11 Hydrocolloid Formulations Engineered for Properties in the GI Tract

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11.1 INTRODUCTION

Hydrocolloids have been and still are very important structures for food formulations, where they exhibit a number of different functionalities, including gelling, thickening, water holding, stabilising, foaming, etc. They have been used in a plethora of processed food products, including mayonnaises, dressings, ice creams, etc. Hydrocolloids currently used in foods come from many different natural sources, such as seaweeds (e.g. alginate), plant seeds (e.g. guar gum), citrus or apple peels (e.g. pectin), micro-organisms (e.g. gellan gum) and chitin from animals (e.g. chitosan), and others.

For a number of years now hydrocolloids have been considered as the ingredient of choice for textural control, which is arguably their main function when used in foods. Overall they are excellent candidates for imparting a range of functionalities to foods that, however, are currently limited to those required prior to food being consumed (e.g. stability) or perhaps during its oral manipulation (e.g. mouthfeel). More recently there has been growing interest to design and develop food formulations by considering the phenomena occurring as these are processed in the gastrointestinal (GI) tract. This approach takes advantage of the current and growing understanding of the physical processes and phenomena occurring in the human body during food digestion and sets the far from trivial challenge of designing foods that impart "real" health benefits, e.g. by responding to digestive events in the GI tract to promote those with beneficial effects and/or to diminish others that could present or lead to health risks.

This chapter argues that hydrocolloids and/or hydrocolloid-based formulations have a significant role to play in the design of such (functional) foods that are "engineered" to convey properties in the GI tract

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mainly relating to the promotion of good health. The number of different functionalities in foods that hydrocolloids can potentially help to create/design are reflected in the themes chosen for discussion in this chapter. Firstly, hydrocolloid-based delivery systems for the encapsulation and targeted delivery of nutrients (e.g. vitamins), microbial supplements (probiotics), dietary fibre (prebiotics), lipids or therapeutic species (e.g. drugs) are discussed. These systems include those designed for the protection of encapsulated material, and for the triggered delivery to specific parts of the GI tract (e.g. induced by pH). Hydrocolloids themselves, and/or hydrocolloid-based structures, can also have an effect on physiological functions in the GI tract. Discussion in this chapter includes effects on gastrointestinal transit time, as a result of increased viscosity or gel formation, and absorption rates (as a result of enzymatic activity). The concluding section of this chapter examines hydrocolloids' additional benefits, such as the ability to aid in mucosa healing, reduce post-prandial blood glucose levels, reduce cholesterol absorption and the ability to bind mutagens and heavy metals present within the intestinal lumen, thus reducing carcinogenic effects.

11.2 ENCAPSULATION AND RELEASE

Functional foods are promising delivery systems for living cells, nutrients, vitamins, etc., but also, and perhaps more importantly, for the targeted delivery of a range of therapeutic agents to the human body. Biopolymers have attracted considerable attention for the formulation of functional foods due to their properties, i.e. non-toxic, biodegradable, biocompatible, are generally regarded as safe and are currently used in food industry (as thickeners, emulsifiers, stabilisers) extensively (Chen *et al*., 1995). Proteins and polysaccharides are also excellent material for formulating, either individually or as mixtures, delivery structures within food matrices (Brownlee, 2011). A range of food-grade polysaccharides have found applications as delivery systems: alginate, chitosan, carrageenan, xanthan gum, pectin, gum Arabic, inulin and methyl cellulose (Jones and McClements, 2010). Proteins, the polypeptide chains of amino acids, are often used to construct functional food assemblies and offer additional benefits mainly due to their valuable nutritional attributes; proteins employed for such purposes in the past include: β-lactoglobulin, casein, bovine serum albumin, ovalbumin, soya glycinin and gelatin. The type of biopolymer building blocks to be used and the interactions (electrostatic, hydrophobic, steric, hydrogen bonding) between like or unlike species in the system will significantly determine overall functional characteristics (Jones and McClements, 2010).

Encapsulation of lipophilic compounds, such as vitamins, nutrients, bioactive and functional lipids, allows their protection from as well as targeted delivery and release to specific parts within the GI tract (McClements and Li, 2010). Successful targeted delivery of encapsulated components to the GI tract would also require preventing/hindering their premature degradation, release and/or absorption. Release of encapsulated species at desired locations in the GI tract from within an encapsulating matrix of particulate nature would take place via one or more of the following mechanisms: diffusion through the pores of the particulate matrix (strongly enhanced by swelling); erosion of the outer layer or the whole matrix due to physical/chemical or enzymatic degradation; fragmentation of the carrier particulate structure due to stresses (Lesmes and McClements, 2009, 2012). Potential issues these delivery systems encounter can be caused by the low solubility and permeability of such structures within the stomach and intestine(s) (e.g. due to pH conditions, presence of enzymes, interactions with other food components) but also due to sources of instabilities during their storage (e.g. with reference to temperature, oxygen, light).

In order to design a hydrocolloid-based delivery system to successfully transport and release its load to a specific location in the GI tract (e.g. the large intestine), all the characteristics of subsequent parts of the tract have to be carefully considered. This is the first step towards predicting the stability and response of the delivery system to the range of environment conditions (Table 11.1) encountered in the GI tract and until the target location is reached. For the purpose of such considerations, knowledge of GI tract section-specific characteristics such as the presence of enzymes and other components (e.g. microflora), pH conditions, typical transition/residence times and the extent of stresses (mixing) involved, is crucial (Lesmes and McClements, 2009).

Release of encapsulated species from a hydrocolloid-based delivery system (e.g. hydrogel) at a certain site within the GI tract can be triggered by a response to specific conditions, such as those discussed earlier, associated with the target GI tract location (e.g. changes to pH).

Table 11.1 Characteristic of human gastrointestinal tract. Reproduced with permission from Lesmes and McClements (2009) Structure–function relationships to guide rational design and fabrication of particulate food delivery systems. *Trends in Food Science & Technology* 20(10), 448–457. Elsevier.

	Stomach	**Small intestine**	**Large intestine**
Enzymes and other components	Pepsin, trypsin, mucin, microflora ($0–10^3$ CPU/g)	Pancreatin, bile acids, mucin, microflora ($10^5–10^7$ CPU/g)	Metabolites, undigested food, GI tract secretions, microflora ($10^9–10^{12}$ CPU/g)
pH conditions	1.0–2.5	5.5–6.0	6.5–7.0
Transit time	1–5 h	4–6 h	24–72 h
Mixing intensity	+++	++	+

Release from a hydrogel delivery system responding to changes to the pH conditions of its environment would take place by diffusion across the gel network or even due to the network degradation. For instance, alginate, a water-soluble polysaccharide containing α-L-guluronic and β-L-mannuronic blocks (e.g. see Smidsrød and Skjåk Bræk, 1990), will create gel networks which, under highly acidic conditions (pH ~2 and lower), will tend to "shrink", creating highly insoluble structures (George and Abraham, 2006). Therefore it is expected that under the pH conditions typically encountered in the stomach during digestion (pH ~1.2) release from an alginate gel encapsulating matrix will be inhibited (George and Abraham, 2006). Subsequent transport of the stomach acidic chyme to the duodenum (small intestine), where neutralisation of the previously low pH conditions occurs, will result in the breakdown of the alginate encapsulant and the eventual release of its content(s) (George and Abraham, 2006).

Controlled release from a gel matrix can also take place due to swelling. Gelatin can be used as a microencapsulating material and its swelling properties, in an aqueous environment, can be controlled in order to modulate degradation and release of species encapsulated within its structure. The relatively high isoelectric point (IEP) of gelatin (type A gelatin IEP: pH 8–9 and type B IEP: pH 4–5) makes it an attractive encapsulating component in those cases where protection from the stomach's acidic environment is required. As such, gelatin can "exist" as a (positively) charged biopolymer over a wide range of aqueous pH, and it is able to create concentrated coacervates with negatively charged biopolymers, such as alginate, at specific pH values. During the process of formation of these coacervates in solution, dissolved components can be subsequently encapsulated within the created structures (Gómez-Guillén *et al*., 2011). Encapsulation of lycopene within (type A) gelatin hydrogels resulted in excellent control of its release characteristics. At pH 5.5 and 7.0, lycopene was released immediately, whereas at lower pH values (pH 2.0 and 3.5) no release was observed. These findings demonstrate that encapsulation within carefully selected and fabricated biopolymer structures can result in the targeted release of active inclusions (i.e. by successfully "bypassing" specific GI tract sites), but additionally, in those cases where the carried active load is susceptible to "damage" upon exposure to conditions found in specific GI tract sites, in its effective "protection" (Gómez-Guillén *et al*., 2011).

11.3 DRUG DELIVERY AND AVAILABILITY

The efficient delivery of therapeutic agents (drugs) to specific sites in the human body is an area of research that has been attracting signifi-

cant interest for a number of years. One type of such therapeutic agents that has recently been investigated more extensively is protein drugs, mainly due to their high activity and great selectivity. A number of studies have been carried out in order to increase circulatory half-life of these therapeutic proteins, restrain proteolysis, improve storage stability and immunogenicity as well as protein drugs' permeability and denaturation (Chen *et al*., 1995). Administration of drugs to the systemic circulation, and hence to the targeted tissues, reaches 100% only when these are directly injected into the human veins, with any other drug delivery method resulting in reduced drug fractions reaching the systemic circulation. The fraction of absorbed drug from the whole dosage is described in terms of its bioavailability. In return, bioavailability is greatly affected by the action of the digestive system, which inherently presents issues related to diffusion and enzymatic barriers that need to be overcome (Lehr, 1994).

Hydrogels, and specifically particulate (hydro)gels, have great potential in terms of overcoming these issues. Care should be taken in selecting the process used for the formulation of particulate gels. Preferably technologies that offer very mild processing conditions for the manufacture of gel particle systems, whilst encapsulation of protein drugs also takes place, should be selected (Reis *et al*., 2006). Once a suitable processing protocol has been established and satisfactory encapsulation efficiencies can be achieved, particulate gel systems can be excellent candidates for the protection of protein drugs from the stomach environment; hence from degradation promoted by the acidic environment and proteolysis (enzymatic protein breakdown) in the GI tract (Xing *et al*., 2003). Also, controlled release in the proximal colon can be achieved by the use of carefully designed drug delivery hydrogel systems that can protect the drug during its transfer to the colon (Jose *et al*., 2010). In addition, hydrogels with mucoadhesive properties can offer prolonged drug release in the intestine's mucosa, effectively resulting in a circulatory half-life boost, and hence increasing drug bioavailability (Lehr, 1994; George and Abraham, 2006).

The origin of the term of mucoadhesive stems from adhesive; i.e. substance(s) able to adhere and remain attached to a surface, which in his case is the mucosa of tissues; thus the substance(s) or even the structure it is used to formulate is called mucoadhesive. There are some biopolymers with known mucoadhesive properties (e.g. chitosan) and hydrogel delivery systems fabricated using these have the potential of prolonging the contact time of the active therapeutic ingredients (drug) with the mucosa of tissues (e.g. in the intestine) thus enhancing drug bioavailability as well as targeted absorption (Woodley, 2001; Andrews *et al*., 2009).

The ability of mucoadhesive biopolymers to attach to the organ mucosa from the luminal part is governed mainly by its very physiological properties. Mucus is synthesised by goblet cells and its very viscous consistency, although composed of 95% of water, and gel-like properties are mainly due to high-molecular-weight glycoproteins (mucins), with a small fraction of salts, proteins, mucopolysaccharides and lipids also present (Bansil and Turner, 2006). Glycoproteins are composed of single-chain polypeptide units with little and largely glycosylated central protein regions. Non-covalent bonds are responsible for the highly entangled network of glycoproteins which reveals an anionic character (pH ~7) caused by the presence of sialic acid and sulfates (Andrews *et al*., 2009). Calcium ions shield the negative interactions between mucins during "storage" (in submucosal, goblet cells), thus allowing them to occupy less space. However, during release to the lumen, transferred calcium "uncovers" the negatively charged glycoprotein parts, causing expansion of the entangled network through electrostatic repulsion (Willits and Saltzman, 2001). Such expansion can be therefore promoted by carefully altering the balance of charges in the mucus layer at specific sites in the human body, thus altering its barrier properties and subsequently the rate at which certain species (including those of therapeutic effect) migrate through the mucus layer (Willits and Saltzman, 2001).

Several theories have been suggested to describe the process of mucoadhesion, namely the wetting/spreading, adsorption, diffusion/interlocking, electrostatic and fracture theories (Andrews *et al*., 2009; Woolfson *et al*., 2011). The wetting theory, best applied to liquid or low-viscosity bio/muco-adhesive species, proposes that the larger miscibility of biopolymers in the mucus layer results in considerable spreading of the material over the tissue surface, and therefore in enhanced mucoadhesion. According to the adsorption theory, biopolymers adhere to the mucus layer as a result of surface forces which can be particularly strong (e.g. covalent, ionic bonding; chemisorption) and/or weaker secondary forces (e.g. van der Waals, hydrophobic and hydrogen bonding). The diffusion/interlocking theory proposes that mucoadhesion is a result of interpenetration of the biopolymer network within the glycoprotein chain network (Woolfson *et al*., 2011).

The oral drug delivery to gastrointestinal tissues using mucoadhesive biopolymers facilitates attachments to the epithelial surfaces, therefore enhancing transit time and bioavailability (Woolfson *et al*., 2011). The release of protein drugs is more favourable via diffusion through the pores of the gel network rather than gel matrix degradation, which might lead to the rapid release. In the case of alginates, the structure of the gel network can be controlled by, amongst others, the ratio of

mannuronic to guluronic acid domains on the biopolymer backbone, which in turn will also affect the rate of release of species encapsulated within the gel matrix (Dettmar *et al*., 2011). The structure of alginates can be further modified in order to impart additional properties to its hydrogel drug delivery systems. Mucoadhesive properties can be induced by thiolation (Bernkop-Schnürch *et al*., 2001), while alginate hydrogels providing prolonged drug release can be formulated by hydrophobisation of the alginate's molecular structure through binding of alkyl chains onto the polysaccharide backbone (Leonard *et al*., 2004).

The charge of the encapsulated (protein) drug can also strongly affect the rate of release; i.e. negatively charged proteins will be "repelled" from the also negatively charged alginates, whereas interactions with positively charged proteins will take place, thus leading to the inhibition of release (George and Abraham, 2006). Encapsulated species will release rapidly from the alginate matrix (e.g. alginate gel beads) in the absence of charge interactions, unless the size of the molecular structure of the encapsulated material (in this case that of a high-molecular-weight protein) exceeds that of the typical pore size within the gel matrix. For uncharged encapsulated species, delivery systems constructed from biopolymer complexes, such as pH-sensitive coacervates of polyelectrolytes, are more suitable, e.g. those between alginate and chitosan (Dettmar *et al*., 2011).

11.4 ENCAPSULATION OF LIVING CELLS

Living cells, microbial supplements, can be microencapsulated within a hydrocolloid matrix (such as gelatin, alginate, chitosan, carrageenan and locus bean gum) in order for them to be protected from exposure to conditions that can significantly compromise their viability. Bacterial viability can become very low during incorporation within the food formulation (due to stress effects during processing) and storage of the produced foods, but also during transit through the upper parts of the GI tract. Microencapsulation within a hydrocolloid matrix not only protects living cells from such "harmful conditions" but also can significantly enhance their growth (Krasaekoopt *et al*., 2003).

Intestinal microbial species are claimed to have anticarcenogenic and antimutagenic activity and overall to improve the human immune system (Krasaekoopt *et al*., 2003). Though many food products, such as fermented milk and yoghurts, have probiotic bacteria incorporated within their formulations, the transfer to specific sites in the GI tract of the cell quantities required for the manifestation of such health

claims has proven to be rather problematic (Doleyres and Lacroix, 2005). Bifidobacteria are a good example of cells that have low viability during food processing, storage at low temperatures and are sensitive to the low pH, enzymes and bile in the gastrointestinal environment (Marteau *et al*., 1997). For this reason a number of studies have been focusing on encapsulation strategies for the protection of such living cells and thus the extension of their viability (Chávarri *et al*., 2010).

Biopolymers (e.g. alginate, gelatin, gums) are promising material for bacteria microencapsulation. The use of alginate offers microencapsulation under mild conditions (minimal processing stresses) but is limited due to its low stability to low pH (acidic) conditions and to chelants (phosphate, lactate and citrate). The latter agents have a high affinity to calcium, which tends to destabilise the cation crosslinked alginate gels (Smidsrød and Skjåk Bræk, 1990). Increased stability can be restored by coating of the alginate matrix with other polymers (proteins and polysaccharides), such as chitosan (Overgaard *et al*., 1991; Krasaekoopt *et al*., 2003, 2004; Chávarri *et al*., 2010). Once the negatively charged alginate gels are coated with a positive polyamine (e.g. chitosan) the overall gel stability is increased and, due to the formation of a physical barrier, cell release is reduced (Smidsrød and Skjåk Bræk, 1990). Incorporating a starch (liquid) core within the gel matrix can be further used to enhance the survival of the bacteria (Krasaekoopt *et al*., 2003).

11.5 BIOPOLYMERS AS PREBIOTIC MATERIAL

Microbial metabolism, probiotics, within the human body involves biochemical activity with, at least in theory, significant health benefits (Reid *et al*., 2003). Prebiotics, however, the non-digestible substances, favour the growth and activity of native bacteria. Probiotics and prebiotics have been suggested to be beneficial for the treatment of several conditions associated with the human diet; inflammatory conditions of the colon and small intestine, such as Crohn's disease, allergies, gut disorders, infections of the vaginal and urinary tract and even colorectal cancer (Reid *et al*., 2003).

The soluble dietary fibre (indigested plant cells) affects the mass of the bacteria as well as the activity of enzymes. The presence and population of bacterial flora within the colon depends on the nutrition available for consumption. Though the type of the bacteria in the colon remains the same, the consumption of dietary fibre increases significantly their population. The prebiotic properties of dietary fibre is related to the susceptibility for bacterial fermentation (Eastwood, 1992).

Microbes present in the colon are responsible for the fermentation of dietary fibre, which conveys the largest amounts of energy for the bacteria. It is expected that 10^{13}–10^{14} bacteria are present within the colon of a typically healthy person. Though the dietary fibre obtained from different sources is fermented up to different points, the anaerobic bacterial degradation of ingested substances leads to the production of short chain fatty acids (SCFAs) as the major products, as well as H_2, CO and biomass. SCFAs affect colonic function and mucosa but can also affect the post-abortive tissues. The main function of the large intestine is the production of energy from the absorption of SCFA through fermentation of carbohydrates, undigested in the upper parts of the GI tract (Guillon and Champ, 2000).

At this stage it is worth considering the typical pathway for prebiotic delivery to the large intestine, which can be described based on the digestion of starch. Digestion of starch begins in the mouth by the action of amylase present in the saliva. A bolus is formed in the mouth and subsequently, by oesophageal peristalsis, is moved to the stomach where the low pH (~2.6) conditions inhibit amylase action and improve hydrolysis (HCl). Next, peristaltic actions cause gastric fluids to progress to the first section of the small intestine, the duodenum. There, pancreatic secretion reduces acidity (~pH 8) and starch is further hydrolysed by amylase action to glucose and oligosaccharides. The latter are further digested in the small intestine. Insufficient amounts of enzymes in the small intestine and the presence of the indigestible parts of the polysaccharides, such as resistant starches and/or dietary fibre, result in the substrate(s) for the colon microbial flora (Wong *et al*., 2006; Dona *et al*., 2010).

11.6 APPETITE CONTROL: SATIETY

Consumption of hydrocolloids has been increasingly associated with the promotion of satiety. The presence of undigested macronutrients in the ileum (the third and final section of the small intestine) has been shown to contribute significantly to the sensation of fullness. Several physiological functions have been suggested to encourage satiation, and hydrocolloids can potentially intervene to enhance and/or trigger these. Intestinal motility and ingested food transit time through the GI tract significantly affect the desire for further food uptake. The intestinal rate of absorption of digested food, as well as bioaccessibility (digestion/absorption) of nutrients can also play a major role in satiety. These are discussed in more detail in the following sections of this chapter.

11.6.1 Reduced gastrointestinal motility and transit time

The rheological properties of hydrocolloids within the GI tract are the main factors that determine motility and transit time. The swelling and gel-forming properties of hydrocolloids cause an increase in the mass:volume ratio of gastrointestinal fluids (Brownlee, 2011). Gastric emptying and nutrient absorption are strongly delayed when soluble dietary fibre is present. The source of this fibre and its properties, especially viscosity, affect absorption rates in different ways (Eastwood, 1992). High viscosity and/or gel-forming abilities under GI conditions are responsible for the lowering of the rate of nutrient absorption. Soluble dietary fibre has the ability to increase the chyme viscosity in the stomach. The effect is more pronounced when high-molecular-weight dietary fibre is ingested as compared to lower-molecular-weight fibre (Brownlee, 2011). Therefore slower gastric emptying is a direct consequence of dietary fibre consumption (Schneeman, 1998).

It is also known that hydrocolloids can reduce the amount of food consumed due to their gel- forming capacity (Dettmar *et al*., 2011; Norton *et al*., 2011). Alginate is one such hydrocolloid that has been reported to have the potential to moderate appetite (Norton *et al*., 2011). This is ascribed to the hydrocolloid's tendency to form so-called acid gels; i.e. gelation induced under acidic conditions (pH < 3.5) relating to those found in the stomach (Draget *et al*., 1994). The ability of alginate to gel under stomach-like acidic conditions is already "exploited" for the treatment of gastro-oesophageal reflux diseases (Dettmar *et al*., 2011). Since the pH conditions in the stomach strongly depend on its fed or fasting state, acid gelation in the stomach can become problematic. In those cases where pH values in the stomach are not significantly low enough for acid gelation to take place, gelation through ionic crosslinking (e.g. using calcium) can be induced instead (Dettmar *et al*., 2011). Although this means that gel formation in the stomach can be carried out at higher pH values, this approach is faced with a number of significant challenges, namely the means by which the crosslinking ion is introduced in the stomach. If the ions are within the same (food) formulation carrying the gelling hydrocolloid, then stability issues (gelation prior to consumption) during storage will be almost unavoidable.

11.6.2 Reduction of intestinal absorption rates

One of the major purposes of the GI tract, and in particular of the first part of the small intestine (duodenum), is the absorption of digested micronutrients (such as peptides, amino acids, fatty acids etc.) vitamins, minerals etc. (Brownlee, 2011). Dietary fibre can affect metabolism and

can modulate digestion and absorption, and hence in many ways the "destination" of the food components within the GI tract of the human body. The presence of dietary fibre is especially important in the metabolic processes for lipids and carbohydrates (Schneeman, 1998).

The previously discussed effect of viscous and gelling hydrocolloids on the delay of gastric emptying has a direct impact on the rate of intestinal absorption. Lower intestine uptake caused by the high(er) viscosity and/or (partially) gelled nature of chyme reduces the postprandial absorption of digested nutrients. However, changes to the rheological properties of chyme are only part of the reason for the observed lower absorption rates. It has been proposed that hydrocolloids/dietary fibre is able to change gastrointestinal enzymatic activity (Englyst *et al*., 1992). Reported evidence suggests that alginate, besides a resulting increase in the viscosity of chyme entering the duodenum, also results in the inhibition of enzymatic activity (Brownlee, 2011).

11.6.3 REDUCED LIPID BIO-ACCESSIBILITY (DIGESTIBILITY)

Consumption of fats of low calorific value still remains one of the most effective approaches that can be taken to minimise the impact of obesity and its related health issues. Through the inhibition of the digestion of lipids, satiety and the onset of hunger can be modulated with excellent health benefits. It has been shown that dietary fibre can indeed reduce the adsorption of lipids/fats (Dutta and Hlasko, 1985).

Lipid digestion is controlled by the action of mechanical and chemical processes; the former relates to characteristics of the food being digested (e.g. viscosity) in the GI tract, whereas the latter process includes all the catabolic reactions that break down triglycerides (lipids) into 2-monoglycerides and fatty acids by the action of enzymes. Within the GI tract the digestion of lipids first occurs in the stomach by the action of (acid-resistant) lipases and subsequently in the duodenum by the action of pancreatic lipases (Brownlee, 2011). The presence of undigested lipids in the ileum contributes significantly to the feeling of satiety.

Lipids are digested following hydrolysis (lipases) of triacylglycerols (triglycerides) to monoglycerols and fatty acids. The presence of the latter activates the ileal brake mechanism; defined as "a distal to proximal feedback mechanism to control transit of a meal through the gastrointestinal tract in order to optimise nutrient digestion and absorption" (Maljaars *et al*., 2008). As a consequence of this feedback mechanism, detection of fatty acids by the receptors present in the intestinal mucosa results in a reduction in the GI tract motility in order for greater digestion to occur, which subsequently promotes the feeling of satiety and

causes the lowering of food intake (Maljaars *et al*., 2008). The delay of lipolysis (breakdown of lipids) results in an increase in the concentration of undigested lipids reaching the ileum, and thus in the activation of the ileal brake feedback response. Undigested nutrients (including lipids) reach the ileum typically only in small proportions, hence the design and formulation of delivery systems that are able to delay the digestive and absorptive processes could have a significant effect in terms of satiety.

A very important step in the digestion of lipids is the process of emulsifying (oil-in-water emulsion) these in order for the oil "surface area" available for enzymatic action (hydrolysis) to be increased. The emulsification process of lipids is greatly facilitated by mastication and peristaltic movements in the GI tract, and once small lipid droplets are created, their coalescence is prevented by, amongst others, adsorption of proteins at the lipid–water interface (Dona *et al*., 2010). Bile acids also play a crucial role in this emulsification step, since their amphiphilic nature allows for the breakdown of lipid phases (large droplets) into (smaller) droplets. Bile acids are produced by the liver and are synthesised from cholesterol, while they are excreted in the duodenum and reabsorbed in the ileum, remaining within the enterohepatic circulation (Kahlon *et al*., 2005).

Certain dietary fibre is able to bind with lipases and/or bile acids, thus effectively reducing their concentration during digestion in the intestine. Certain hydrocolloids have also been found to significantly reduce lipase activity, mainly as a result of interactions with lipases/bile acids (McClements and Li, 2010). Consequently the emulsification process of lipids is less effective, leading to the formation of lipid droplets of larger sizes and the lower interfacial area available for enzymatic activity causes a reduction in lipid digestion (Guillon and Champ, 2000; Kahlon *et al*., 2005; Harris and Smith, 2006; Brownlee, 2011). The binding interactions involved are affected by charge, physico-chemical structure and composition, metabolites or interaction with active binding sites.

Hydrocolloids can affect the absorption of lipids when used as encapsulating structures; e.g. hydrocolloid hydrogel beads can be used to alter the delivery of lipids to the main site for their digestion and absorption in the small intestine (Hoad *et al*., 2009). Hydrogels represent one class of delivery system which could offer the potential of delaying the digestion of lipids, thus inducing the ileal brake. The mechanism of the decrease in digestion is mostly caused by the presence of a physical barrier created by the hydrogel structure around the lipids. As a consequence, diffusion of lipases to the lipid surface can be significantly decreased, thus allowing the transportation of undigested lipid droplets to the distal parts of the intestine (McClements

and Li, 2010). In addition, the encapsulating gel matrix can potentially "disturb" the action of bile acids in terms of their role in the emulsification process of lipids.

In fact even coating of the lipid droplets by one or more "layers" of biopolymers/hydrocolloids, in the absence of a gelled network, can create an effective physical barrier against the action of lipases and/or bile acids (McClements and Li, 2010). Such coatings formed by biopolymer layer(s) can be designed to respond to "external stimuli" such as changes to pH conditions, ionic strength or the presence of enzymes, and as such can offer the possibility of transferring lipid droplets to the distal parts of the small intestine. For example a layer stable at low pH conditions can be used for the "safe" transferal of encapsulated lipid material through the stomach and to the first section of the small intestine (duodenum), where the low pH chyme is neutralised. Once in the duodenum, bioavailability of the encapsulated lipids can be also controlled by several mechanisms. Biopolymers forming the protective layer(s) can be displaced by the competitive adsorption of surface-active components such as bile acids or can undergo enzymatic degradation; i.e. due to the action of amylases for polysaccharides and of proteases for proteins (McClements and Li, 2010). In addition, where several layers are created (through electrostatic interactions) to enclose the lipid phases, these can be weakened by changes to ionic strength and/or pH variations. For example, coverage of lipids with protein–carbohydrate (β-lactoglobulin–dextran) conjugates was found to change the responsiveness of lipid emulsion droplets to *in vitro*-simulated gastrointestinal conditions, such as pH, the presence of pepsin and bile acids, and overall showed great potential in terms of delaying the digestion of lipids (Lesmes and McClements, 2012). In another study (Mun *et al*., 2006), the layer-by-layer approach was taken to cover lipid droplets and a clear link between interfacial composition and lipid digestibility was shown. Lecithin, lecithin–chitosan and lecithin–chitosan–pectin layers, formed as a result of electrostatic interactions, were used to "encapsulate" lipid droplets, and the activity of lipases was significantly reduced when droplets were covered by lecithin-chitosan layers. This was ascribed to the creation of a thick cationic interfacial layer around the lipid droplets, which promoted droplet flocculation, and thus lipase activity, due to the reduction in the effective interfacial area "available" to the enzymes (Mun *et al*., 2006).

In vivo experiments where lipid droplets were encapsulated within alginate beads (core–shell particles) showed that digestibility of lipids was delayed within the GI tract (Hoad *et al*., 2011). It was also observed that secretion of bile acids was less in the case of encapsulated, rather than free (not encapsulated), lipid droplets, probably due to the lower concentrations of free fatty acids associated with the former systems,

and thus to a "reduced response" from the duodenal receptors; in terms of triggering the secretion of bile acids (Hoad *et al*., 2011).

11.7 OTHER HEALTH BENEFITS

The consumption of hydrocolloids, specifically in the form of soluble and insoluble dietary fibre, has been associated with a number of health benefits to (parts of) the GI tract itself, as well as to the human body as a whole. Dietary fibre, i.e. indigestible material, are the substrates for colonic microflora and their consumption can ultimately enhance "colon health" in many ways, which directly depend on the chemical composition and the physico-chemical properties of dietary fibre itself (Lebet *et al*., 1998; Brownlee, 2011). Apart from perhaps these well-known benefits, hydrocolloids have started to emerge as food components with potentially some more unique advantages to our health, even as far as preventing colonic diseases including colorectal cancer, the second most commonly occurring cancer in the world (Parkin, 2001). Some of these health benefits are discussed here, in the final section of this chapter.

11.7.1 Enhancement of the protective capacity of mucus and mucus healing

The intestinal mucus acts as a protective layer to the internal walls of the GI tract, reducing the shear stresses that the mucosa is subjected to, as well as offering the required lubrication for the transferal of luminal material. In addition, mucus forms a selectively permeable barrier between the GI tract walls and the lumen environment, which can potentially carry components harmful to the human body (Brownlee *et al*., 2005; Brownlee, 2011; Dettmar *et al*., 2011). Intestinal diseases are usually developed as a result of infections to parts of the intestinal walls where the mucus layer is diminishing. Therefore an increase of the thickness of the (intestinal) mucus layer could lead to an enhancement of its capacity to protect the intestine and consequently the whole of the human body.

Dietary fibre has been also found to enhance the protective potential of intestinal mucus. Measuring the mucus barrier directly in humans would involve extremely invasive procedures and as a result only indirect measures currently exist, as well as data from studies using animal models. In a study of the latter type (Enss *et al*., 1994) it was reported that the presence of dietary fibre results in an increased challenge in terms of processing for the GI tract, which was then associated with an increase in the number of mucus-producing goblet cells. Another study

(Brownlee *et al*., 2003) using an *in vivo* animal model demonstrated that a very low fibre intake (fibre deficiency) is associated with a decrease in the protective potential of the mucus layer (the mucus layer thickness of the fibre-deficient group was much lower than a respective control) and also that the dynamics of colon mucus secretion are dependent on specific fibre types (e.g. the group given cellulose as the dietary fibre source showed a reduction in the overall mucus secretion compared to that of the control). The study concluded that a diet comprising of both soluble and insoluble types of fibre is optimal for mucosal protection (Brownlee *et al*., 2003).

Certain alginates have also been found to promote and/or have the ability to induce healing of mucus (Brownlee *et al*., 2005; Dettmar *et al*., 2011). It has been suggested that, due to their hydrophilicity, alginate gels are able to adhere to damaged sites of the mucus layer and provide excellent hydration. Formation of a gel over the wound, in the case of calcium alginate, facilitates the exchange of calcium ions from the gel matrix with sodium from the plasma, which has been suggested to promote clotting, thus assisting haemostasis (Matthew *et al*., 1994). In an animal study on oral mucosa, alginate was indeed found to significantly promote/increase haemostasis although no evidence of a similar effect in terms of wound healing was observed (Matthew *et al*., 1994).

11.7.2 Lowering of glycaemic index

The rate of release of (digestible) nutrients from dietary fibre in the intestine significantly differs from that of simple monosaccharides (Eastwood, 1992). The absorption of simple monosaccharides is very fast within the duodenum (as compared to that of the more complex polysaccharides) and a high intake of these species leads to a drastic rise in the level of glucose in blood (glycaemic index), which subsequently results to an increased post-prandial perception of hunger. Dietary fibre is known to decrease the post-prandial glucose levels in blood via two main mechanisms (Eastwood, 1992). Firstly by reducing intestinal uptake due to the (hydrocolloid-induced) increase in the viscosity (or even gelation) of the transferred material, but also due to the ability of some hydrocolloids (e.g. alginate) to inhibit the activity of certain enzymes in the stomach and duodenum, thus resulting in slower digestion/absorption (Englyst *et al*., 1992).

11.7.3 Impact on cardiovascular diseases and cholesterol levels

Cardiovascular diseases are the leading cause of death and disability worldwide. Food intake associated with increased levels of “bad

cholesterol" (low-density lipoprotein (LDL) cholesterol) promotes a series of health issues and is a main contributor to the development of cardiovascular diseases; cholesterol and saturated fatty acids are considered atherogenic fats (Stehbens, 1990). Consumption of dietary fibre reduces the risk of hypercholesterolemia (which induces fat and cholesterol accumulation on the walls of blood vessels) and post-prandial triglyceridaemia. These health benefits are ascribed to the ability of dietary fibre to lower cholesterol levels, through binding of bile acids and increasing their fecal excretion. By binding bile acids, fibre prevents their reabsorption and stimulates plasma and liver to convert cholesterol to additional bile acids (Zhang *et al*., 2011), thus reducing cholesterol levels (Eastwood, 1992).

Indirect effects of dietary fibre on the reduction of cholesterol levels have also been reported; e.g. via the production of SCAFs following anaerobic fermentation of fibre by the colonic microflora (Wong *et al*., 2006; Dona *et al*., 2010). *In vitro* tests have shown that the presence of propionic acid, a product of the fermentation process of dietary fibre, inhibits the production of cholesterol (Eastwood, 1992).

11.7.4 Protection against toxic and mutagenic species

Dietary fibre have been shown to offer protection against species harmful to the body (e.g. heavy metals, toxic species, mutagens, etc.) present in the intestinal lumen (Zhang *et al*., 2011). Possible mechanisms for this type of protective capacity induced by fibre can be both direct and indirect. Fibre aids the elimination or reduction of the impact of certain species by directly binding to them (Harris and Ferguson, 1993; Zhang *et al*., 2011). As such, binding of these components to fibre results in a reduction in the level of interaction they have with the colonic mucosal cells and help the body remove them from the alimentary tract and in the faeces. In addition to decreasing the magnitude of interactions between harmful species and mucosal cells, fibre also decreases the overall time period over which these interactions can occur by inducing a reduction in the transit time through the gut via an increase in faecal bulk (Harris and Ferguson, 1993). Possible indirect mechanisms include the lowering of the colon pH as a result of SCAF production by bacterial fermentation, and the specific effects of butyrate (Harris and Ferguson, 1993; Ferguson *et al*., 2005; Harris and Smith, 2006).

There is growing evidence to suggest that dietary fibre may provide a platform for both preventing and treating colonic disease, including colorectal cancer (Harris and Ferguson, 1993). The mechanisms by which they do so are similar to those (direct or indirect) outlined above;

e.g. carcinogens are bound to undegradable dietary fibre (soluble or insoluble) and the possibility of effectively interacting with the colonic mucosal cells is reduced. For example, there is a plethora of epidemiological, animal and cellular evidence supporting the argument that iron excess drives both inflammatory bowel disease and colorectal cancer (Radulescu *et al*., 2012). In particular it is suggested that it is an excess of unabsorbed colonic luminal iron which represents the major carcinogen. Exactly how this excess luminal iron is exacerbating colonic disease is somewhat unclear but one of the main hypotheses is that it induces free radical generation. Certain hydrocolloids (e.g. alginate) have been found to bind iron and thus have the capacity to suppress its (free luminal iron) activity and/or levels, and as such could potentially become excellent candidates for the prevention and even treatment of colorectal cancer (Radulescu *et al*., 2012).

11.8 FUTURE TRENDS

There is significant evidence suggesting that hydrocolloids are indeed prime candidates for the "engineering" of novel functional foods, which could potentially impart significant health benefits through their action at specific parts of the GI tract. It is clear that further data are required to substantiate the existing evidence and, in light of the growing interest in this area of research, both at an academic and at an industrial level, there is confidence that such studies will be taking place in the future. In the opinion of the authors, the future direction of activities in this area should be also focusing, without being limited to, the following themes of research:

- Advances in the existing understanding of the "engineering" aspects of the GI tract as an additional process that food formulations are subjected to.
- Definitively establish health benefits (or risks) arising from the uses of hydrocolloids in real food systems where they exist in the presence of a range of other food components.
- "Link" together existing studies that currently demonstrate evidence of hydrocolloid functionality exhibited at different parts of the GI tract in isolation.
- Design/development of non-invasive techniques to monitor, ideally both qualitatively and quantitatively, the activity of hydrocolloid-based formulations *in vivo* in humans.
- Utilise the encouraging evidence that exists on the uses of hydrocolloid-based formulations as delivery systems for functionality in the GI tract and extend these for applications in cell therapy.

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