 2016). The main fractions of plant proteins can be divided into glutenin, globulin, albumin and prolamin. The digestibility of plant proteins, i.e. the fraction of amino acids that are absorbed in the GI tract, is low compared to animal and milk proteins due to the presence of antinutritional factors (protease inhibitors, phytases, polyphenols, fibers, and non-starch polysaccharides) (Sá, Moreno, & Carciofi, 2020) and their lower solubility thus a lower bioaccessibility. These factors may be either positive or negative when the plant protein is used for delivery systems, depending on their application in the food product and the characteristics of their consumers.

For example, the digestibility of lentil protein should be improved in order to enhance its nutritional quality and to be used in structured delivery systems (Aryee & Boye, 2016). Raw lentil flour

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(RLF), cooked lentil flour (CLF) and lentil protein isolate (LPI) present *in vitro* protein digestibility (quantified using the pH-drop/multi-enzyme method) of 77.1, 81.9 and 85.4%, respectively. This was explained by (1) modification in protein structure, which altered accessibility of enzyme, (2) increase of solubility, and (3) the cooking and protein extraction reduced the anti-nutritional elements, increasing the digestibility. Moreover, LPI and CLF were subjected to processes, which promoted modifications in their structure and exposed peptide bonds to enzyme activities. In addition, the heating process may change the secondary structure of protein and inactivated protease inhibitors, both of which also increase its digestibility. Furthermore, the higher digestibility of lentil protein isolate was also enhanced by its isolation from other compounds, and thereby removing or reducing the amount of anti-nutritional compounds. These behaviors were observed by Aryee & Boye (2016), when they evaluated the difference in digestibility when the lentil protein is subjected to heating treatment. Hence, the use of lentil proteins for structured delivery systems could be considered according to the purpose of these systems: if the main aim is to promote the fast and complete digestion of the encapsulated compound, lentil protein isolate could be used instead of other forms of this protein.

Quinoa is another source of plant protein. However, in the same way as the other plant proteins, its application in food products and structured delivery systems is hampered due to the relatively low protein digestibility of the quinoa seeds. For this reason, Nasir et al. (2015) evaluated the protein digestibility of various genotypes of quinoa. Depending on the type of quinoa, its protein presented digestibility values in the range of 75.95-78.11% due to the occurrence of starch and protein interaction, and the molecular weight of protein (lower molecular weight, faster digestion process). Another important factor is that different protein arrangements may present different digestibility behaviors due to their tertiary and quaternary structures and their susceptibility to enzyme activities (Sandoval-Oliveros, & Paredes-López, 2013). In other words, the digestibility of proteins may vary according to their origin and composition of their source, affecting their use in structured delivery systems and the digestibility of these systems.

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Chia proteins are of interest to researchers due to their functional properties, which may improve the health benefits of functional foods. However, their digestibility studies need to be more investigated by virtue of their heterogeneity and solubility (Sandoval-Oliveros, & Paredes-López, 2013). For this reason, Sandoval-Oliveros, & Paredes-López (2013) studied the isolation and digestibility of proteins from chia seeds and observed values of 82.5 and 78.9% digestibility for globulins and defatted flour, respectively. They compared to casein (control), which presented 88.6% of *in vitro* digestibility, which is considerably lower than literature data of >95%.

It is important to highlight that even though the mentioned researchers have used different *in vitro* digestibility methods, plant proteins generally have the lowest rate of digestion and overall digestibility. However, when they are isolated or subjected to heat treatment, their behavior in gastrointestinal conditions may be improved.

Besides proteins, polysaccharides are widely used to prepare structured delivery systems. Cellulose, hemicellulose, pectin, gums, starch, carrageenan and alginate are some examples of plant polysaccharides (Liu, Willför, Xu, 2015). Moreover, the use of plant polysaccharides, by itself or in combination with plant proteins, makes it possible for new alternatives for structured delivery systems to be applied into vegetarian/vegan food products.

Polysaccharides are classified mainly in starch, glycogen and fibers, and their digestibility process is different from protein digestion. Starches, for example, can be divided into three groups: (1) rapidly digesting starch; (2) slowly digesting starch and (3) resistant starch. These different groups can influence the controlled release of bioactive compounds when starch is used as a carrier agent, accelerating or delaying the digestion process, as presented in the next sections (Singh, Dartois, & Kaur, 2010). Moreover, the maintenance of starch digestion is important in regulating blood glucose levels since starch is broken down into maltose and maltose is later digested into glucose. In addition, it is important to study ways to decrease the rate of starch digestion and this may be achieved with the addition of viscous fibers, such as guar gum. For this reason, Zheng et al. (2019) evaluated the effect of

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different concentrations of guar gum (GG) on the *in vitro* digestibility of lotus seed (LS) starch and observed that the addition of GG delayed starch digestion. The same feature may be achieved with xanthan gum (Sasaki, 2020) and gum arabic (Bae, Oh, Jung, & Lee, 2019). This decrease in the digestion rate can be explained by the high viscosity of the system, the higher crystallinity of starch and the complex formed between starch and gum, which reduces or even inhibits the enzyme action. Hence, the use of starch in a structured delivery system may delay the digestibility of the whole system and the encapsulated compound when the starch is composed mainly of resistant starch or when it is combined with gums.

Furthermore, dietary fiber (pectin, beta glucans, cellulose, guar gum, inulin, lignin, resistant starches) may bind to compounds present in the digestion process (calcium ions, bile salts or free fatty acids, for example) and delay the digestive process, lipid digestion in particular. It is known that long chain fatty acids produced during digestion can precipitate when in contact with calcium ions. In addition, the attachment of lipase to droplet surfaces is facilitated when bile salts are also adsorbed to the surface, promoting the solubilization of free fatty acids produced during the digestion process. Lastly, dietary fibers have a high viscosity and their use may also increase the viscosity within gastrointestinal lumen, thereby slowing down the transport and diffusion of enzymes. In other words, the binding of dietary fiber to these compounds may influence digestion and delay the process rate (Qiu, Zhao, Decker, & McClements, 2015; Verrijssen et al., 2014).

In this way, the digestibility of proteins and polysaccharides differs according to their origin and composition, food processing and matrices, and can influence the release of encapsulated compounds from structured delivery systems, as detailed in this review. Moreover, the *in vitro* digestibility of plant proteins can be increased, which makes their use feasible for human health. In addition, plant proteins and polysaccharides may be desirable materials for the food industry and replace animal polymers as food ingredients and carrier materials, enabling a high level of bioaccessibility and bioavailability of bioactive compounds during the digestion process.

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4. Digestibility of plant oils

Lipids can be used as carrier material (for solid lipid particles, for example) and are often encapsulated by complex coacervation or emulsification (single, double, Pickering, or multi-layered emulsions). Since they are one of the main components of food and play an essential role in nutrition, their digestion should also be discussed (McClements, 2021). They are formed mainly by fatty acids (FAs), which are composed of an aliphatic chain with a carboxylic acid group; FAs are classified as saturated (with single bonds) and unsaturated (with double bonds) (Svennerholm, 1977). The main lipids are oils and fats, which are liquid and solid at room temperature, respectively. The lipids can be of animal and vegetable origin and have many functions, including the structuring of membranes, energy source, transportation of lipophilic vitamins, and thermal and physical insulator (McClements and Decker, 2008; McClements, 2021).

Like plant protein, the interest in vegetable oils by food industries has increased in the last years. There are numerous plant oil options, the most popular oils being coconut, linseed, canola, sunflower, sesame, sacha inchi, and soy oils. However, their low solubility in the aqueous gastrointestinal fluids and the different compositions of fats make them suitable for incorporation into delivery structures. The digestion of lipids depends on many factors, including gastric and intestinal pH, bile salts concentration, enzyme activity, oil droplet size, lipid concentration and food matrix complexity (Salhi, Carriere, Grundy, Aloulou, 2021; Pascoviche, & Lesmes, 2021).

Lipid digestion commences with the action of gastric lipases in the gastric compartment, reaching approximately one third of the total lipolysis during GI transit. One of the main enzymes responsible for lipid digestion in the intestinal phase is pancreatic lipase, which requires co-factor (co-lipases). Also, the presence of bile salts promotes the removal of proteins and free fatty acids from the oil droplets surface, resulting in more surface area available for enzyme action (Maldonado-Valderrama, Wilde, Macierzanka & Mackie, 2011; Sarkar, Ye, & Singh, 2016; Calvo-Lerma, Asensio-Grau, Heredia, & Andrés, 2020). Lipids can be ingested in different ways, such as in the form of liquid

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emulsions (milk and mayonnaise) or as part of the structure of the solid or semi-solid food matrix (e.g. meat and chocolate) (Calvo-Lerma, Asensio-Grau, Heredia, & Andrés, 2020).

In emulsions, the emulsifiers (proteins and polysaccharides, for example) used to stabilize these systems are strongly affecting the lipid digestion rate since it determines the oil droplet size and stability of the system. Tan, Zhang, Mundo, and McClements (2020) studied the effect of different emulsifiers (synthetic surfactant, natural surfactant, protein, polysaccharide, and phospholipid) on lipid digestion of corn oil emulsions. The oil droplets stabilized by Tween 20, quillaja saponin, and gum arabic were digested faster. They had a smaller droplet size with a bigger surface area available to lipase action. On the other hand, oil droplets stabilized by caseinate and lysolecithin had a bigger droplet size, smaller surface area, hence lipase action was lower. In addition, different food compositions may affect lipid digestion; according to Paz-Yépez, Peinado, Heredia, & Andrés (2019), the lipid digestion of milk, dark and white chocolate differs due to the composition and structure of the food. Fast lipid digestion in milk chocolate occurs due to the high concentration of lipid and its accessibility to the enzyme. On the other hand, the lipid digestion in dark and white chocolate is lower due to other compounds, such as polyphenols and cocoa butter, decreasing the activity of lipases.

5. Advantages of structured delivery systems on digestibility

As mentioned, structured delivery systems can be classified as (1) Pickering emulsions; (2) nanoemulsions and emulsions; (3) double emulsions; (4) multi-layered emulsions & coacervates; (5) nanogels and microgels; (6) micelles and (7) liposomes (Figure 2). They are used to tailor the digestion process since some of them are pH-dependent and present different charges, droplet and particle size, interfacial and core compositions, in addition to the number and types of layers on the interface.

[FIGURE 2]

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Gastric and intestinal phases have different pH values and some of the structured delivery systems are pH-dependent, especially those composed of protein or complexes formed by electrostatic interaction. In this case, the pH of the digestion phase can regulate or trigger the release of these delivery systems. The pH of the gastric phase decreases from close to neutral pH after food intake (depending on the food) to a basal level of pH 1 to 2 after complete digestion and gastric emptying. The average gastric pH is 3 (INFOGEST method), which is approximate to the isoelectric point (pI) of most food proteins. A pH around the protein pI often promotes aggregation and precipitation, which can lead to the formation of agglomerate or flocculation (in the case of emulsions), all of which can destabilize the delivery systems (Mulet-Cabero, Torcello-Gómez, et al., 2020; Sousa et al., 2020; Ye et al., 2020). On the other hand, the low gastric pH benefits the maintenance of coacervate structures since they are formed below the pI of protein, when the overall charge of the protein is positive. In addition to the pH, the particle/droplet size of the delivery systems is one of the most decisive factors during the digestion process due to the available surface for enzymes activity: systems with smaller particle/droplet size have a larger surface area accessible for enzymatic action, which increases the digestion rate of proteins/polysaccharides and encapsulated compounds in the interface (Salvia-Trujillo et al., 2013; Bourlieu et al., 2015; Infantes-Garcia et al., 2020).

Interfacial and shell compositions are another critical characteristic of delivery system for the digestion of food and food ingredients since the presence of proteins, polysaccharides or their combination will influence the digestion of the delivery system. If the system is composed of polysaccharides (mainly starch), its digestion starts in the mouth due to salivary amylase activity, which promotes the hydrolysis of starch into maltose. This reaction is inhibited when in contact with lower pH in the gastric phase. However, starch digestion continues in the intestinal phase with the essential enzymes including maltase, lactase, proteases and lipases being activated. However, if the system is composed of proteins, their breakdown starts in the gastric phase due to the action of pepsin. Meanwhile, if the system is composed of complexes with protein-polysaccharide combination, other

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371 factors (including particle size and pH) will be more significant in relation to their digestion. These
372 factors are described in more details in the following sections.

373

374 **a) Nano-emulsions, single emulsions and Pickering emulsions**

375 Depending on the structured delivery systems, the interface may accelerate or delay the
376 digestibility of encapsulated lipids and proteins/polysaccharides (McClements, & Jafari, 2018). The
377 digestibility and bioavailability of nutrients in emulsions (oil-in-water or water-in-oil systems) can be
378 regulated by the composition of the oil-water interface, the droplet size and the composition of disperse
379 and continuous phases and their interface. In the present section, we will present the influence of
380 structured emulsions for the delivery of bioactive compounds during *in vitro* digestibility. It is important
381 to highlight that due to their simple structure, emulsions are one of the most used delivery systems such
382 as incorporation of oil-soluble-compounds into water-based food.

383 The emulsions droplets may vary from nano scale (nano-emulsions) to micro scale (emulsions)
384 and this range influences digestive behaviour since smaller droplets have a higher surface area. One of
385 the important factors of digestibility is the enzyme activity, which is accelerated when a large surface
386 area is available (Salvia-Trujillo et al., 2013; Infantes-Garcia et al., 2020). In other words, emulsions
387 with smaller droplet size can accelerate the digestive process of food ingredients. In addition,
388 modifications caused by crosslinking are very common with proteins and also very common for
389 emulsions. Crosslinking has a significant influence on protein digestibility because new inter and
390 intramolecular bonds are formed, which decrease the rate of digestion due to the formation of new and
391 stronger bonds and structures. These characteristics can lead to a positive effect in relation to the
392 improvement of satiety and energy intake, the impact on allergenicity and the provision of systems with
393 more resistant layers (Isaschar-Ovdat & Fishman, 2018).

394 It is known that the nature and properties of emulsifier can influence the digestibility of
395 structured delivery systems due to the conformational changes when proteins are located at an interface

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(Shani Levi et al., 2017) and because it contributes to a stable system, thereby delaying the digestion process. Chickpea is a legume rich in protein with similar or better emulsifier properties than pea or soy protein. These properties may be influenced or improved with the addition of an enzymatic crosslinking (transglutaminase, for example), and it can influence emulsions digestion as well. For this reason, Glusac, Isaschar-Ovdat, & Fishman (2020) studied the effect of transglutaminase on the digestibility of chickpea protein-stabilized emulsions. Emulsions with and without transglutaminase showed that major proteins were hydrolyzed already at the beginning of gastric digestion due to the action of pepsin. Also, the acid medium of gastric conditions affected the solubility of proteins, promoting their aggregation. However, the emulsion with protein crosslinked with transglutaminase presented a decrease in the digestibility of protein during the gastric phase due to the action of transglutaminase. In other words, the presence of isopeptide bonds between protein and crosslinks hinders the action of digestion enzymes. Moreover, emulsions with crosslinked proteins presented larger droplet sizes, which may help delay the lipid digestion process. Even with a decrease in the rate of digestion, all proteins (with and without transglutaminase) were digested at the end of intestinal phase. For emulsions with transglutaminase, it happened because the crosslinks eventually broke down and became available for enzymes activity.

Pickering emulsions present the same structure as nano- and emulsions, but instead of conventional surfactants or emulsifiers on the interface, colloidal solid particles are used (Shi, Feng, Wang, & Adhikari, 2020). Pickering emulsions may present improved stability when compared to conventional emulsions due to the high desorption energy. In other words, more mechanical work is necessary to detach the colloidal solid particle from the oil-water interface and destabilize the system (Mehrabian, Snoeijer, & Harting, 2020). Another reason for their improved stability is that these solid particles present partial wettability for both oil and aqueous phases; the contact angle and surface tension are used to reveal it. That is, these solid particles are difficult to disrupt when they are at a water-oil interface, are almost irreversibly adsorbed and remain intact upon adsorption to the interface (Sarkar et al., 2016). Because of this, unlike nano-emulsions and emulsions, Pickering emulsions may

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significantly delay the digestion of encapsulated lipids (Araiza-Calahorra & Sarkar, 2019). However, proteolytic action of digestive enzymes needs to be taken into consideration as various types of proteins are commonly used to produce solid particles for Pickering emulsions.

Soy protein isolate (SPI), besides its use as an emulsifier, can form nanoparticles when subjected to heat, hence Pickering emulsions can be prepared using these nanoparticles at the interface. Notably, these SPI particles remain intact when attached to the surface of emulsion droplets. Moreover, the digestibility of Pickering emulsions may be improved with the incorporation of other nanoparticles (rich in phenolic compounds, for example). According to this, Ju et al. (2020) evaluated the digestibility and the release of free fatty acids of a novel Pickering emulsion using soy protein and anthocyanin complex nanoparticles. The SPI -anthocyanin complex nanoparticles were prepared using a black rice extract powder rich in anthocyanins, adjusting the system's pH, heating and concentrations of anthocyanins. The complex composed of SPI and anthocyanin formed a dense and intact layer attached to the surface of the emulsion droplets and caused a delay in lipid digestion. The rate of digestion decreased with an increase in anthocyanins concentration. Since enzyme activity is a significant factor in the digestion process, its action was lowered by the limited interfacial area due to the formed particles.

Besides the use of anthocyanins, other compounds including polysaccharides may also be applied to form complexes with plant protein nanoparticles in order to produce more stable Pickering emulsions. One example is the combination of flaxseed protein particles and flaxseed mucilage. Pickering emulsions stabilized with this complex are more resistant to lipid digestion due to the thicker interfacial layer and the smaller surface area (Nasrabadi et al., 2020). The smaller surface area is explained by the larger droplet size and the presence of protein particles-mucilage complexes. The authors compared Pickering emulsions with emulsions containing the synthetic emulsifier polysorbate 80 and flaxseed protein (not in particle form). These classic emulsions presented a fast rate of lipid digestion caused by the smaller droplet size and thinner interfacial layer.

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In this way, emulsions with proteins crosslinked at the interface and/or Pickering emulsions (even when combined with other compounds to form complexed) are recommended for application in functional foods, which can increase satiety and the feeling of fullness and possibly reduce obesity since (1) crosslinking reactions result in new inter and intramolecular bonds and (2) solid nanoparticles may be intact and attach to the surface of emulsion droplets contributing to a thicker interface with little or no available surface left for enzymatic access. In summary, all these factors favor a lower digestibility rate. The use of nanoparticles or complexes at the oil-water emulsion interface to decrease the digestibility rate of bioactive compounds has gained a lot of attention in recent years. Because of that, exciting research has been performed around the globe, including the digestibility of different types of oils, curcumin, β-carotene, vitamin E, and 5-demethylnobiletin isolated, for example. Table 1 details these examples of plant-based emulsions subjected to *in vitro* digestibility processes and Figure 3 summarizes the digestion of these emulsions.

[TABLE 1] and [FIGURE 3]

b) Double emulsions

Double emulsions are systems composed of three immiscible phases: (1) water-in-oil-in-water (W/O/W) emulsion or (2) oil-in-water-in-oil (O/W/O) emulsion, stabilized by the addition of an emulsifier, usually protein. This double system allows the simultaneous encapsulation of hydrophilic and lipophilic compounds and their release at different times and rates due to their different positions inside the emulsion.

However, relatively few studies have been carried out on the preparation of double emulsions with plant-based protein nanoparticles at the interface and their digestibility. Studying the mechanism of these particles in double emulsions during the digestion process is fundamental to explore whether they are influenced by the same factors as single emulsions and if they can be applied to food products. Xiao

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et al. (2017) investigated the use of karifin nanoparticles, the protein from sorghum grain, to stabilize W/O/W double emulsions. Anthocyanin was encapsulated in the inner aqueous phase; the oil phase was composed of soybean oil and polyglycerol polyricinoleate (PGPR) and the continuous aqueous phase consisted of kafirin nanoparticles. The pepsin action during gastric digestion promoted the breakdown of protein particles present in the outer phase, resulting in the flocculation of the emulsion droplets. The same behavior was observed by Ju et al. (2020) and Nasrabadi et al. (2020). In this way, the double emulsion lost its initial structure due to the digestion of protein particles during gastric digestion, releasing the encapsulated compounds (anthocyanins and soybean oil) to be digested during the intestinal phase. For comparison purposes, a double emulsion was also applied to simulated intestinal fluid without gastric digestion. It was observed that even with the presence of protein particles, free fatty acids were released, and the system resulted in a single emulsion at the end of the digestion process. Hence, the digestibility of double emulsions stabilized by protein particles was affected by the same factors as single emulsions: digestion enzymes and overall charge of proteins. Hence, if protein particles are used for structured delivery systems, single emulsions would be recommended since they present the same or similar digestive behavior as double emulsions.

Unlike systems with protein in the continuous aqueous phase of a double emulsion, the presence of polysaccharides in the continuous phase may retard the digestion process of encapsulated compounds. The addition of gum arabic to the continuous phase is able to limit the release of anthocyanins during stomach digestion. Even with a small amount of protein in gum arabic's molecular structure, it is digested by pepsin when subjected to the gastric transit, resulting in fast and total release of anthocyanins during incubation in the simulated intestinal fluid (SIF). This behavior was observed by Huang & Zhou (2019), who also encapsulated anthocyanins in a water-in-oil-in-water double emulsion. Black rice extract solution was used as the inner aqueous phase, sunflower oil as the oil phase and gum arabic solution as the continuous aqueous phase. Moreover, the degradation of anthocyanins during SIF occurred with the change in pH as the trigger mechanism. It was observed a simple change in color once

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pancreatic lipase was added. In other words, the oil droplets were available for enzyme action, after the breakdown of gum arabic into monosaccharides and amino acids – since gum arabic has glycoprotein in its composition, resulting in the release of anthocyanins. Hence, the use of double emulsions as structured delivery systems could be first taken into consideration as the main objective for their incorporation into food products. In addition, if consumers need a product with beneficial properties for satiety problems, polysaccharides instead of proteins should be recommended in the continuous aqueous phase of double emulsions.

Beside the use of polysaccharides in the continuous aqueous phase of double emulsions, the combination of Pickering and double emulsions may also decrease the rate of digestibility of encapsulated compounds. This idea was applied when stable systems were produced with probiotics and a sodium alginate solution in the inner aqueous phase, soybean oil and polyglycerol polyricinoleate (PGPR) as the oil phase and β-cyclodextrin particles solution in the continuous aqueous phase. Wang et al. (2020) observed that a high number of encapsulated probiotics was still alive after 1 h of gastric digestion. On the other hand, free probiotics completely lost their viability after 1 h of gastric digestion. It was possible to keep most of the double emulsion droplets with the same structure due to the use of β-cyclodextrin particles in the outer phase. β-cyclodextrin are carbohydrates composed of seven glucose rings and are digested only by pancreatic amylase during the intestinal phase. In other words, the incorporation of polysaccharides in the continuous aqueous phase may again delay the digestibility process more than protein, mainly in the gastric phase.

These studies allowed us to understand that a double emulsion stabilized with protein in the outer phase, even when combined with a Pickering emulsion, presents similar digestion behavior when compared to a single emulsion because the protein in the outer phase is available for enzymes during gastric digestion, regardless of whether the system is a single or double emulsion. However, the use of polysaccharides other than starch in the outer aqueous phase or their combination with protein may delay digestibility since polysaccharides rapidly pass through the mouth with the polysaccharide

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remaining largely intact. Hence, the polysaccharide molecules that have not been broken down during this first step are digested in the intestine by pancreatic amylase. Therefore, the materials to be used in the continuous phase of double emulsions should be considered depending on the food application. Figure 3 summarizes the digestion of double W/O/W emulsions.

c) Multi-layered emulsions & coacervates

Multi-layered emulsions and coacervates are systems based on electrostatic interactions between at least two oppositely charged polymers (protein and polysaccharides in most cases). Encapsulation by complex coacervation occurs when an oil-in-water emulsion is prepared with the incorporation of protein in the continuous aqueous phase, followed by the addition of the second polymer solution (polysaccharide). A change in pH to a value below the protein isoelectric point results in both polymers having opposite charges. The pH adjustment is done after the addition of the second biopolymer in order to achieve interaction of polymers and formation of complexes. In the case of multi-layered emulsions, an oil-in-water emulsion is first prepared with the protein (or polysaccharide with emulsifier properties) in the aqueous phase, followed by the addition of another polymer solution with opposite charge in order to achieve oppositely charged polymer layers. In that way, multiple layer (rather than complexes) can be formed, which could reach up to five layers (Corstens et al., 2017). Besides, complex coacervates precipitate (it is a liquid-liquid associative phase separation), while stable multi-layered emulsions present the phases in equilibrium. The use of these systems can be considered as an alternative to improve the stability of single emulsions and protect against coalescence and flocculation (Burgos-Díaz et al., 2016).

In the same way as presented for double emulsions, it is expected that multi-layered emulsions and coacervates present improved protection to encapsulated compounds in different pH, temperature, environmental and process conditions, decrease lipid oxidation and allow delayed lipid digestion due to the formation of a thicker layer and complex interface composition (Burgos-Díaz et al., 2016).

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However, sometimes it does not occur due to different materials used for each layer and their particular properties (Corstens et al., 2017). Some examples of plant-based combinations for these systems are soy protein-pectin (Ma et al., 2020; Ansarifar et al., 2017; Nori et al., 2011; Mendanha et al., 2009), soybean protein-flaxseed gum (Wang et al., 2011), rice bran protein-flaxseed gum (Hasanvand & Rafe, 2018), soybean protein-gum arabic (Mansour, Salah, & Xu, 2020; Rascón et al., 2011; Jun-Xia et al., 2011), soybean protein-soy polysaccharides (Tran & Rousseau, 2013;Yin et al., 2012), pea protein-gum arabic (Liu et al., 2010), and pea protein-pectin (Lan et al., 2020a and 2020b; Aberkane et al., 2014; Gharsallaoui et al., 2012; Gharsallaoui et al., 2010).

As mentioned above, coacervates and multi-layered emulsions are formed by electrostatic interactions and are therefore affected by the ionic strength of the serum. Low amounts of salt may enhance the formation of delivery systems; on the other hand, high amounts of salt may suppress this process due to the decrease in the electrostatic interaction between the biopolymers (Ogawa, 2015). When considering the gastro-intestinal transit of multilayered systems, the change of pH between oral, gastric and intestinal phase is a major destabilizing effect, especially since most of them are formed in low pH. It is expected that these delivery systems are stable in the gastric system. However, the higher pH in the intestinal phase would promote the variation in charge of biopolymers and the disintegration of the system. Hence, the action of the enzymes, pH and salt concentration influence multi-layered emulsions and the digestibility of the coacervates.

Intramolecular attractions are strengthened when a crosslinking compound is incorporated in systems formed by electrostatic interactions between proteins and polysaccharides. These can promote the formation of compact structures and delay the digestion of encapsulated compounds. A compact structure is formed when there are no intermolecular gaps in the complexes and the crosslinker occupies sites inside the complexes. However, the concentration of crosslinker should be considered since a high amount may promote the aggregation of proteins. Depending on the type of crosslinker, it can inhibit electrostatic repulsion due to the reduced charge caused by protein aggregation, making the charge

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570 insufficient to stabilize the system. Moreover, the ideal amount of crosslinker may result in the
571 formation of more stable structures (due to stronger intramolecular attractions) and a controlled release
572 during gastrointestinal digestion (Wei et a., 2020; Sun et al., 2017). This is confirmed by Wei et al.
573 (2020) when they observed that the addition of Ca^{2+} into zein-propylene glycol alginate and tea saponin
574 complexes delayed the release of resveratrol during the digestion process. More resistant complexes can
575 also be obtained with the combination of pea protein isolate and high methoxyl pectin, crosslinked with
576 Ca^{2+}. This system promoted a delay in the release of curcumin (Guo et al., 2020). When these
577 biopolymers interacted with each other without a crosslinker, systems with unstable particle size were
578 obtained, resulting in a larger surface area available for the enzymes.

579 However, in some cases, the use of protein and polysaccharide combinations does not delay the
580 lipid digestion when compared to systems composed of proteins only, as would be expected. Some
581 polysaccharides (pectin, cellulose, guar gum and some starches, for example) have the ability to change
582 the aggregation of oil droplets, increasing the lipid phase surface available for enzyme activity and the
583 digestion rate. Moreover, delivery systems formed by electrostatic interactions are very stable with a
584 small particle size (and a higher surface area), which facilitates the action of enzymes and increases
585 digestibility. This behavior was observed in several studies (Xu, Sun, & McClements, 2020; Qiu, Zhao,
586 Decker, & McClements, 2015; Gidley, 2013; Tokle, Lesmes, Decker, & McClements, 2012). The
587 resistance of coacervates at digestion conditions can also be observed for systems with SPI and
588 carrageenan, debranched corn starch with different debranching degrees and xanthan gum, soy protein
589 and fiber, and addition of transglutaminase as a crosslinker. On the other hand, a fast release was
590 achieved when only soy protein was used in the continuous phase in comparison to soy protein-
591 polysaccharide Maillard reaction product. Table 2 presents these examples of multi-layered emulsions
592 and coacervates, focusing on their digestibility and Figure 3 summarizes the digestion of complex
593 coacervates.

594

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[TABLE 2]

Summarizing the main factors for digestibility of multi-layered emulsions or coacervates, we can say that their formation may delay lipid digestion due to the presence of more resistant and thicker layers. However, at times this does not happen because some polysaccharides are able to change the aggregation of oil droplets, making the lipid phase more available for enzymes. Moreover, these delivery systems present great stability, small particle size and, consequently a higher surface area. The use of plant proteins may delay the digestion process compared to milk protein (and animal protein in general) due to the presence of antinutritional factors (protease inhibitors, phytases, polyphenols, fibers, and non-starch polysaccharides) (Sá, Moreno, & Carciofi, 2020) in crude, unpurified protein products. In addition, the presence of polysaccharides may protect the protein against enzyme action if both interact; on the other hand, if the complex did not form a resistant structure, the polysaccharide would not be able to form a protective layer and then the protein would be available for proteolysis by digestive enzymes (Guo et al., 2020). The use of crosslinker may also delay the lipid digestion and it is also influenced by its concentration. And finally, particle size may have one of the most important influences on the digestibility of multi-layered emulsions and coacervates since systems with this complex interface were rapidly digested when presented in a small particle size. The information presented here is essential for the food industry: systems with animal protein and protein-polysaccharide combinations without crosslinker may be useful for the development of functional foods intended for consumers who need fast, easy and/or complete digestion (consumers with gastrointestinal problems, for example). Conversely, functional foods intended for weight management by controlling satiety or the feeling of fullness may consider the use of systems with plant proteins or protein-polysaccharide complexes with the addition of crosslinkers.

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d) Micro- and Nanogels

Micro- and Nanogels are systems composed mainly of crosslinked hydrogel and water, with particles in microscale (microgels) or nanoscale (nanogels). The most commonly used polymers as carrier agents are polysaccharides, including cellulose, alginate, gums, pectin and modified starches (Oh, Lee, & Park, 2009) and proteins (Nicolai & Chassenieux, 2019).

As observed for the aforementioned structured delivery systems, it would be expected that crosslinked systems form rigid and compact structures and promote the best protection and controlled release of the encapsulated compound. However, it may not happen to all types of delivery systems. Hence, this particular characteristic has a decisive influence on their digestibility process. Furthermore, structured delivery systems composed of gels, due to the increase in pH during the intestinal phase, end in the reduced stability and hardness of the gel (Santos & Cunha, 2019). Structures formed of gellan gel crosslinked with calcium chloride presented a higher release of the encapsulated compound when compared to gel without crosslinking reaction. This behavior was observed by Santos & Cunha (2019) when they studied the *in vitro* digestibility of gellan gels loaded with anthocyanin extract. The release mechanism can be explained by calcium ions competing with cations from anthocyanins for anionic sites of gellan gum and alginate, resulting in the presence of extract on the surface of gels and in the degradation of anthocyanins even before being subjected to the digestion process (Santos & Cunha, 2019; Vilela, Cavallieri, & Cunha, 2011). It is worth mentioning that anthocyanins are stable at low pH, and for this reason they are easily absorbed during gastric digestion, resulting in their low absorption in the intestine (Pérez-Vicente, Gil-Izquierdo, & García-Vigueira, 2002: McGhie & Walton, 2007). The incorporation of anthocyanins in a structured delivery system such as gellan gels would be an alternative for this limitation. For this reason, Santos & Cunha (2019) prepared gellan gels in two sizes loaded with *jabuticaba* extract (rich in anthocyanins) and compared the systems when crosslinked with calcium chloride. Moreover, besides the crosslinker characteristics, gels of a smaller size promoted a greater release of encapsulated extract due to the larger surface area, in the same way as described above for the

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644 other structured delivery systems. Therefore, the increased digestion rate for delivery systems with
645 smaller particle/ droplet sizes should be considered for all types of structured systems. However, it is
646 necessary to know that not all crosslinked systems promote a delay in the digestion process.

647 Pectin is one of the polysaccharides commonly used for gel-based structured delivery systems
648 and they belong to dietary fiber; in other words, they are resistant during gastric and small intestinal
649 digestion, but are fermented in the colon, resulting in the delayed release of encapsulated compounds
650 (Guibaudo et al., 2018; Assifaoui, Chambin, & Cayot, 2011; Liu et al., 2013). Moreover, the
651 digestibility process of structured delivery systems formed of pectin is related to the swelling degree,
652 which is pH-dependent. In this case, the swelling is higher in the simulated intestinal medium than in
653 the gastric one. During the acidic gastric digestion, the carboxyl groups are in a protonated state, which
654 reduces the electrostatic repulsion and the overall polymer solubility. On the other hand, during
655 intestinal digestion, solubility is increased, and the higher pH causes an increase in electrostatic
656 repulsion between polymer strands. This was confirmed by Guibaudo et al. (2018), who studied the
657 encapsulation of iron in pectin beads and evaluated the digestibility of the system. In the case of iron
658 encapsulation, the increased swelling at a higher pH may also be related to the presence of hydroxyl
659 anions, promoting the releasing of Fe(II). Therefore, pectin is considered as an alternative to be used in
660 delivery systems applied to food products for improved satiety effects.

661 Another example of polysaccharides used as a carrier in gel-based systems is alginate. Alginate
662 has shown to be a compound favorable to delay the digestion of lipids due to the progressive dissolution
663 of the gel at digestion pH, the increase of system's viscosity, and, as observed for pectin gels, they are
664 resistant during gastric and small intestinal digestion, but fermented in the colon. This aspect was
665 observed by González et al. (2020), who compared the lipid digestion of O/W emulsion and O/W
666 emulsion-filled gel. However, according to Gómez-Mascaraque et al. (2019), this behavior depends on
667 the type of alginate grades. These authors observed that microcapsules produced with alginate rich in α-
668 L-guluronic acid residues maintained better their structure at pH values ≤ 3 and at intestinal conditions;

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669 on the other hand, microcapsules produced with alginate rich in (1→4)-linked β-D-mannuronic acid lost
670 their structure at pH ≥ 3. It can be explained due to the presence of monovalent cations in the simulated
671 fluids, promoting the weakening of the network (Gómez-Mascaraque et al., 2019).

672 Moreover, the release of encapsulated compounds from alginate-based structured delivery
673 systems may be affected when part of the alginate is replaced by starch. Starch granules are composed
674 of amylose and amylopectin (Singh, Singh, Kaur, Sodhi, & Gill, 2003) and their ratio and concentration
675 strongly affect the starch digestibility, and consequently the digestibility of alginate-starch gels. For this
676 reason, Feltre et al. (2020) evaluated the influence of alginate, starch gelatinization and the amylose
677 content on the digestibility of seven gel formulations, such as: (1) ALG – with alginate only; (2) NGCS
678 – with alginate and non-gelatinized common corn starch; (3) GCS - with alginate and gelatinized
679 common corn starch; (4) NGAM – with alginate and non-gelatinized high amylose corn starch; (5)
680 GAM – with alginate and gelatinized high amylose corn starch; (6) NGAP - with alginate and non-
681 gelatinized high amylopectin corn starch; and (7) GAP – with alginate and gelatinized high amylopectin
682 corn starch. Gels with gelatinized starch showed a higher glucose release (after maltose release, which is
683 later digested into glucose) during intestinal digestion due to a structural disintegration of the granules
684 during gelatinization and the high accessibility to pancreatic amylase. Moreover, the higher the amylose
685 content, the lower the glucose releases. This can be is explained by the fact that amylose has more
686 resistance to amylase action than amylopectin. Amylopectin has a larger surface area than amylose and
687 branched chains of glucose, which makes it more suitable for enzyme action. The delay in digestion
688 provided by microgels systems is also observed for systems composed of alginate and rice starch gels
689 complexed with gallic acid. These other studies of gel-based structured delivery systems with focus on
690 their digestibility are presented in Table 3.

691 The digestibility of protein gels systems has been studied mainly with animal and milk proteins
692 (Schmitt et al., 2010: Doherty et al., 2011). The *in vitro* digestion of plant proteins-based nano- and
693 microgels as delivery systems should be considered for further researches once the digestion of these

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694 structures is studied essentially when they are applied as colloidal particles for Pickering emulsions (Liu
695 & Tang, 2016; Shao & Tang, 2016).
696
697 **[TABLE 3]**
698
699 In summary, the application of gel-based structured delivery systems in food products should
700 take into consideration the composition of encapsulated compounds and polysaccharides used.
701 Crosslinked gels do not offer the same digestive behavior as crosslinked emulsions or coacervates
702 because ions from the crosslinker may compete with ions from encapsulated compounds for
703 polysaccharide sites, promoting the release of encapsulated compounds and their faster digestion.
704 Moreover, the use of delivery systems with polysaccharides, which belong to the dietary fiber
705 classification, or with non-gelatinized starch with high amylose may be applied to food products
706 intended for consumers who want the bioactive compounds to be absorbed in the colon. In addition,
707 systems with gelatinized high amylopectin starch may be used in products intended for fast release
708 during intestine digestion.
709
710 **e) Micelles and liposomes**
711 Micelles, which are colloidal molecular aggregates in the nano-scale, are commonly used by the
712 pharmaceutical industry and are suitable for encapsulating hydrophobic compounds. The structure is
713 somewhat similar to emulsions (oil droplets stabilized by surfactant at the oil/water interface). Their
714 formation is possible with the addition of surfactants at specific concentrations (from/above critical
715 micellar concentration) and is temperature and pH-dependent (Narang, Delmarre, & Gao, 2007); hence
716 their digestion behavior is important to understand the release, bioavailability and bioaccessibility of
717 encapsulated compounds.

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718 The structure of micelles is directly affected by pH and temperature. Wu et al. (2021) studied the
719 encapsulation of β-carotene in octenylsuccinated oat β-glucan (a modified starch) micelles. *In*
720 *vitro* release was studied at pH 1.2, 4.5, 6.8, 7.4, and 8.5, and 25, 37.5, and 45°C. At low pH values, a
721 higher rate of release was observed during the first 120 min, with a low release in the next 480 min.
722 This effect can be explained by the absence of electrostatic interaction in the acidic gastric medium,
723 which made the hydrogen bonding interaction weaker and destroyed or weakened the micelles.
724 Moreover, the release of encapsulated compound increased at higher temperatures. The hydrogen-
725 bonding interaction was destroyed by high temperature, resulting in weak micellas shell with various
726 cracks. Hence, in addition to the accelerated molecular movement, the infiltration of βC molecules
727 through this shell increased, promoting higher release of encapsulated compound (Wu et al., 2021). The
728 same behavior was observed by Liu et al. (2021). These authors studied curcumin encapsulation using
729 acetylated debranched starch micelles as a structured delivery system and their release behavior during
730 simulated gastric (pH 1.5 and 37℃) and intestinal (pH 6.8 and 37℃) digestion. In this case, curcumin-
731 loaded micelles presented a higher release rate at the start of digestion followed by a more sustained
732 release. Moreover, the rate was higher during the intestinal phase, probably due to the weakening of
733 micelles by pancreatin and bile salts. In other words, the application of micelles systems into food
734 products should be considered since the digestion process for this delivery system can start at the gastric
735 phase but can continue at the intestinal phase, therefore promoting a slower digestion process.

736 Like micelles, liposomes are colloidal structures stabilized by surfactants (phospholipids, in this
737 case). However, they are stabilized by double layers of molecules, with their nonpolar groups facing
738 each other, see schematic in Figure 2. In other words, they present amphiphilic property, which allows
739 the encapsulation of either hydrophilic or hydrophobic compounds (McClements, 2015; Esposto et al.,
740 2021). They can be used to encapsulate food ingredients due to their biocompatible and biodegradable
741 characteristics; nonetheless, they do not have adequate stability during digestion due to the acidic
742 conditions and enzyme activity (Esposto et al., 2021). Hence, the digestibility behavior of these

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743 structured delivery systems should be taken into account since many factors have to be improved to
744 enhance the ideal digestion behavior for liposomes.

745 The digestion of liposome can be improved by changing the type and concentration of the
746 phospholipids. Vergara, López, Bustamante, & Shene (2020) studied the *in vitro* digestion of
747 encapsulated lactoferrin (LF) in rapeseed (RP) phospholipid-based liposomes using combinations of RP
748 with stigmasterol (ST) or hydrogenated phosphatidylcholine (HPC). The gastric and intestinal medium
749 promoted the increase of liposome particle size due to the vesicle aggregation caused by the acidic pH
750 (1.5) during gastric and osmotic effects. Encapsulated LF was compared to the free one: There was no
751 intact free lactoferrin after 120 min of gastric digestion; however, when it was encapsulated in
752 liposomes, LF only gradually decreased over time (120 min). The lower degree of LF digestion during
753 the intestinal phase is attributed to the reduced action of pancreatin and bile salts on the liposome
754 system. Even with the decrease of LF during gastric and intestinal phases, its encapsulation into
755 liposomes promoted its protection compared to the free protein. Also, the use of HPC and higher
756 concentration produced a more rigid and stable structure than ST. It can be explained due to its saturated
757 structure, which has higher phase transition temperatures and can form a gel with lower fluidity (Tai et
758 al., 2020). Moreover, the digestion process was also evaluated according to the release of free fatty
759 acids (FFAs). The amount of released FFAs increased for all formulations during intestinal digestion for
760 30 min, showing that LF accelerated the lipolysis as bile salts displaced the phospholipid at the
761 interface, which was promoted by the inclusion of lactoferrin.

762 The use of hydrogenated phospholipid was also studied by Tai et al. (2020) to improve
763 liposomes' stability and digestion. These authors encapsulated curcumin and compared formulations
764 with soybean phospholipid (SPC) and with part of it substituted by hydrogenated soybean phospholipid
765 (HSPC). Formulations promoted a small release of curcumin during gastric digestion due to the stronger
766 liposome structure when used a hydrogenated phospholipid. However, curcumin's release increased
767 during the intestinal phase due to the action of pancreatin and bile salts, which promoted the hydrolysis

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of phospholipids. Liposomes with SPC resulted in the fastest and highest release of curcumin (80%), while liposomes with HSPC showed a more sustained release compared to SPC formulation. Nonetheless, liposomes with a ratio of 1:1 of SPC and HSPC promoted the slowest curcumin release during the digestion process. In consonance with the above, encapsulated compounds in liposomes presented delayed gastric and intestinal digestion when hydrogenated phospholipid is used. Moreover, its concentration and combination with different phospholipids may also improve the system's stability and digestion.

6. Future remarks and challenges

The use of plant proteins and polysaccharides as wall/carrier materials has increased over the last years and structured delivery systems based on these plant materials can be incorporated into the human diet in different ways. Both food and pharmaceutical industries are looking to improve the options and properties of functional food products. These functional foods are designed for numerous benefits, including increasing bioavailability and bioaccessibility of bioactive compounds and controlling their digestion. Numerous studies regarding digestibility of structured delivered systems are in the literature. However, investigations of plant-based system are still limited, which shows the importance of future works on digestion of plant-based delivery systems. Digestion of soy-based food (commercial soy milk and tofu), plant-based beverages, and plant-based infant formula were interestingly studied (Roux et al., 2020; Silva et al., 2020; Reynaud et al., 2021). However, there is still a literature gap regarding the digestibility of plant-based delivery systems incorporated in food products; moreover, it requires sound knowledge of food structures as different matrices are likely to affect the digestive behaviour of the delivery systems.

The digestion of structured systems also brings attention to one of the challenges discussed in this review: influence of particle sizes on the digestibility of food compounds. Particle size was

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discussed separately for each structured delivery system and should always be considered when the encapsulated compounds are applied to food products.

7. Conclusions

This review outlined the importance of structured food ingredient delivery systems and the influence of their structure and composition on the digestibility of encapsulated bioactive compounds and the proteins/polysaccharides used as carrier agents. Plant-based systems were the focus, which have been an innovative alternative to animal proteins in recent years. To date, the digestibility of proteins may change depending on their composition (plant or animal origin) and when combined with a polysaccharide, mainly during the gastric phase due to the low pH and the action of pepsin. The types of structured delivery systems (conventional, nano-, Pickering, double or multi-layered emulsions, coacervates, nano- and microgels, micelles and liposomes) also have a significant influence on their core and wall materials *in vitro* digestibility. Emulsions with proteins as emulsifiers, due to their fast digestion with the enzyme action during the gastric step, are recommended for food matrices used to improve the transport of encapsulated bioactive compounds. Moreover, the presence of many compartments as observed for double emulsions does not always improve or delay digestibility as expected, but the use of polysaccharides in the outer phase may help that. In addition, multi-layered emulsions or coacervates may delay lipid digestion, depending on the composition of the interface/surface. And finally, particle size can be considered one of the most important parameters for controlling the digestibility of all types of structured delivery systems, since a smaller particle size promotes faster digestion due to the larger surface area available to enzymes. This is the first review that focuses on the digestibility of structured food ingredient delivery systems based on plant proteins and polysaccharides.

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FIGURE CAPTIONS

Figure 1. Diagram of simulated in vitro digestion: oral, gastric and intestinal phases. Adapted from Minekus et al. (2014) and Brodkorb et al. (2019).

Figure 2. Diagram of the most common structured delivery systems: Pickering emulsion; Nano-emulsion and emulsions; double emulsions; multi-layered emulsions and coacervates; liposomes; micelles; nanogels and microgels.

Figure 3. Diagram of digestion of main structured delivery systems: O/W emulsion; Pickering emulsion; W/O/W double emulsion and complex coacervate.

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Table 1. Examples of digestibility studies of plant-based emulsions.

Emulsion type	Stabilized by	Encapsulated compound	Main digestibility results	References
Pickering high internal phase emulsions	Gliadin particles	Algal oil and curcumin	Reduced oil digestion (release of free fatty acids was below 30%) and improved the curcumin bioaccessibility	Zhou et al. (2018)
O/W emulsion	Tamarind seed gum (TSG)	Soybean oil	The use of TSG as emulsifier promoted the inhibition of lipid digestion (33-70%) compared to control (without TSG)	Udomrati et al. (2020)
O/W emulsion	Gum arabic (GA), quillaja saponin (QS) and whey protein isolate (WPI)	Vitamin E and corn oil	Free fatty acids production was faster during first 10 min of digestion process due to the lipase action. QS-emulsion presented slower lipid digestion rate due to the saponins behavior at the emulsion interface and the possible complexes formed by saponins and calcium ions.	Lv et al. (2019)
Gel-like Pickering emulsion	Soy glycinin (SG), compared to sodium caseinate and whey protein	β-carotene, and mix of sunflower and soy oils	Fast increased release of β-carotene during the initial digestion process; β-carotene release correlated to release of free fatty acids. Unheated SG-emulsion promoted lower β-carotene release due to smaller droplet size. The formation of gel-like network also influenced the compounds release and digestion.	Liu & Tang (2016)
Pickering emulsion	Peanut protein nanoparticles,	5-demethylnobiletin	Emulsions released more free fatty acids than the	Ning et al.

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	compared to Tween 80	isolated from chenpi (5DN)	free oil in the following order: Tween emulsion > Pickering emulsion> free oil. The bioaccessibility of 5DN increased with the increase of free fatty acids release.	(2019)
Gel-like Pickering emulsion	Pea protein	β-carotene, and mix of sunflower and soy oils	Gel-like emulsion (with higher amount of oil) presented lower β-carotene release and degradation during digestion time.	Shao & Tang (2016)

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Table 2. Examples of digestibility studies of plant-based multi-layered emulsions and coacervates.

System type	Stabilized by	Encapsulated compound	Main digestibility results	References
Oil-in-water emulsion	Soy protein isolate (SPI), soy soluble polysaccharide (SSPS) and soy protein-polysaccharide Maillard reaction product (SPPMP)	Citral (mixture of cis and trans isomers)	SPPMP emulsions droplet size was constant and SPP or SPI emulsions droplet size increased under gastric conditions; the release of citral during digestion (2h) was in the order: SPI (70%) > SPP (62%) > SPPMP (36%). Complete release observed after 4h of digestion (SPPMP).	Yang et al. (2015)
Coacervates	Soy protein isolate and carrageenan	*Bifidobacterium longum*	Viable cells were reduced during digestion for 60 min for coacervates. Control (free bacteria) presented higher viability at the beginning but decreased after gastric digestion. Coacervates were resistant at low pH, reducing the diffusing of acids to the microcapsules and to the bacteria.	Mao, Pan, Yuan, & Gao (2019)
Coacervates	Debranched corn starch with different debranching degrees and xanthan gum	Tea polyphenols	Four coacervates were prepared with starch hydrolyzed by Pullulanase: (a) for 1 h with 12 U/g; (b) for 1 h with 18 U/g; (c) for 2 h with 18 U/g and; (d) for 3 h with 18 U/g. Coacervate B presented delayed release due to its viscosity and better synergism with xanthan gum. The gel resulted in a	Hong et al. (2019)

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			more compact complex.	
Emulsion-Coacervates	Soy soluble polysaccharides (SSP), pectinase-hydrolysed soy soluble polysaccharide (PH-SSP) and soy protein	Rice brain oil	Hydrolysis with pectinase increased SSP solubility, which induced the self-association of PH-SSP and promoted the destabilization of emulsion and oil release under stomach conditions. The oil released under stomach conditions when the system had PH-SSP in the concentration of 0-2% (w/v), helping the lipid digestion. The presence of high amount of fiber (enough to form coacervates with protein) promoted the delay of lipid release and protein digestibility.	Fafaungwithayakul, Hongsprabhas, & Hongsprabhas (2011)
Coacervates	Soy protein isolate (SPI), SPO with sucrose (MC-C/S), with ribose (MC-C/R), with sucrose and transglutaminase (MC-MTG/S) and with ribose and transglutaminase (MC/MTG/R)	Fish oil	Fast release of oil for all samples in the first hour of digestion; 60 and 30% of oil were release by MC/C/S and MC-MTG/S, and MC/C/R and MC/MTG/R, respectively, after 5h of digestion with pepsin. This difference is due to covalent cross-links obtained by Maillard reaction; pepsin action was reduced due to wall materials. Core release was affected by crosslinking reaction.	Gan, Cheng, & Easa (2008)

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Table 3. Examples of digestibility studies of plant-based microgels systems.

Polysaccharide	Encapsulated compound	Main digestibility results	References
Alginate, rice bran, inulin and resistant starch (Hi-maize)	*Lactobacillus acidophillus*	The incorporation of probiotics into structured delivery system promoted their protection during gastrointestinal digestion when compared to free one. The systems were ruptured when subjected to acid conditions; however, even with this rupture, the probiotics presented counts of within 8.06-11.18 log CFU/g compared to the free one (5.69 log CFU/g).	Poletto et al. (2019)
Sodium alginate	Anthocyanins extract	The particles were spray (P-SD) and freeze-dried (P-FD). The encapsulation promoted the protection of anthocyanins during digestion. The retention of anthocyanins after gastric digestion was 83, 70 and 45% for P-SD, P-FD and free one, respectively, while the retention after intestinal digestion was 24.5, 15 and 1% for P-SD, P-FD and free one, respectively.	Zhang et al. (2018)
Rice starch gels complexed with gallic acid	--	The complexation (or crosslinking) with gallic acid promoted the reduction of rice starch gels digestibility. The higher the concentration of gallic acid, lower the amount of digested starch and higher the value of resistant starch.	Chi et al. (2019)
Sodium alginate	*Lactobacillus plantarum* NCDC201 and *L. casei*	The free probiotics presented low survival after incubation in simulated intestinal tract. Double layer of alginate promoted the protection of bacteria during digestion process due to the low	Rather et al. (2017)

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		diffusion of bile salts through the wall of structured system.	
Ca (II)-alginate beads	--	The Ca (II)-alginate beads slightly changed their structure during oral and gastric phase, but partially modified during intestinal phase.	Aguirre-Calvo et al. (2020)
alginate-based emulsion gel beads	lycopene	The alginate-based emulsion gels showed stabilized systems when combined with protein (WPI), but weak interactions with soy protein. The presence of protein in the gel beads increased shrinkage during gastric digestion and postponed the release of encapsulated compound.	Lin, Kelly, Maidannyk, & Miao (2021)
Sodium alginate	--	Sodium alginate beads were prepared in the presence of $CaCl_2$ and $BaCl_2$. Barium alginate beads presented greater stability in conditions which mimic the passage of beads from mouth to colon.	Bajpai & Sharma (2004)
alginate	Lactoferrin (apo-, native-, and holo-)	Encapsulated lactoferrin was more protected during SGF than un-encapsulated forms, but pure and encapsulated systems were digested very rapid in the SIF.	Bokkim, Bansal, Grondahl, & Bhandari (2016)
Calcium alginate	Corn oil	The alginate particles remained stable at pH from 1 to 7 and shrinkaged at pH 1 and 2. The particles promoted the protection of encapsulated oil once the free fatty acids release decreased from 100% to 12% after 120 min of digestion.	Li et al. (2011)

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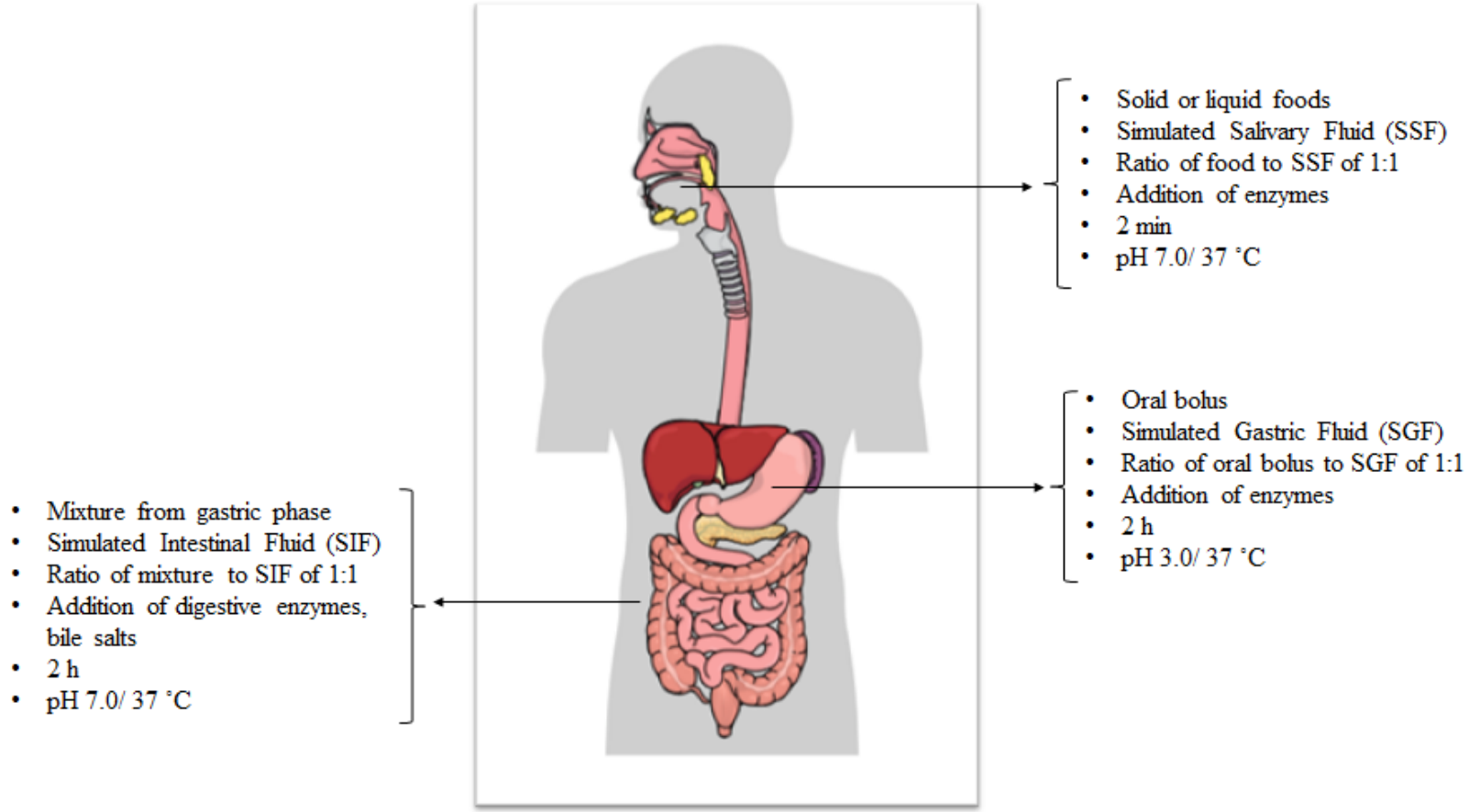

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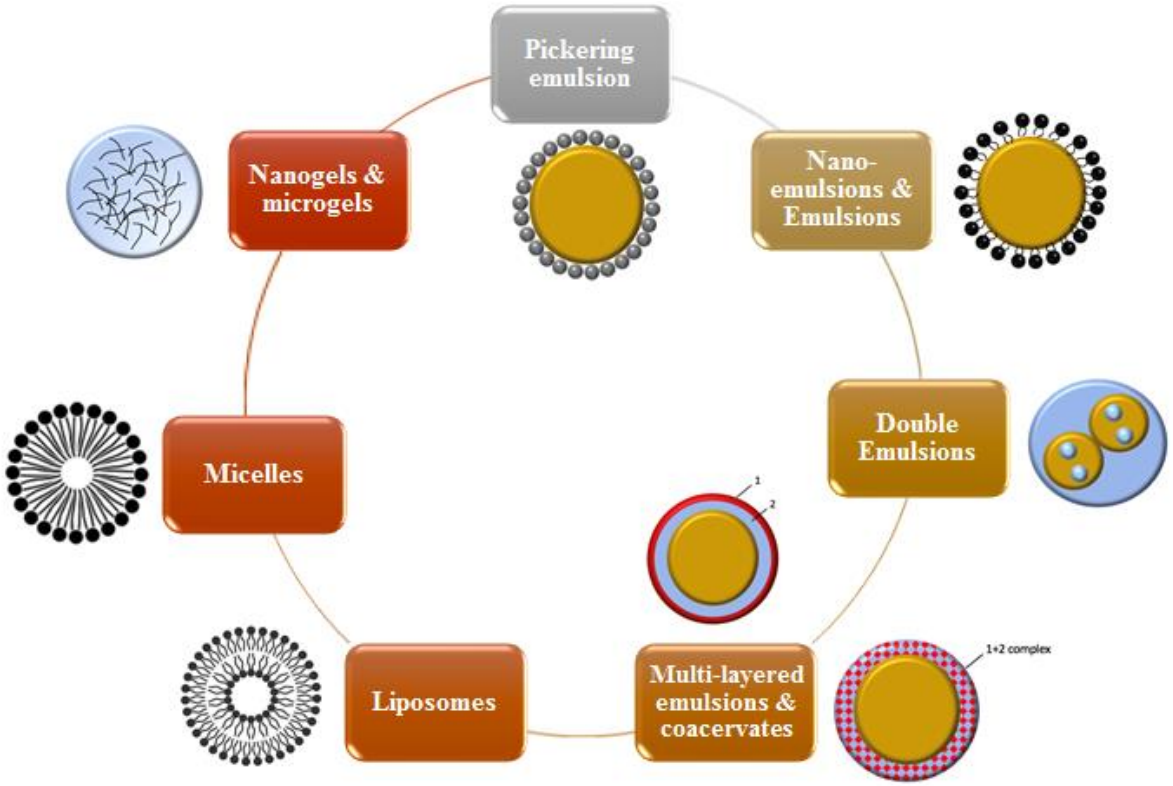

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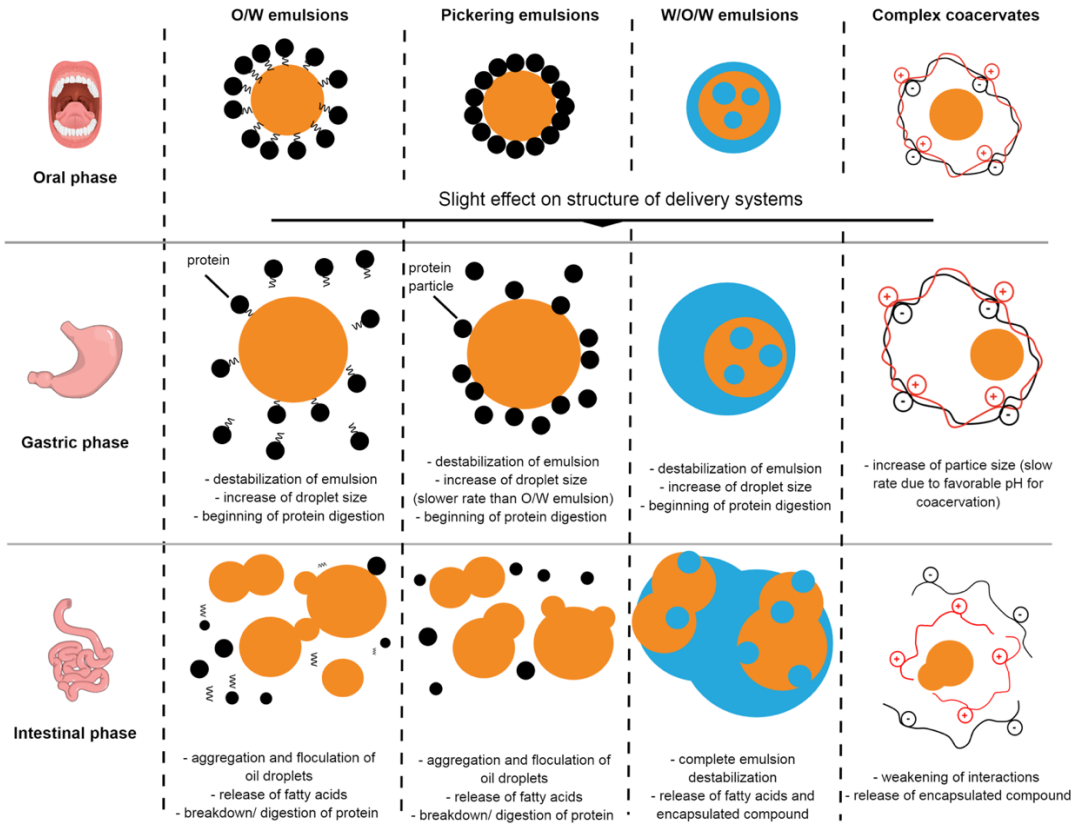

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Figure 3. Diagram of digestion of main structured delivery systems: O/W emulsion; Pickering emulsion; W/O/W double emulsion and complex coacervates**.** By Comunian *et al.*, 10.1080/10408398.2021.1902262 Figure 3