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REVIEW

Structured soft particulate matters for delivery of bioactive compounds in foods and functioning in the colon

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The present review discusses challenges, perspectives, and current needs of delivering bioactive compounds (BCs) using soft particulate matters (SPMs) for gut health. SPMs can entrap BCs for incorporation in foods, preserve their bioactivities during processing, storage, and gastrointestinal digestion, and deliver BCs to functioning sites in the colon. To enable these functions, physical, chemical, and biological properties of BCs are integrated in designing various types of SPMs to overcome environmental factors reducing the bioavailability and bioactivity of BCs. The design principles are applied using food grade molecules with the desired properties to produce SPMs by additional considering the cost, sustainability, and scalability of manufacturing processes. Lastly, to make delivery systems practical, impacts of SPMs on food quality are to be evaluated case by case, and health benefits of functional foods incorporated with delivery systems are to be confirmed and must outweigh the cost of preparing SPMs.

1. Introduction

It has become evident that our diet is significant to the prevention and treatment of diseases occurring in the colon, including inflammatory bowel diseases (IBDs) and colorectal cancer (CRC).[1, 2] In addition to nutraceuticals that have bioactivities such as antioxidant, anti-inflammation, and anti-cancer,[3] focuses have been on the significance of the gut microbiota (GM) in health and diseases.[4] Microbiota, "bacteria, archaea, viruses, and some unicellular eukaryotes living in a specific environment (community),"[5] and microbiome, "the entire collection of all the genomic elements of a specific microbiota,"[5] sometimes are used interchangeably.[6] GM can be manipulated by supplementing live beneficial microorganisms, i.e., probiotics, compounds facilitating the growth and activity of probiotics, i.e., prebiotics, or "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host," i.e., synbiotics.[7-9] Dietary fibres are not digestible in the gastrointestinal (GI) tract and not directly bioactive.[3] However, dietary fibres, especially soluble ones, can be fermented by GM in the colon, and the metabolites contribute to gut health. Some dietary fibres are also potential prebiotics.[3] Most food products have low contents and low bioavailability of nutraceuticals, soluble dietary fibres, and probiotics,[3] which are referred to as bioactive compounds (BCs) hereafter for simplicity unless specifically described. Incorporating BCs in foods, i.e., functional foods, has drawn much interest in both scientific communities and relevant industries. With advances in delivery systems initially intended to improve the efficacy of drugs, soft matter physics, and materials science and engineering, a research area has emerged to study soft particulate matters (SPMs) with the potential of delivering these BCs in food systems.

When designing delivery systems to incorporate BCs, lipophilic (LBCs) or hydrophilic (HBCs), evenly in food systems, the polarity and dimension of BCs are the first physical parameters that are to be considered for enclosure in SPMs. SPMs enclosing BCs also shall have mechanisms protecting BCs from deactivation by various physical, chemical, and biological factors during food processing and storage, as well as after ingestion. These techno-functional goals have provided opportunities to study various delivery systems for a wide variety of BCs. While many delivery systems have shown promise, constraints also exist regarding their cost, sustainability, scalability, and impacts on food quality. Additionally, the fate of delivery systems after incorporation in a food product and after ingestion is to be characterized, and the subsequent impact on human health is largely unknown or inconclusive.

In the present review, a brief overview of colon diseases and the significance of BCs on these diseases is first given, with much emphasis on GM. The article is then focused on the functions expected from delivery systems used to incorporate BCs in food systems to improve gut health, types of molecules suitable for forming the structure of these delivery systems, and types of SPMs suitable for delivering BCs in foods and functioning in the colon. The intent of the present review is not to summarize all existing studies but rather to provide principles that can be used to design these delivery systems, further illustrated with some example studies. Lastly, impacts of delivery systems on food quality are briefly discussed, and future research needs are proposed.

2. Diseases related to the colon

2.1. Inflammatory bowel diseases

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IBDs have emerged as a global public health challenge.[10] The IBDs typically include subtypes of Crohn's disease and ulcerative colitis.[11, 12] Crohn's disease can be found in the entire GI tract,[13] while ulcerative colitis is limited to the colon.[11, 14] The pathogenesis of IBDs is still under study. However, associations among the immune system, intestinal microbiota, and environment in genetically susceptible hosts are the most prevailing factors.[12] GM is significant to IBDs because GM impacts the immune system and affects host metabolism and GI development.[15] Environmental risk factors include breast-feeding and antibiotic use in early ages, as well as hygiene hypothesis, exposure to gastroenteritis, cigarette smoking, and diet in later ages.[16] Food intake is an important factor that affects the development of IBDs. Studies have provided evidence that intake of fruits and vegetables has been associated with decreased risk of Crohn's disease, while intake of fast foods rich in fat and sugar may exacerbate the development of Crohn's disease.[17] Dietary changes can alter the balance between GM and the host, termed "dysbiosis."[16, 18] In patients with IBDs, the predominant dysbiosis has been characterized by the decreased numbers of *Bifidobacterium* spp. and *Lactobacillus* spp.[19] and the increased numbers of *Escherichia*, *Bacteroidetes*, and *Enterococci* when compared to healthy individuals.[9, 18] Probiotics, prebiotics, and synbiotics are therefore studied to enhance human health.[7-9]

2.2. Colorectal cancer

CRC ranks the third in the prevalence of most common cancers,[20] and the probability of suffering this cancer is about 4%–5%.[21] Age, environmental and dietary habits, chronic diseases, and hereditary conditions are among the factors that have been linked to an increased risk of CRC.[22, 23] CRC is a slowly developing cancer, and a tumour or tissue growth, i.e., polyps, on the inner lining of the rectum or colon is observed at the beginning.[24] Benign polyps result from the localized growth of abnormal cells or their aggregate within the intestinal mucosa, leading to protrusion into the intestinal lumen.[22] If polyps become cancerous, tumours are observed on the rectum or colon wall, and these tumours can further grow into blood vessels or lymph vessels, leading to the increased chance of metastasis in other anatomical sites.[24]

There are several mechanisms that GM can influence the colorectal carcinogenesis. Driver bacteria are those that are directly pro-carcinogenic, while opportunistic microorganisms (passenger bacteria) are those that can proliferate in the tumour-associated microenvironment.[25] Therefore, host–microbiota interactions are forerunners in studying the pathogenesis of CRC.[26] Additionally, many dietary components such as flavones directly contribute to the programmed cell death (apoptosis) to impact colorectal carcinogenesis.[27] Supplementing effective probiotics and dietary components is therefore frequently studied for CRC therapy and prevention.[28, 29]

2.3. Other diseases associated with gut microbiota

Dysbiosis of GM has been consistently associated with a leaky gut,[30] which contributes to multiple diseases including obesity, diabetes, hypertension, heart attack, liver diseases, cancer, brain disorders, and cardiovascular disease (CVDs)[31]. GM and its metabolites, especially short-chain fatty acids (SCFAs) such as acetic, propionic, butyric, and secondary bile acids have cholesterol-lowering effects and therefore decrease the risk of CVDs.[32] Hypertension is one of the risk factors causing CVDs, and the intestinal microflora have been observed to facilitate vascular dysfunction induced by angiotensin-II that leads to the increased blood pressure.[33] Type 2 diabetes mellitus has been linked to the decreased population of butyrate-producing microbial species and the increased population of *Lactobacillus* species.[34] The association of the intestinal microbiota with obesity and insulin resistance has also been observed.[34] Additionally, intestinal metagenomic changes and inflammatory response have been observed for individuals with artery thickening or hardening (atherosclerosis), and the impairment in the integrity of intestinal barriers caused by dysbiosis of GM can also cause atherosclerosis.[35]

3. Significance of dietary bioactive compounds and probiotics to gut health

BCs in the diet significant to gut health are summarized in Table 1, and their availability is highly dependent on the composition and structure of the food. Several important aspects of BCs in the diet digesta entering the colon on gut health are illustrated in Fig. 1. Some BCs are absorbed from the digesta via both transcellular (active, with assistance of a receiver or receptor, or passive transport) and paracellular routes. Some dietary components are metabolized by the GM or decomposed by GI enzymes in the lumen, with some metabolites being absorbed, and those not entering the colon mucus layers are excreted. For the supplemented probiotics, it is important for them to colonize and proliferate in the colon mucus layer to become a part of GM to enable their functions in Table 1, and prebiotics are selectively fermented by probiotics. GM also can utilize non-prebiotic dietary fibres, proteins, polyphenols, and other substances to produce metabolites.[36] Among the metabolites that are absorbed or function in the mucus layers, SCFAs are an energy source to the colonocytes, regulate the expression of MUC2 (major intestinal gel-forming mucin) for the intestinal barrier function, and activate G-protein-coupled receptor signalling to modulate immune function.[37] The metabolites of proteins and peptides such as amines, phenols, and sulphides impact the host by mechanisms including modulation of metabolism, immunity, and social behavior.[38, 39] Metabolization of plant secondary metabolites by GM, e.g., polyphenols to more water-soluble phenolic acids, can improve the absorption and their biological activities.[40] Metabolites and BCs absorbed into the circulation impact various metabolic pathways and immune homeostasis important to bioactivities such as antioxidant, anti-inflammation, and anti-cancer.[41] Some metabolites are also active against pathogens and important to gut health. In addition, GM stimulates the production of immunoglobulin A (IgA) by plasma cells, and defensins are produced by Paneth cells.[41] The secretions of IgA and defensins in the mucus layers are important to gut health. Although the potential of many BCs in disease therapy and prevention is well established *in vitro* and *in vivo*, the low content, low solubility, and low bioavailability of BCs in foods limit the effectiveness for diet-based disease prevention. To overcome these limitations, strategies of incorporating BCs in the diet are needed to harness their biological activities.[29]

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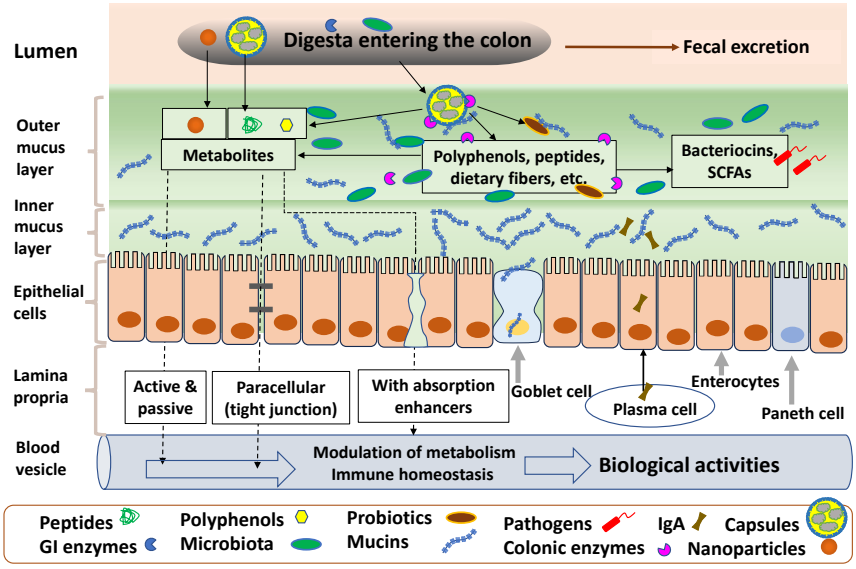

Fig. 1. Schematic illustration of the colon structure, factors significant to gut health,[41] the fate of diet digesta entering the colon,[41-45] and the functions of delivery systems in the colon.

Table 1. Dietary components significant to gut health and their potential challenges aiming for disease prevention.

Components	Chemical nature	Mechanism	Potential challenges
Plant secondary metabolites[46-48]	Phenolic compounds, terpenes, alkaloids, and nitrogen-containing compounds[49]	Antioxidant and anti-inflammatory properties; substrates for health-benefiting metabolites produced by the gut microbiota (GM) and other metabolic pathways after absorption	Low quantity in the diet, low water solubility, low bioavailability, chemical instability, possible degradation and fermentation in the GI, fast elimination after absorption, possible changes in colour, taste, and aroma of foods when supplemented as additives
Probiotics[36]	Commonly, *Lactobacillus*, *Bifidobacterium,* and *Saccharomyces*	Modulation of immune functions, production of small molecular metabolites such as organic acids and bacteriocins, interaction with other gut microorganisms, production of enzymes such as β-galactosidase and bile salt hydrolase, interaction with host tissues, improvement in the barrier function of intestinal epithelial cells	Sufficient quantity needed in food and colonization in the gut, possible viability losses during food processing and storage, and post-ingestion
Prebiotics[36]	Nondigestible soluble oligosaccharides, polysaccharides, lignin, and polyphenols	Impacting satiety, substrates for producing metabolites to inactivate pathogens, modulation of immune functions, facilitating mineral absorption, improving bowel movement	Low quantity in natural foods, low availability due to structural and digestion complexity, high viscosity when supplementing polysaccharides
Peptides and proteins[50]	Oligomers and polymers of amino acid residues	Antimicrobial, anti-inflammatory, antioxidant, antihypertension, lipid-lowering, cholesterol-binding, anticancer, immune modulation, functioning as prebiotics	Digested before reaching the colon; possible bitterness and astringency

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4. SPMs for delivery of BCs in food products and targeted delivery in the colon

4.1. Functionalities of delivery systems to be achieved

4.1.1. Suitability for delivery in foods. When studying colon delivery systems for use in food products, the first consideration is the regulatory status of carrier materials and BCs. Generally recognized as safe (GRAS) ingredients are the first choice, while those considered food grade but not GRAS, e.g., polysorbates (Tween family surfactants), can be adopted based on their intended use, e.g., as emulsifiers, and the permitted level. Although the structure of GRAS or food grade ingredients is frequently modified to improve functional properties, regulatory approvals are needed for the modified ingredients, which require extensive toxicity data to ensure safety. In addition, the ingredients shall be cost-effective, and their supplies shall be sustainable and available in large quantities. Lastly, processes used to manufacture delivery systems shall be scalable to meet the food production capacity and be cost-effective.

From the food quality perspective, SPMs used to deliver BCs shall not impact, but ideally enhance, the texture, smell, and taste of food products. While this is a broad and sophisticated challenge due to variations in food composition, structure, processing, and storage conditions, some SPM parameters relevant to sensory properties and potential strategies overcoming possible sensory defects are listed in Table 2. In addition to physical parameters, BCs with biological activities, e.g., enzymes and probiotics, in food matrices can alter sensory properties. For example, some probiotic strains can produce exopolysaccharides that can impact the texture of yogurt, and some can generate synergistic activities to enhance texture characteristics such as hardness, viscosity, and gumminess of yogurt.[51]

4.1.2. Protection before reaching the colon. BCs are sensitive to adverse environmental conditions during food processing and storage, as well as post-ingestion (Table 3). Ideal delivery systems can survive these conditions to maintain their structures after reaching the colon and protect the entrapped BCs from degradation or deactivation by these environmental conditions.

4.1.3. Functions in the colon. As illustrated in Fig. 1, the structure of colon relevant to the entry, retention, absorption, and metabolism of BCs in the diet is complicated. The less dense outer mucus layer provides habitats for bacteria that are planktonic and digest glycans, while the dense inner mucus layer is bacteria-free and covers all epithelial cell surfaces to provide a barrier for toxins and pathogens.[41] Gel-forming mucins secreted from goblet cells, mainly MUC2, form *O*-glycosylated protein dimers that are further polymerized to form multimers via intermolecular disulfide bonds, and the multimers form the dense mucus skeleton via attractive hydrogen bonding and van der Waals, electrostatic, and hydrophobic interactions.[41, 43] The formation of the inner mucus layer is stimulated by some bacteria, and the mucus layers also lubricate the epithelium and reduce the mechanical stress on the epithelium.[41] As reviewed previously,[43] mucins are continuously secreted and have a turnover time of 3-4 days in the colon mucus, which makes the colon structures more complicated and the delivery of BCs more challenging.

To reach the epithelium, molecules and small enough particles in the digesta or released from capsules in the lumen have to diffuse through the mucus layers by overcoming viscosity, structural barriers, and attractive forces posed by mucins (Fig. 1). The bioaccessibility (percentage reaching the epithelium and available for absorption) is dependent on the dimension, morphology, and surface charge and polarity of molecules and particles.[43, 52] The roles of SPMs in colon delivery are listed in Table 4. Nanoparticles can penetrate through the mucous layers and reach the epithelium cells for absorption by transcellular and paracellular mechanisms (Fig. 1), which is favoured for particles with a smaller dimension, resistant to aggregation themselves, and resistant to binding with mucins.[43, 52] Given the dynamic structure of the mucus layers and the limited transit time in the lumen, mucoadhesion properties increase the transit time of particles in the outer mucus layer to release the encapsulated BCs in an extended time.[43] Mucoadhesive particles bind with the mucin glycoproteins through hydrophobic attraction, hydrogen bonding, and/or electrostatic attraction.[53] Capsules in the outer mucus layer can also be hydrolysed by enzymes secreted by GM to release the entrapped probiotics for colonization in the mucus layer, substrates for microbial fermentation, including prebiotics, and nanoparticles or BCs available for absorption or fermentation (Fig. 1). The absorbed BCs then can perform their bioactivities, including antioxidant, anti-inflammation, and anti-cancer functions. Nanocapsules have the advantage of high surface area-to-volume ratio to increase the possibility of mucoadhesion to release the entrapped BCs in the mucus layer.[43]

Additionally, some molecules can enhance the intestinal permeability (Fig. 1) and thus the absorption of BCs through temporarily opening the tight junctions between epithelial cells, enhancing transcellular permeation by alternating membrane lipid bilayer to form structural defects, or forming membrane permeable complexes.[54] These absorption enhancers include food ingredients of medium chain fatty acids that dilate the tight junctions and enhance transcellular permeation.[54] Pelargonidin, the red pigment in strawberries, was recently discovered to be a potential absorption enhancer for macromolecules.[55] The insulin capsule orally administered together with pelargonidin had a similar bioactivity as insulin injected subcutaneously, and the effects were due to association with actin and tight junction rearrangement and were reversible in 2 h.[55] These absorption enhancers therefore may be significant to the development of food grade delivery systems.

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Table 2. Key sensory properties to be considered when incorporating delivery systems in food matrices.

Parameter	Potential sensory defects	Strategies
Dimension, morphology, light scattering, and physical state	Thickness, hardness, springiness, cohesiveness, gumminess, and chewiness	Customized systems to make sure no negative impact on empirical sensory properties and fundamental rheological properties of food products
	Sandiness	Production of particulates smaller than 10 μm for use in dairy products[56] and ice creams;[57] prevention of particulate aggregation; for solid products, preparing particulates smaller than 2 mm for swallowing[58]
	Turbidity	Reduction of particulate dimension to achieve clarity of beverages, e.g., smaller than 100 nm, ideally 40 nm,[59] or adoption of clouding agents to obtain the required turbidity
	Visible phase separation	Adopting strategies preventing creaming or precipitation: reducing particulate size, preventing aggregation, increasing continuous phase viscosity, and matching the densities of continuous phase and particulates[60]
Chromophore	Alternation of food colour due to inherent molecular structures of bioactive compounds (BCs)	Matching product specification; colour masking[61]
Volatility	Undesirable aromas of some volatile BCs such as essential oils or impurities	Reducing vapor pressure by binding with other ingredients such as cyclodextrins or encapsulation in tightly sealed micro/nanocapsules; storing foods at low temperature to reduce evaporation[62]
Taste receptor binding	Bitterness or other undesirable tastes of many BCs	Reducing the concentration in the continuous phase (unencapsulated fraction) by increasing encapsulation efficiency or removing the unencapsulated molecules using filtration and the surface/near-surface molecules by solvent washing; taste masking[63]

Table 3. Factors impacting the stability and activity of bioactive compounds, probiotics, and delivery systems to be incorporated in food and delivered to the colon.

Factor	Compound impacted	Mechanism	Possible solution
Food processing and storage[3, 64-67]			
Mechanical force	Probiotics	Cell membrane disruption	Alternative processes
Thermal pasteurization or sterilization	Plant secondary metabolites (PSMs) in Table 1	Oxidation or decomposition	Encapsulation, adopting strategies lowering oxidation, e.g., other antioxidants as free radical scavengers
	Proteins	Denaturation	Thermo-protectant
	Probiotics	Cell membrane disruption, enzyme/protein denaturation	Encapsulation, sub-lethal heat stress for better thermal stability, non-thermal technologies
Freezing/thawing	Probiotics	Cell membrane disruption	Cryoprotectant
Oxygen	PSMs	Oxidation	Encapsulation, adopting strategies lowering oxidation
	Probiotics	Increased cell membrane permeability	Antioxidants, modified atmospheric packaging, low oxygen permeability packaging
UV/light	PSMs	Oxidation, decomposition	Encapsulation
Humidity	Probiotics	Increased water activity (reactivity)	Encapsulation, use of humectants
Food matrix[3, 68, 69]			

pH	Proteins	Denaturation, molecular structure changes	Encapsulation
	Polyphenols	Structural changes through proton loss at high pH	Encapsulation, chemical modification to improve stability
	Probiotics	Reduced cytoplasmic pH, disrupting glycolytic enzyme activity	Acid-tolerant strain, encapsulation
Preservatives	Probiotics	Cellular stresses such as intracellular acidification	Strain resistant to specific preservative used, encapsulation
Chelating agents	Probiotics	Removal of multivalent cations such as calcium and magnesium important to cell membrane structure and function	Encapsulation to improve cellular barrier
Food components	Polyphenols, proteins, prebiotics	Binding to form complexes	Encapsulation to reduce the binding
Oral cavity (pH 7 in saliva, affected by pH of food; 37 °C, affected by food temperature, typically less than 2 min food transit time)[58]			
α-amylase	Gelatinized starch	Hydrolysis of α-1,4 and α-1,6 glycosidic bonds	Use of resistant starch or non-starch ingredients as carrier materials
Mechanical force	Various	Destruction by mastication	Reducing dimension to < 2 mm
Gastric conditions (pH <2 when empty, increase by > 3 units with a meal; 37 °C; 0.5-4 h food transit time)[3, 58]			
pH	Probiotics	Reduced cytoplasmic pH, disrupting glycolytic enzyme activity	Acid-tolerant strain, encapsulation, enteric coatings, use of prebiotics
	Proteins	Denaturation	Encapsulation
Pepsin	Proteins and peptides	Hydrolysis of bioactive proteins and peptides, digestion of proteins on particle surface	Pepsin-resistant peptides, low digesting proteins, non-protein carrier materials
	Probiotics	Cell membrane leakage or rupture, degradation of cell surface proteins	Pepsin-resistant strain, encapsulation, enteric coatings, use of prebiotics
Lipases	Acylglycerols, phospholipids	Hydrolysis of intramolecular ester bonds	Coating with molecules resistant to the enzyme
Small intestinal conditions (pH 6.5-7.5;37 °C; 2-6 h food transit time)[58, 70-74]			
pH	Polyphenols	Structural transformations	Encapsulation using digestion resistant materials such as dietary fibres
Pancreatin (pancreatic lipase and amylase)	Probiotics	Cell membrane disruption	Strain resistant to the enzymes, encapsulation using digestion resistant materials, use of prebiotics
	Proteins and peptides	Hydrolysis of bioactive proteins and peptides Digestion of proteins on particle surface	Pepsin-resistant peptides, low digesting proteins, non-protein carrier materials
	Gelatinized starch	Hydrolysis of α-1,4 and α-1,6 glycosidic bonds	Use of resistant starch or non-starch ingredients as carrier materials
Bile acids	Polyphenols	Binding to bile acids, reduced bioaccessibility	Encapsulation using digestion resistant materials
	Probiotics	Cell membrane disruption, DNA damage	Bile-resistant strain that synthesizes bile salt hydrolases, encapsulation, use of L-malic acid
Large intestinal (colon) conditions (pH 5.5-7.5; 37 °C; 10-59 h food transit time)[75, 76]			
Colon disease-associated GM	Probiotics	Competitive exclusion	Strain with good mucoadhesive and penetrating abilities, use of prebiotics
Enzymes produced by gut bacteria	Carbohydrates, proteins, lipids, bile salts	Hydrolysis of substrates	Use of prebiotics

Table 4. Mechanisms of soft particulate matters (SPMs) enhancing the delivery of BCs in the colon to improve gut health.

Mechanism	Role of SPMs	Example food materials
Mucoadhesion	Particles with mucoadhesive properties stay in the mucus layer and extend the transit time.	Mucoadhesive biopolymers: Chitosan, pectin, alginate, hydroxypropylmethylcellulose, hyaluronic acid, chondroitin sulphate, and proteins (zein, lysozyme, bovine serum albumin, etc.)[43, 77]
Enzyme-triggered release	Particle structures are hydrolysed and disintegrated by enzymes secreted by the gut bacteria to release the entrapped compounds in the mucus layer for absorption or fermentation.	Pectin-based capsules or those surface-coated by pectin that is hydrolysed by pectinase secreted by the gut bacteria[78]
Diffusion	Particulates with small enough dimensions and right surface characteristics diffuse into and through the complex structures of mucus layers to reach the epithelial cells.	Surfactant micelles, lipid nanodroplets, solid lipid nanoparticles, nanostructured lipid carriers, and biopolymer nanoparticles[79]
Absorption	Small enough particles diffuse through tight junctions between epithelial cells; absorption-enhancing molecules facilitate the transport through the tight junctions.	Nanoscale particulates; medium chain fatty acids, chitosan[52, 54]

4.2. Carrier materials for fabricating food grade colon delivery systems

4.2.1. Mucoadhesive biopolymers. Some mucoadhesive food molecules are listed in Table 4. These molecules have numerous hydroxyl groups available to form hydrogen bonds with mucin glycoproteins, positive charges of amine groups to bind with negative charges of mucin glycoproteins, or hydrophobic surfaces.[43, 77] In addition to chitosan, amine groups of basic amino acid residues on the surface of acidic and basic proteins having an isoelectric point below (e.g., bovine serum albumin) and above (e.g., lysozyme) 7.0, respectively, provide positive charges.[3] Although amidation has been done for proteins and polysaccharides,[80] the amidated biopolymers may no longer be used for food applications.

4.2.2. Food grade enteric polymers. Enteric polymers have a sharp change in their solubility with changes in pH, showing insolubility at gastric acidity but solubility at intestinal acidity (Table 3), which enables the maintained structure of SPMs in the stomach before reaching intestines and therefore is suitable for fabricating colon delivery systems.[81, 82] Among enteric polymers used to manufacture enteric capsules and tablets of drugs, shellac and hydroxypropylmethylcellulose (HPMC) are food ingredients. Shellac is an amphiphilic resin secreted by the insect *Kerriar lacca* and is approved for fruit coating in the U.S. (21 CFR 175.300).[81, 82] Molecularly, shellac consists of hydrophobic aleuritic acid esterified with hydrophilic sesquiterpenoid acids,[83, 84] and intermolecular ester bonds formed between the carboxyl group of sesquiterpenoid acids and the hydroxyl group of aleuritic acid determine the oligomeric structure of native shellac.[85, 86] The amphiphilic nature of shellac is responsible for the formation of micelles,[82] complexation with polymers,[87-89] and preparation of emulsions.[90] The solubility characteristics of shellac allowing its use as an enteric polymer are enabled by its pKa value of 6.9-7.5, resulting in its insolubility at a pH below about 7.[91]

HPMC is a food grade polysaccharide and has been used to make the matrix of tablets to enable the gradual release of drugs in intestines.[92] In an example, the gradual release of melatonin in HPMC tablets was observed at up to about 30% during the 2-h simulated gastric digestion (SGD) and up to >90% during the 4-h simulated intestinal digestion (SID).[93] Tablets made with HPMC and shellac mixtures resulted in no release of a model red pigment during SGD but the gradual release with a zero-order kinetics of up to about 60% or a first-order kinetics of up to about 90% after 9 h of SID.[94] Shellac-HPMC mixtures after coating on pectin beads enabled the less than 15% release of entrapped malvidin-3-*O*-galactoside (an anthocyanin) after 3-h SGD and 4-h SID but more than 85% release after 15-h simulated colonic digestion.[95]

Modified rice protein (MRP) is derived from proteins extracted from rice bran after alkaline treatment at -20 °C overnight and grinding the frozen matter.[96] The MRP has a solubility of <10% at pH ≤6.0 and >90% at ≥pH 7.0.[97] During simulated digestions, gradual peptic hydrolysis of MRP at pH 1.3 by up to 40% was observed, and the digestibility increased to 80% after 2-h SID with pancreatin.[97] These characteristics of MRPs enable their use as enteric coatings together with shellac[98] and the engineering of emulsion structures, digestion properties, and the release of compounds loaded in emulsion droplets.[97]

4.2.3. Undigestible but fermentable molecules. Molecules used to fabricate SPMs for colon delivery ideally are not hydrolysed by enzymes in the oral cavity, stomach, and small intestine to maintain the particle structure before reaching the colon and being hydrolysed by colonic enzymes (Table 3). Such molecules include a large variety of dietary fibres, some of which are mucoadhesive (Table 4) and/or prebiotics (Table 1). Resistant starches include native starches after chemical modification and those recrystallized from individual native starch molecules.[3] Non-starch polysaccharides such as cellulose, chitin, galactomannan, alginate, starch, and pectin can be hydrolysed by carbohydrate-active enzymes produced by gut bacteria in the colon.[76] Waxes are another group of undigestible molecules.[99] Combination of these molecules may lead to the improved functional properties for colon delivery.[43]

4.2.4. Slow-digesting molecules. Some molecules are digested to a limited extent by enzymes in the GI tract despite being potential substrates. Some prolamins, alcohol-soluble storage proteins in grains, e.g., zein in maize and kafirins in sorghum, are such examples due to their amino acid composition and three-dimensional structures controlled by intramolecular disulfide bonds and physical

forces making peptide bonds inaccessible by proteases.[100, 101] Starches are naturally present as highly crystalline granules that have a low digestibility, and heating is needed to break hydrogen bonds to produce gelatinized starches that are digestible.[3] Gelatinized starches can recrystallize to form slow digesting or undigestible (resistant) starches after cooling.[3] These slow digesting molecules can also be used to synthesize SPMs as colon delivery systems.[102]

4.2.5. Digestible molecules. Digestible molecules can be used to form SPMs such as emulsion droplets that can be surface-covered with indigestible or slow-digesting molecules. Some digestible molecules are protectants of proteins and probiotics (Table 3). The fate of these molecules and the stability of the prepared SPMs are to be analyzed individually.

4.3. Types of SPMs

Common SPMs applicable to deliver BCs in Table 1 are presented in Fig. 2. They represent a dimension from tens of nanometres to several millimetres and are applicable for LBCs, HBCs, or both. While general applicability of each category of SPMs in food systems is listed in Table 5, selection of a specific type of SPMs shall start with food products to be implemented taking into consideration of food safety, labelling, and marketing. Notably, because many proteins are allergens for certain groups of consumers, SPMs fabricated with a protein may be more appropriate for food products with this protein, e.g., dairy products for dairy protein-based SPMs. Once a specific food product and relevant environmental factors (Table 3) are identified, physicochemical properties of BCs and carrier materials are used together to select a specific type of SPMs. In general, SPMs shall be much bigger than the dimension of BCs to enable the enclosure and high loading capacity. Processes loading BCs in SPMs shall not deactivate BCs, and SPMs ideally can maintain their structures and protect BCs from environmental stresses before responding to colonic conditions to release BCs (Fig. 1). Processes of making these structures have been reviewed previously.[103, 104] The present section discusses their structural characteristics and their function for colon delivery of BCs in example studies.

4.3.1. Undigestible surfactant micelles. The hydrophobic core of surfactant micelles can be used to dissolve LBCs (Fig. 2A). In addition to small molecular surfactants, amphiphilic biopolymers form micellar structures that can be used to load LBCs with characteristics feasible for colon delivery. The *in vivo* fate of micellar delivery systems depends on the susceptibility to digestive enzymes in the GI tract and the competition or displacement by surface active bile salts in the intestines. Ideally, these micelles are not digested in the gastric fluid and maintain their structures in the small intestines to be available to function in the colon.

Shellac is an example of small molecular surfactants forming micelles.[82] When dissolved at pH 12.0, the intermolecular ester bonds in the oligomeric shellac are cleaved, and the monomeric shellac forms micelles.[105] For shellac and curcumin co-dissolved at pH 12.0, the self-assembled micellar structures after neutralization to pH 7.0 had a diameter of 14.1-38.3 nm, larger at a higher curcumin load.[105] After the SGD and SID, about 40% of curcumin was present in the supernatant phase with bile salts after centrifugation, i.e., bioaccessibility, micellar structures were observed, and the digesta remained active against the proliferation of human CRC cells.[105] Co-encapsulation of curcumin and quercetin in shellac micelles enabled the synergistic antioxidant and cytotoxic properties of the polyphenols, while maintaining the characteristics feasible for colon delivery.[106]

Curdlan was hydrolysed to form oligosaccharides that were further modified with hydrophobic octenyl succinic anhydride, and the formed amphiphilic molecule formed micelles with a diameter of 230 nm.[107] Micelles were used to dissolve curcumin, quercetin, or both, forming particles smaller than 150 nm according to dynamic light scattering and smaller than 50 nm according to transmission electron microscopy. The release of encapsulated polyphenols was limited during the SGD but was gradual during the SID. During the simulated human faecal fermentation, the micelles alone facilitated the production of SCFAs, and the co-encapsulated polyphenols promoted the growth of *Bifidobacterium* and inhibited the growth of *E. coli* and *Shigella* spp.[107]

The loading capacity of LBCs in micelles is dependent on the molecular characteristics of amphiphilic molecules. Shellac has distinct polar and non-polar regimes in its molecular structure, and the small dimension of shellac micelles (14 nm) leads to a loading capacity of less than 8%.[105] Whereas, addition of octenyl succinate on curdlan oligosaccharides provides numerous binding sites leading to a loading capacity of over 20% when co-encapsulating curcumin and quercetin.[107] With the relative small dimensions, surfactant micelles are suitable for delivering LBCs in transparent beverages.

4.3.2. Liposomes. Liposomes are the self-assembled structures of surfactants, commonly phospholipids in food systems, in forms of unilamellar vesicles with one surfactant bilayer (Fig. 2B) and multilamellar vesicles with multiple surfactant bilayers.[108] The surfactant bilayers can be used as regimes to dissolve LBCs, while the inner aqueous compartments are used to dissolve/suspend HBCs. Phospholipids and cholesterol used to prepare liposomes are susceptible to digestion in the GI, and the gastric acidity and bile salts can modulate liposome structures.[109] As a result, although liposomes have been used to load BCs,[108] structural modifications of surfactants before forming liposomes or surface coating of liposomes are needed for stability in intestines.[109] In drug delivery systems, modifications of surface composition and surfactant structures have enabled the targeted delivery and triggered release of encapsulated hydrophobic and hydrophilic drugs, as well as generic materials, to cure CRC.[110] Regulations of the chemically modified liposomes and the high cost are likely obstacles for food applications. The low loading capacity and multi-steps needed for preparation are additional drawbacks of liposomes for industrial food applications.

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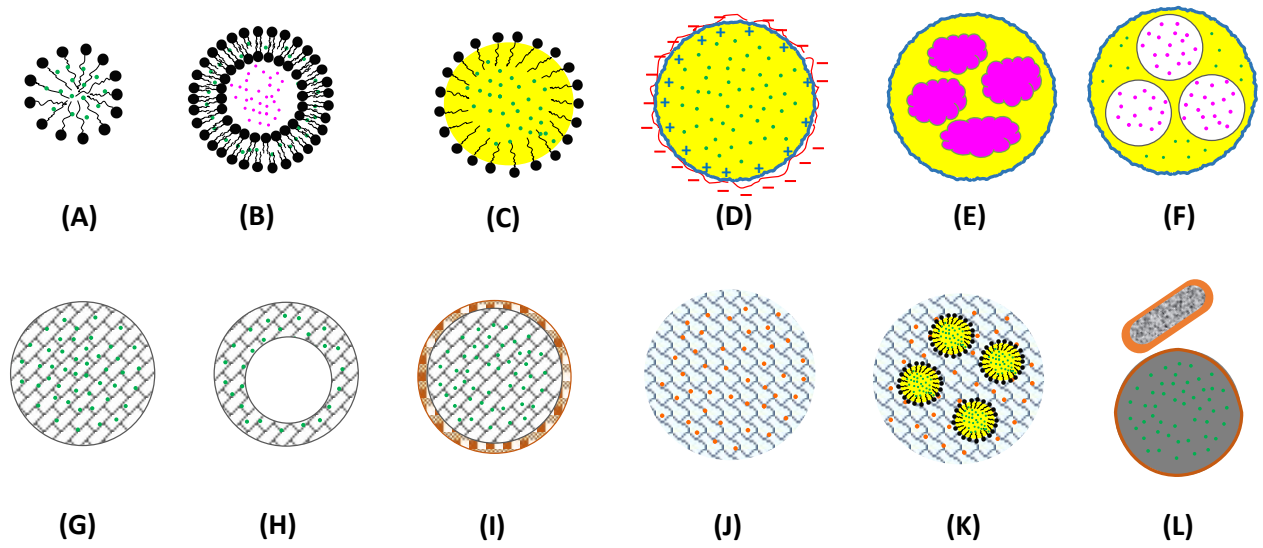

Figure 2. Schematic illustrations of (A) surfactant micelles dissolving lipophilic bioactive compounds (LBCs), (B) liposomes with the bilayer dissolving LBCs and the inner aqueous core dissolving hydrophilic BCs (HBCs), (C) lipid droplets with dissolved LBCs, (D) lipid droplets with multiple layers of molecules on the surface, (E) HBC-containing solid-in-oil-in-water emulsions, (F) water-in-oil-in-water emulsions with the inner water phase dissolving HBCs and the oil phase dissolving LBCs, (G) solid biopolymeric particles with entrapped BCs, (H) hollow biopolymeric particles with BCs, (I) BC-containing core-biopolymer shell particles formed by self-assembly, (J) porous micro/nanogels with entrapped BCs, (K) microgels filled with solid particles or lipid droplets, and (L) solid particles with entrapped BCs or single probiotic cells coated with a layer(s) of molecules by dipping, spraying, or adsorption.

Table 5. Example studies on food grade soft particulate matters (SPMs) and their characteristics for delivering bioactive compounds (BCs) to the colon.

Type of soft particulates	Bioactive compound	Carrier material	Notable features
Micelles for dissolving lipophilic BCs (LBCs), suitable for transparent beverages			
Surfactant micelles[105]	Curcumin	Shellac	• Smaller than 50 nm • Remained active against colorectal cancer (CRC) cells after the simulated gastric (SGD) and intestinal digestion (SID) • Retained micellar structure after SGD and SID
Oligosaccharide micelles[107]	Curcumin	Octenyl succinate-curdlan oligosaccharide	• Diameter of 230 nm • Prebiotic carrier producing short chain fatty acids • Curcumin promoting beneficial bacteria and inhibiting harmful bacteria
Emulsions			
Emulsions prepared with undigestible biopolymeric surfactant[111]	Glyceryl tripropionate (propionic acid after lipolysis)	High methyl pectin as emulsifier, equal masses of glyceryl tripropionate and soybean oil as the oil phase	• Thicker interface with a higher pectin content • Digestion-resistant emulsion with a high enough pectin content • Less than 10% release after 2-h SGD • Less than 40% release after 2-h SID
Complex emulsions for enclosing probiotics and dissolving LBCs and/or hydrophilic BCs (HBCs), suitable for turbid liquid and semi-solid foods or solid foods after dehydration			

Multi-layered emulsions[112]	Curcumin	Medium chain triacylglycerols as the oil; primary emulsion with whey protein as emulsifier; secondary emulsions with chitosan or carboxymethyl konjac glucomannan, tertiary emulsion with both	• Droplets smaller than 2 μm • Less than 15 and 15-22% release of curcumin in the secondary emulsions after 3-h SGD and 3-h SID, respectively, contrasting with about 40% and 10% for the primary emulsion and 5% and 15% for the tertiary emulsion, respectively • About 15% release of curcumin for the primary emulsion and the secondary emulsion with chitosan, contrasting with >30% for the other secondary emulsion and the tertiary emulsion after 3-h simulated colonic digestion (SCD)
Solid/oil/water (S/O/W) double emulsions[113, 114]	β-glucosidase (lactase)	Milk fat as the oil phase, Span® 80 used to lower S/O interface, whey protein or casein as the outer surface layer	• Capsules smaller than 10 μm • Capsules dispersible in milk • Enhanced survival of encapsulated lactase after thermal pasteurization • Less than 20% lactose hydrolysis in milk after 14-day refrigerated storage • ~70% lactose in milk hydrolysed during 2-h SGD and 4-h SID
S/O/W double emulsions[115, 116]	*L. salivarius* NRRL B-30514	Milk fat or soya oil as the oil phase, double whey protein/casein-pectin layers or sugar beet pectin as the outer surface layer, Ca^{2+} cross-linking of surface pectin	• Capsules smaller than 10 μm • Capsules dispersible • Enhanced probiotic stability during storage at acidic pH • Enhanced thermal stability • Enhanced survival after 2-h SGD and 4-h SID
S/O/W double emulsions[117]	Konjac glucomannan (a prebiotic[118])	Corn oil as the oil phase, lecithin used to lower S/O interface, whey protein as the outer surface layer	• Emulsion viscosity as low as <0.05 Pa-s allowing incorporation of highly viscous prebiotics in liquid foods • Gradual increase in viscosity during SGD and SID
$W_1/O/W_2$ double emulsions[119]	*L. plantarum*	Probiotics in W_1, medium chain triacylglycerols as O, alginate with ethylenediamine-tetraacetate and Ca^{2+} in W_2; polyglycerol polyricinoleate for W_1/O interface, whey protein-epigallocatechin-3-gallate conjugate for O/W_2 interface	• Gel-like structure at gastric pH • Returning to fluidic at intestinal pH • Encapsulated 7.8×10^7 CFU/mL bacteria • Over 7.8×10^7 CFU/mL bacteria after SGD and SID for the best formulation
Self-assembled biopolymer nanostructures for LBCs and probiotics, suitable for beverages, turbid liquid and semi-solid foods, or solid foods after dehydration			
Nanocomplexes with proteins[120]	Apigenin	Whey protein	• Loading capacity up to ~20% • Enhanced apigenin uptake by CRC cells and apoptosis • Remained active against CRC cells after SGD and SID • Increased apigenin content in the blood and colon mucosa of mice
Nanocomplexes with polysaccharides[121]	Curcumin	Chitosan and pectin	• Mucoadhesive • Acid stable capsules • Negligible release without pectinase • 80% release with pectinase in SCD

Nanocomplexes with covalent polypeptide-polysaccharide conjugates[122]	Curcumin	Soluble soybean polysaccharide	• Stable at pH 2-7 • Stable after heating at 95 °C for 1 min • Remained active against CRC cells after SGD and SID
Core-shell capsules[123]	Curcumin	Zein and sodium caseinate complexing curcumin as the core; alginate on the surface as shell	• 85-92% encapsulation efficiency • Storage and heat stability • Stable at pH 3-8, 0-400 mM NaCl
Bacteria core-layered biopolymer shell microcapsules[124]	*L. plantarum*	Cationic zein nanoparticles and anionic pectin deposited on anionic bacteria layer-by-layer	• >7.1 log CFU/mL after 2-h SGD and 6-h SID • <1 log CFU/mL reduction after heating at 65 °C for 10 and 30 min • <1 log CFU/mL loss after 60-d storage at 4 °C
Spray-dried microcapsules for enclosing LBCs, HBCs, and probiotics, suitable for direct use in solid foods or turbid liquid and semi-solid foods after rehydration			
In situ cross-linked microcapsules[125]	*Lactobacillus*	Alginate, cross-linked by calcium ions	• Adoption of a coaxial nozzle, with alginate and probiotics in the inner fluid and $CaCl_2$ in the outer fluid • Cross-linking and encapsulation in one step • Enhanced survival of probiotics during storge and SGD and SID
Microgels for enclosing probiotics and LBCs, suitable for turbid liquid and semi-solid foods			
Microgels[126]	*Staphylococcus succinus* and *Enterococcus fecium*	Alginate, with prebiotics	• Up to 95% survival after 35-d storage at 4 °C • 87.7-98.8% survival of probiotics at pH 2 and 3 after 24 h at 37 °C • 85-95.5% survival of probiotics in 0.3-0.8 g/100 mL bile salts after 24 h at 37 °C • >7.1 log CFU/mL after 2-h SGD and 6-h SID
Microgels[127]	Quercetin	Alginate, inulin as filler, chitosan for surface coating	• Microgels of 25-80 μm • Chitosan preserved microgel structure during SGD and SID • Microgels were fermented in 24 h *in vitro*.
Filled microgels[128]	Curcumin	Curcumin-loaded carboxymethyl chitosan microspheres as fillers; hyaluronic acid-gelatine composite forming microgel	• <25% release after 2-h SGD and 3-h SID; >60% release after subsequent 45-h SCD • Positive *in vivo* results: Increased and maintained curcumin content in colon tissue; lowered colon colitis; lowered inflammation
Filled microgels[129]	Curcumin	Curcumin-loaded nano-oil droplets alginate beads; beads coated with an enteric polymer	• Beads smaller than 2 mm • No release of curcumin after 2-h SGD and 3-h SID; >90% release after subsequent 19-h SCD • Inhibition of CRC cells by released curcumin
Nanocoating of single bacterial cells, probiotics pellets, and dried hydrogel beads enclosing HBCs, suitable for turbid liquid foods or solid/semi-solid foods			
Single cell coating[130]	*Bacillus coagulans*	Chitosan-alginate-chitosan coating	• Reduced deactivation during SGD and SID • Enhanced adhesion on and growth in the intestines of mice
Single cell coating[131]	*E. coli* Nissle 1917	Iron-tannic acid (metal-phenolic network)	• Improved resistance against antibiotics *in vitro* and *in vivo* • Improved stability in SGD and SID • Improved colonization *in vivo*
Probiotic pellets[98]	*L. salivarius* NRRL B-30514	Shellac, shellac-modified rice protein	• Reduced deactivation during SGD and SID

			• Rice protein enhanced the disintegration of coating at neutral pH
Beads dried from amidated pectin microgels[95]	Malvidin-3-*O*-galactoside (an anthocyanin)	Pectin matrix, shellac/HPMC composite coatings	• About 1 mm for dried beads • Fluidized bed coating of beads • Limited release (<15%) after 3-h SGD and 4-h SID, more than 85% release after 15-h SCD

4.3.3. Lipid-surfactant mixture colloids. Lipid-surfactant mixtures are one of the most studied delivery systems because of the flexibility and scalability in preparation, the capability of dissolving LBCs in the lipid body, and the possibility to engineer surface properties (Fig. 2C). Based on the structure of the lipid body, the dimension of lipid droplets, and the thermodynamic stability, these systems include conventional emulsions with droplet diameters bigger than 200 nm, nanoemulsions with droplet diameters smaller than 200 nm, and microemulsions with a droplet diameter smaller than 100 nm, typically 10-50 nm.[132, 133] Different from thermodynamically unstable nanoemulsions, the interfacial tension in microemulsions is extremely low, making microemulsions thermodynamically stable, monodispersed, and with the ability to return to the starting properties after temperature fluctuations and storage.[132] Microemulsions are formed at a particular set of composition, temperature, and pressure, and the dilution effect, changes in pH, and presence of surface-active compounds such as bile salts and proteins in the GI tract can destabilize microemulsions.[132] The lipid body can also be at the solid state at the application temperature, including solid lipid nanoparticles with the lipid molecules forming crystalline structures and nanostructured lipid carriers composed of lipid molecules forming both crystalline and amorphous structures.[134] The solid lipid body with high resistance against diffusion enables the sustained release of the encapsulated LBCs.[134]

Several studies reported the activity against human CRC cells for LBCs loaded in conventional emulsions,[135] nanoemulsions,[136] microemulsions,[137] and solid lipid nanoparticles.[138] However, the structure and activity of these systems after *in vitro* or *in vivo* digestions are unknown. The digestion instability of lipid body surface due to enzymes in the GI tract and the displacement of emulsifiers on the surface by bile salts are known to change the colloidal structure and also likely the effectiveness for delivery to the colon.[139] In an emulsion prepared with high methoxyl pectin (70% esterification) as an emulsifier and glyceryl tripropionate-corn oil as the oil phase, a high enough pectin content (≥2.5% w/v in the aqueous phase) led to a thick enough interfacial layer to resist displacement by bile salts to maintain the oil droplet structure.[111] The encapsulated glyceryl tripropionate was released by less than 10% after 2-h SGD and less than 40% after 2-h SID,[111] implying the possibility of delivering the majority of glyceryl tripropionate (propionic acid after lipolysis) in the colon. However, these emulsions may be too viscous in some food applications.

4.3.4. Complex emulsions. To overcome drawbacks of lipid bodies with only one layer of surfactant molecules, complex emulsions are developed by physical modification of surface composition through layer-by-layer deposition of a layer or multiple layers of undigestible molecules with opposite charges (Fig. 2D) or fabrication of multi-phased lipid bodies. For HBCs, dispersing HBC powder in the oil phase before emulsifying into an aqueous phase forms solid-in-oil-in-water emulsions (Fig. 2E), and the oil phase provides a barrier for the HBCs interacting with environmental stresses in the continuous water phase (Table 3). Alternatively, HBCs are dissolved or dispersed in an aqueous phase (W_1) that is then emulsified in an oil phase, and the prepared water-in-oil emulsion is emulsified in the continuous water phase (W_2) to form a $W_1/O/W_2$ emulsion (Fig. 2F). Despite the possibilities to encapsulate HBCs and LBCs in one system, the limited loading capacity in the solid or W_1 phase, the need to maintain the stability of two interfaces, the additional emulsification step, and the possible large dimension of final droplets are potential drawbacks of multi-phased emulsions.[140]

4.3.5. Biopolymer particles. Food biopolymers, proteins and polysaccharides, form diverse structures feasible for entrapping BCs through self-assembly driven by physical forces or processing such as spray drying. For LBCs, hydrophobic interaction is a dominant force enabling the binding of LBCs to hydrophobic amino acid residues of proteins or hydrophobic functional groups of hydrophobically modified polysaccharides to form self-assembled capsules, with secondary contribution by hydrogen bonding.[103] The cavity in crystalline structures formed from self-assembled amylose and debranched starch is hydrophobic and provides sites for inclusion of guest molecules to enhance the stability and release properties during digestion.[141] For HBCs, electrostatic attraction, hydrophobic attraction, and hydrogen bonding are possible mechanisms for binding with carrier biopolymers.[142] Although most biopolymer capsules have a solid continuous matrix (Fig. 2G), hollow particles (Fig. 2H) can be produced by spray drying[143] or adopting a template.[144, 145] Hollow particles have advantages of the increased surface area per unit volume and the reduced density that may be unique for some applications.[144] Adsorbing a layer of digestion-resistant non-starch polysaccharide on biopolymer particles (Fig. 2I) is important to maintain the particle structure during the gastric and intestinal digestion, and cationic chitosan and anionic polyelectrolytes such as pectin and alginate are common choices.[78, 146, 147]

Spray drying is the most feasible encapsulation technology for the food industry due to its low cost, scalability, and simplicity, and the powder form of microcapsules has the convenience for storage, transportation, and application. LBCs can be dissolved with a carrier material in a mutual solvent for spray drying, e.g., curcumin and sodium caseinate in 40% ethanol at 60 °C,[148] or pre-encapsulated for dispersion in water for spray drying with and without an additional material.[149] With the feed composed of water-soluble molecules or dispersible colloids, spray-dried microcapsules are likely disintegrated after incorporation in moist food products or ingestion, which may lose the protection effect for BCs designed to function in the colon, especially for HBCs and probiotics. To overcome this challenge, physical cross-links created *in situ* during spray drying are potential solutions. Cross-linking alginate by divalent calcium ions (Ca^{2+}) available after atomization of the feed has been studied using

two approaches. In one approach, one inner feed containing alginate and probiotics met with the other outer feed of $CaCl_2$ solution during atomization through a three-fluid (the third fluid being compressed drying hot air) nozzle, and the produced microcapsules preserved probiotics during storage and simulated digestions.[125] In another approach, the feed contained alginate, insoluble $CaHPO_4$, succinic acid titrated to pH 5.6 with ammonium hydroxide, and the compound to be encapsulated; the removal of volatile ammonium hydroxide (decomposed to ammonia gas and water) during drying lowered the feed pH to dissolve $CaHPO_4$, releasing Ca^{2+} to cross-link alginate in the same feed.[150, 151] These approaches simplify microcapsule production which is critical for the practicality of delivering BCs in foods.

4.3.6. Micro/nanogels. Microgels used for potential delivery of BCs in foods are porous particulates composed of a biopolymer network physically cross-linked by a gelling agent (Fig. 2J),[152] which can be used to load pre-formed biopolymeric particles[128] or oil droplets[129] known as filled microgels (Fig. 2K). Alginate microgels are the most studied system for encapsulation of probiotics and enzymes because alginate is a widely available food ingredient and its cross-linking by divalent Ca^{2+} is well established. Commonly, a mixture with alginate, a protectant (e.g., prebiotics for probiotics), and BCs is extruded to a $CaCl_2$ solution to form millimetre-sized beads. As reviewed previously,[153] the displacement of Ca^{2+} by protons at acidic gastric conditions leads to formation of an alginic acid skin and a strong internal matrix of alginic acid that minimize the release of the encapsulated BCs; once reaching the intestines, deprotonation of alginic acid leads to the swelling and dissolving of the beads, which is facilitated by displacement of Ca^{2+} initially cross-linking alginate by sodium ions and chelation of Ca^{2+} by phosphates, resulting in gradual release of the encapsulated compounds in 2-4 h. These characteristics of alginate microgels have resulted in the improved survival of entrapped probiotics under the SGD and SID.[126] Inclusion of sodium caseinate[154] and surface coating with cationic chitosan[155] have also been studied to enhance the pH-responsive (reduced pore size at gastric pH) and GI survival properties, respectively.

To reduce the dimension of alginate microgels feasible for food applications, attempts have been made to first include alginate in the inner water phase of $W_1/O/W_2$ emulsions, followed by cross-linking with $CaCl_2$ nanoparticles dispersed in the oil phase to prepare particulates with a diameter from 200 nm to <5 μm.[156] The principle was later used to fabricate alginate microgels (25-80 μm) with inulin and quercetin, which was further coated with chitosan to strengthen the survival of microgels during SGD and SID.[127] The prepared microgels were digested by GM in 24 h during the simulated pig faecal fermentation, with the release of quercetin being delayed until after 3 h into fermentation.[127] The reduction of alginate particle dimension makes it more plausible for food applications (Table 2) and likely maintains the release mechanisms triggered by physiological conditions and colonic enzymes. The added complexity however requires additional materials and processes and may be too costly for food systems. In addition, the scalability of producing alginate beads using extrusion technology is a concern, and structural changes due to dehydration (needed for storage) and rehydration can compromise functional properties as delivery systems.[157]

4.3.7. Nanocoating on probiotic cells and solid particles. Metal-phenolic networks have been studied as a biocompatible approach to coat individual living cells. Polyphenols have mucoadhesive properties that are vital for probiotic delivery in the colon.[158] Individual cells of *E. coli* Nissle 1917,[131, 159] *Bacterioides thetaiotaomicron*,[160] *Bacillus subtilis*,[161] and lactic acid bacteria[131] have been individually coated with ferric ions and tannic acid, gallic acid, or epigallocatechin gallate. The metal-phenolic network on cells improved the resistance against antibiotics *in vitro* and *in vivo*, stability during SGD and SID, and colonization in the colon mucus layer.[131] An additional layer of pharmaceutical grade enteric polymer Eudragit L100 has also been adsorbed on *E. coli* Nissle 1917 coated with tannic acid, showing additional resistance against hydrogen peroxide, enhanced mucoadhesion, and reduced colitis induced by dextran sulphate sodium.[159] Single cell coating of probiotics with the layer-by-layer (chitosan-alginate-chitosan) deposition technology improved the survival of probiotics at GI conditions and the adhesion and growth in the intestines (Table 5).[130] Multiple steps required to form metal-phenolic networks or multi-layers of biopolymers on cells and low concentrations used in fabrication likely make these systems too expensive for food applications.

Powders and pellets of BCs can also be coated with protective layers by dipping or spraying. For example, pellets prepared with a powder mixture of probiotic *L. salivarius* NRRL B-30514 and protective whey protein isolate/lactose showed the significant improvement in bacterial survival in the GI conditions after coating with shellac or shellac-MRP mixture that had the enteric delivery characteristics.[98] Fluidized bed spray coating is an industrial technology with the potential to coat powders or granules with enteric biopolymers for release in the colon (Table 5),[95] but the high temperature during spray coating may be detrimental to BCs.[162]

5. Evaluation of food products incorporated with delivery systems

When delivery systems are incorporated in foods, the impact on food quality is to be evaluated for practical applications. Examples studying the impacts of delivery systems on sensory properties of foods are given in Table 6. Positive, indifferent, or negative impacts on the sensory properties were reported. With these limited studies varying in the types of food products and delivery systems, the impact of delivery systems on sensory properties is inconclusive. These studies also did not examine the structural changes of SPMs in food matrices and after digestion. It also remains an ongoing research question for the release, stability, and bioavailability of BCs after digestions and the impact on gut health, both *in vitro* and *in vivo*.

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Table 6. Example studies on the impact of delivery systems on sensory properties of foods.

Bioactive compound	Carrier material	Soft particulates	Food	Sensory properties impacted
Curcumin[163]	Sodium caseinate and the Maillard conjugate with maltodextrin	Nanocomplexes (diameter of 120-150 nm)	Basmati rice	• Higher hardness and stiffness and lower adhesiveness of rice with nanoencapsulated curcumin • Comparable overall sensory acceptability
Quercetin[164]	Sunflower oil as the oil phase, Tween 80 and Brij 30 as surfactants	Nanoemulsions (diameter of 180-200 nm)	Chicken pâté	• Similar odour but different colour and taste compared to the control without quercetin • Higher acceptability of chicken pâté with encapsulated quercetin than the free form
Zeaxanthin[165]	Cactus mucilage as structuring material, chia seed oil as the oil phase, Tween 80 as surfactant	Nanoemulsions with and without cactus mucilage (diameter of 200 nm)	Yogurt	• Lower firmness, consistency, and viscosity compared to control yogurt • Differences in instrumental analyses not perceived in sensory analysis
L. plantarum[166]	Acid whey	Spray-dried microcapsules (could be disintegrated after rehydration)	Cream cheese	• Comparable sensory properties in terms of appearance, aroma, taste, texture, and overall acceptance of cream cheese
L. rhamnosus, also with anthocyanin [167]	Alginate, assisted with whey protein, pullulan, and/or cocoa butter	Microgels (diameter of 406–504 μm)	Strawberry nectar beverage	• Reduced sourness of strawberry nectar with encapsulated probiotics • Decreasing overall acceptability during storage

6. Conclusions and Outlooks

With the integration of soft matter physics and materials science and engineering, rapid advances have been made for SPMs fabricated with food ingredients with potential for delivery of BCs in the colon to improve gut health. Some systems have shown promising characteristics for colon delivery, and their applicability depends on the properties of food matrices and the processing and storage conditions. However, comprehensive evaluations of these systems are scarce, and there remains a big gap toward applying these systems in food products. Studies are needed to address the following issues.

Efficacy, cost, and availability of BCs. Compounds and probiotics with high efficacy to prevent and cure colon diseases are still the ongoing research topics. Most BCs are presented at low quantities in food resources and are to be extracted and purified, which increases the cost. Cost-effective synthesis of BCs with a structure identical to the natural equivalent is a possible solution, like β-carotene.[3] For probiotics, screening of microbes from various sources or bioengineering[168] is still needed to improve the efficacy for gut health, resistance against environmental stresses in Table 3, and colonization in the colon.

Carrier materials, functional properties, and cost and scalability of delivery systems. In addition to achieving the functional properties, the loading content and encapsulation efficiency of BCs in delivery systems must be sufficiently high to lower the cost of encapsulation. The ingredients must be cost-effective, available, and sustainable, and the processing steps must be minimal, cost-effective, and scalable. Integration of proper storage/packaging technologies may overcome some environmental stresses in Table 3.

Multi-scale understanding of structure-function correlations. Multi-length scale structures of SPMs in Fig. 2 are to be fully understood to provide soft matter principles in designing and preparing delivery systems. While structural characterizations at nanometre and micrometre scales are becoming routine, advanced experimental techniques such as X-ray and neutron scattering and computational tools may be critical to understand the formation of SPMs at molecular and atomic levels.[169, 170] Experimental results may reveal the spatial distribution of constituent molecules important to understand the formation, stability, instability, and release mechanisms of SPMs, types and strengths of molecular interactions, defects and cavities within SPMs for enclosure of BCs, and openings

causing leakage and deactivation of BCs. Conditions used to prepare samples for analysing SPM structures, e.g., drying, however may lead to results not representative of food systems. Computational tools may provide such information as sites and energy involved in forming physical and/or chemical bonds, and self-assembly and disassembly properties of constituent molecules as affected by thermodynamic parameters that may be challenging in experimentation. The scale (number of molecules) may be limited in computational studies, but the rapid advancements in computational power, data science, and artificial intelligence may revolutionize this area.

Structure and stability of delivery systems in food matrices and the impact on sensory properties. The impact of delivery systems on food quality is to be evaluated using various techniques to understand the structure and stability of delivery systems in food matrices and the resulting physicochemical properties of food products. The instrumental characteristics are to be confirmed eventually with sensory panels and consumer testing to determine the acceptability and practicality of incorporating delivery systems in food products, as in the development of any new food product.

Structure and stability of delivery systems in foods after ingestion. Like the previous point, the structure, release, and stability of BCs and delivery systems for food products incorporated with delivery systems are to be determined after *in vitro* and *in vivo* digestions, ideally following standardized protocols.

Impacts of functional foods containing delivery systems on human health. Eventually, successful functional foods incorporated with delivery systems must show health benefits for consumers without safety concerns. Different from drugs that are used following the strict dose subscribed by caretakers, there is no control on how much a food product and therefore BCs is consumed in a period. Toxicological studies are needed to address safety concerns, particularly for nanoscale delivery systems that have different bioavailability from bulk BCs and therefore possibly different toxicity limits.[171, 172] Possible allergenicity of BCs and carrier materials, especially those containing proteins, is to be seriously considered. The eventual health benefits and the safety will justify the cost used for researching, developing, and implementing delivery systems in foods.

Author Contributions

Qixin Zhong: Conceptualization, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition, Project administration, Supervision
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Conflicts of interest

There are no conflicts to declare.

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