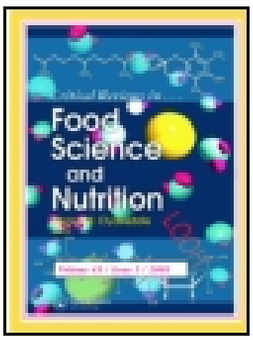

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REVIEW

Co-encapsulation of probiotics with prebiotics and their application in functional/synbiotic dairy products

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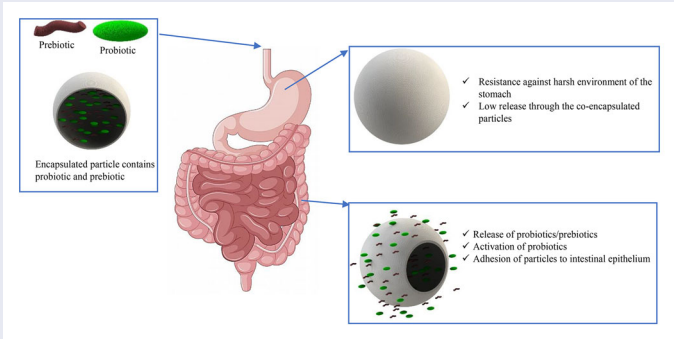
ABSTRACT

Oral administration of live probiotics along with prebiotics has been suggested with numerous beneficial effects for several conditions including certain infectious disorders, diarrheal illnesses, some inflammatory bowel diseases, and most recently, irritable bowel syndrome. Though, delivery of such viable bacteria to the host intestine is a major challenge, due to the poor survival of the ingested probiotic bacteria during the gastric transit, especially within the stomach where the pH is highly acidic. Although microencapsulation has been known as a promising approach for improving the viability of probiotics in the human digestive tract, the success rate is not satisfactory. For this reason, co-encapsulation of probiotics with probiotics has been practised as a novel alternative approach for further improvement of the oral delivery of viable probiotics toward their targeted release in the host intestine. This paper discusses the co-encapsulation technologies used for delivery of probiotics toward better stability and viability, as well the incorporation of co-encapsulated probiotics and prebiotics in functional/synbiotic dairy foods. The common encapsulation technologies (and the materials) used for this purpose, the stability and survival of co-encapsulated probiotics in the food, and the release behavior of the co-encapsulated probiotics in the gastrointestinal tract have also been explained. Most studies reported a significant improvement particularly in the viability of bacteria associated with the presence of prebiotics. Nevertheless, the previous research has mostly been carried out in the simulated digestion, meaning that future systematic research is to be carried out to investigate the efficacy of the co-encapsulation on the survival of the bacteria in the gut in vivo.



KEYWORDS

Co-encapsulation; prebiotics; probiotic live organisms; probiotic viability; symbiotic/functional dairy foods; targeted controlled release

1. Introduction

Probiotics are live microorganisms with the ability to transit through the gastrointestinal tract (GIT), and improve the health of the host organism substantially (Kerry et al. 2018; Kim et al. 2019). These microorganisms are part of the most fermented dairy products, nondairy fermented foods, and probiotic-fortified foods. They possess some important functional attributes not only for basic nutritional requirements, but also for the positive responses to clinical treatments against several disorders and diseases such as diabetes, obesity, bowel syndrome, and even different types of cancer, where there is an advancing arena of research (Kerry et al.

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2018; Kim et al. 2019; Mohajeri et al. 2018). Therefore, evaluation of different strains of probiotics (e.g., *bifidobacteria* and *lactobacilli*) and their applicability in biomedical research, and correspondingly, the new methods for the delivery of these beneficial bacteria is a fast-growing research endeavor and of the particular interest for nutraceutical, pharmaceutical, feed, and food industries. Along these lines, the efforts for expanding the range of probiotic viability in both carrier products and in the GIT have focused on the delivery of probiotics using encapsulation technology in order to protect them against the adverse conditions to which probiotics can be exposed (i.e., during the manufacture and storage of the food products, as well as the upper part of GIT), and finally, their targeted release in the lower part of GIT (Afzaal et al. 2019; Haffner, Diab, and Pasc 2016; Terpou et al. 2019; Yao et al. 2018).

The effects of various encapsulation parameters (e.g., the concentration of wall material, carrier size, cell load, encapsulation time, etc.) on the viability of probiotic cells in both food and GIT have been well-studied (Chandramouli et al. 2004; Kim et al. 2008; Sohail et al. 2011). Despite numerous methods that have been used for oral delivery of probiotics, the success rate achieved so far is somewhere limited (Kailasapathy 2002; Praepanitchai, Noomhorm, and Anal 2019). Because, a successful delivery system for delivery of probiotic bacteria and their incorporation into the corresponding functional foods depends on several factors such as wall material, carrier size, manufacturing technique, carrier stability, the dispersion medium, mass transfer, release mechanisms, and like (Mokhtari, Jafari, et al. 2017; Mokhtari, Khomeiri, et al. 2017). Therefore, the further increase in the viability of encapsulated probiotic bacteria has always been a growing research attention, since there is no ideal encapsulation method that can fully protect the viability of these microorganisms.

It has been shown that the presence of non-digestible food ingredients such as prebiotics (characteristically, nondigestible fiber compounds and polysaccharides; e.g., β-glucan, mannanoligosaccharide, xylooligosaccharide, oligofructose, fructooligosaccharide, inulin, and galactooligosaccharide) may be effective for improving the viability of probiotic bacteria either in the food products or throughout GIT, besides the additional health benefits that prebiotics themselves can have on human health (Haffner, Diab, and Pasc 2016; Iyer et al. 2004; Sathyabama et al. 2014). The combination of probiotics and prebiotics, known as synbiotics, has been shown to improve the proliferation of probiotics in the colon and thus, advancing their population in the gut community (Özer, Akin, and Özer 2005). In recent years, co-encapsulation of probiotics with prebiotics has been utilized as an ideal tool (i.e., delivery method) for incorporation of probiotic cells and their stabilization in functional/synbiotic food products, and the findings demonstrate a significant enhancement in the viability of probiotic cells during product manufacture, storage, and subsequent consumption, as well as thought the upper part of GIT (Borrás-Enríquez et al. 2018; Ningtyas et al. 2019; Zamora-Vega et al. 2013). The aim of this review was to summarize the recent research evidence on the co-encapsulation of probiotic cells with various probiotics and their corresponding application in the synbiotic/functional dairy products.

2. Probiotics: Strains, health benefits, and the importance of their encapsulation

The term *probiotics* ie defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Sandoval Mosqueda et al. 2019). This term generally refers to microorganisms such as lactic acid bacteria (mainly *Bifidobacterium* spp., *Lactobacillus* spp., and *Enterococcus spp.*), and some yeasts such as *Saccharomyces* spp., which are mostly known for their health-promoting activities, besides their techno-functional features in food science (Doron and Snydman 2015). *Lactobacillus* spp. that are mostly used as probiotics are *L. plantarum*, *L. acidophilus*, *L. fermentum*, *L. casei*, *L. gastricus*, *L. bulgaricus*, *L. rhamnosus*, *L. reuteri*, *L. kefiri*. Among all *Bifidobacterium* spp., *B. animalis*, *B. bifidum*, *B. breve*, *B. longum*, *B. lactis*, and *B. infantis* have been mostly incorporated into functional food formulations. The use of yeasts like *Saccharomyces* as probiotics is still limited. Two main strains including *S. cerevisiae* and *S. boulardii* have received more consideration as probiotics for human consumptions. Studies revealed that *S. boulardii* is genetically close to *S. cerevisiae*, either physiologically or metabolically; however, in terms of tolerability to temperature and acidic stresses and also growth yield, they have a very different behavior, which is an important feature for a microorganism to be accepted as a probiotic (Fietto et al. 2004). Therefore, *S. boulardii*, which has been used for GIT disorders, is the only commercialized yeast for humans (Suvarna et al. 2018).

Probiotics are considered as one of the health-promoting live biological systems that can sit on the daily diet of people if properly used in food products (Mokhtari, Jafari, and Khomeiri 2019). These microorganisms could provide numerous health benefits such as enhancing intestinal microflora, lactose intolerance amelioration, immunomodulation, cholesterol-reducing action, mutagenicity-reducing effect, alleviating constipation, vaginitis relief, lowering GIT diseases, and anticancer activities (specifically, in the case of colon cancer) (Watson and Preedy 2010). However, they are facing some challenges through the GIT because of enzymatic reactions (proteases), pH variations, and bile salts, which negatively affect their bioavailability. Moreover, probiotics are facing some crucial situations when designing probiotic-based functional foods; e.g., relative humidity (RH), water activity (a_w), temperature, and pH, all of which are crucial for probiotic survivability and long-term storability. Therefore, all these situations have to be considered carefully before formulating functional foods to avoid any significant loss of probiotics. A possible solution to solve these challenges in probiotic-based functional foods is the encapsulation of probiotics. Encapsulation can also enhance disease treatment activities of probiotics, which can be used in production of probiotic-based medicinal foods. In this case, it is reported that encapsulation of *L. fermentum* strain UCO-979C in an alginate-xanthan gum matrix can increase its inhibitory effects on *Helicobacter pylori*, a principle pathogenic risk factor for gastric carcinoma (Vega-

Table 1. A summary on the encapsulation of main probiotics and their incorporation into synbiotic/functional dairy foods.

Probiotics	Encapsulation materials	Encapsulation technique	Key outcomes	References
L. plantarum	Sodium alginate and gum Arabic	Extrusion	High viability at simulated GIT* conditions	Sandoval Mosqueda et al. (2019)
L. plantarum	Ca-alginate/ cellulose composite/ cryoprotectants	Freezing thawing	160 days storability at 4 °C	Li et al. (2019)
L. plantarum	Whey protein isolate (WPI) microgels	High internal phase emulsions (HIPEs)	Increased viability after pasteurization	Su et al. (2018)
L. acidophilus	Alginate	External ionic gelation	Increased viability for 30 days (at 25 °C) and 60 days (at −18 °C)	Poletto, Fonseca et al. (2019)
L. acidophilus	Whey protein and pectin	External ionic gelation	Increased viability for 105 days at −18 °C	de Menezes et al. (2019)
L. fermentum	Whey protein-maltodextrin matrices	Refractance Window drying	Increased viability after 2460s window drying	Aragon-Rojas et al. (2019)
L. casei	Whey protein	Electro-encapsulation	Higher viability at simulated GIT conditions	Alehosseini et al. (2019)
L. gastricus	Skimmed milk and alginate	Extrusion	• High viability at simulated GIT conditions • 5-fold higher survivability after 21 days at refrigerator	Singh et al. (2019)
L. acidophilus	Carrageenan	Spray drying	Kappa-iota carrageenan mixture provided high viability	Nunes et al. (2018)
L. acidophilus	Gum Arabic, maltodextrin, Tween 80, and glycerol	Spray drying	120 days storability at high temperatures and high viability at simulated GIT conditions	Silva, Tulini et al. (2018)
L. acidophilus	Alginate/ alginate-shellac and sunflower	Extrusion and co-extrusion	Co-extrusion showed higher storability after 60 days of storage at 25 °C and high viability at stimulated GI	Vega-Sagardía et al. (2018)
L. acidophilus	Milk-non-fat with xanthan gum	Spray drying	Survivability of 98% after 15 weeks storage at 30 °C	Tantratian, Wattanaprasert, and Suknaisilp (2018)
L. bulgaricus	Alginate-milk microspheres	Extrusion	• Improved tolerance at pH= 2.0 and 2.5, high concentration (1.0% and 2.0%) of bile salt and 30 days storage at 4 °C • No changes in viability after 120 min incubation in SGF* at pH 2.5	Shi, Li, Li et al. (2013)
L. Rhamnosus	Milk proteins	Emulsification method	Mixture of casein and denatured whey showed best survivability (99%) at GIT	Burgain et al. (2013)
L. plantarum	Alginate and pectin beads	Extrusion	Improved cell survivability in pomegranate and cranberry juices	Nualkaekul et al. (2013)
L. acidophilus	Solid lipid microparticles	Spray chilling technology	• Improved cell survivability in SGF and SIF* • High storability for 120 days at -18 °C	Okuro et al. (2013)
L. bulgaricus	Double layered carrageenan-locust bean gum coated with milk	Extrusion	No significant changes in viability after 2 h incubation in SGF with pH= 2.5	Shi, Li, Zhang et al. (2013)
L. plantarum	kappa-carrageenan	Emulsification, freeze-drying, and extrusion	• Freeze-drying showed significantly higher tolerance and survivability at acidity of pH= 2 • No enhancement for the resistance of the probiotic to bile salt	Tee et al. (2014)
L. reuteri	Chitosan-calcium-alginate	Extrusion	Retained antagonistic activity toward *Listeria monocytogenes* after incubation at simulated GIT conditions	Huang et al. (2015)
L. plantarum	Na-alginate, glycerol, xanthan gum, short chain artichoke inulin	Extrusion and internal emulsion microencapsulation	Extrusion showed better survivability in GIT conditions for 30 days	Valero-Cases and Frutos (2015)
L. Rhamnosus	Maltodextrin and gum Arabic	Spray and freeze-drying	High stress tolerance and survivability	Mishra and Athmaselvi (2016)

(*continued*)

Table 1. Continued.

Probiotics	Encapsulation materials	Encapsulation technique	Key outcomes	References
L. casei	Pea protein isolate-alginate hydrogel matrix	Extrusion	High survivability after 84 days of storage at −15 °C but weak buffering effects against acidic gastric conditions	Xu et al. (2016)
L. plantarum	Skim milk coated inulin-alginate beads	Extrusion	No change in viability after 2 h incubation in SGF	Wang et al. (2016)
L. plantarum	Cellulose microgels	Freezing thawing/ extrusion	High viability after 360 min in SIF	Li, Luo et al. (2016)
L. Rhamnosus	Pectin hydrogel beads, glucose, and calcium chloride	Dispersion	• Increased tolerance in the acid conditions • Protected from protease digestion • Improved shelf time at the ambient conditions • Preventing intestinal inflammation	Li, Zhang et al. (2016)
L. plantarum	Maize starch	Freezing thawing/ extrusion	• High viable cells after freeze-drying • Higher total probiotic numbers after exposure to acid (pH = 2.0, 1 h), bile salt (3% w/v, 4 h) and heat (60 °C, 15 min)	Li, Ho et al. (2016)
L. acidophilus	Chitosan	Ionic gelation and electrostatic extrusion	• Good protection against acid injury • High viability in SGF conditions	Kim et al. (2017)
L. kefiri	Alginate microbeads with carboxy methyl cellulose (CMC)	Double aerosol technique	Protective effects against the gastric environment using both SGF pH= 1.2 (fasted state) and pH= 2.2 (feed state)	Demitri et al. (2017)
B. longum	Poly-(vinylpyrrolidone)-poly-(vinylacetate-co-crotonic acid) (PVP:PVAc-CA)	Particles from Gas-saturated Solution (PGSS) system	• Higher viability using WPC at 25 °C, and high humidity condition	Lopez-Rubio et al. (2012)
B. lactis	whey protein concentrate (WPC) and pullulan	Electrospinning	High viability for 40 days at room temperature and 130 days at refrigeration temperature	Lopez-Rubio et al. (2009)
B. animalis	Poly(vinyl alcohol) (PVOH)	Electrospinning	High viabilities for 28 days in yogurt stored at 4 °C	Picot and Lacroix (2004)
B. breve	Milk fat and/or denatured whey proteins	Emulsion and/or spray-drying	• Higher survivability in yogurt during 28 days in refrigerator • Enhanced effect against *Salmonella*	Yasmin et al. (2018)
B. infantis	Low-methoxylated pectin and alginate	Extrusion, vibrating, and electrostatic methods	Higher survivability for 28 days storage at 4 °C	Jasińska et al. (2018)
S. boulardii	Alginate/ chitosan	Extrusion	Alginate microspheres showed high viability after 120 min storage at pH= 1.1	Graff et al. (2008)
S. boulardii	Gelatin, WPC, modified starch, maltodextrin, pea protein isolate and gum Arabic	Spray drying	• Highest yield with WPC and gum Arabic • No changes in survivability with all wall materials • Highest survivability in SGF achieved with gum Arabic • High spray drying temperatures provided better survivability	Arslan et al. (2015)
S. boulardii	Alginate, inulin, and xanthan gum	Emulsification/ immobilization	High ability to grow and survivability in berry juice for 4 weeks of storage at 4 °C	Fratianni et al. (2014)

*GIT: gastrointestinal tract, SGF: simulated gastric fluid, SIF: simulated intestine fluid.

Sagardía et al. 2018). As summarized in Table 1, numerous attempts have been done on the encapsulation of probiotics and their incorporation in functional dairy foods during recent years.

The importance of encapsulation systems in probiotic-based functional foods can be mainly attributed to their probiotic-protecting functions against food matrices and

interactions with food elements, food processing conditions, and GIT fluids. For instance, an encapsulation system based on the extrusion of alginate-milk microspheres, was used to improve the survivability of *L. bulgaricus* and its resistance against adverse environmental situations such as acidic conditions (i.e., pH = 2.0 and 2.5), high concentration of bile salt (i.e., 1.0-2.0%) and long-term storage of 30 days (Shi, Li, Li et al. 2013). Release profile of encapsulated *L. bulgaricus* in simulated intestine fluid (SIF) exhibited that the encapsulation improved its tolerability against the aforementioned situations. Its viability in encapsulated form did not show significant changes after 120 min incubation in simulated gastric fluid (SGF, pH = 2.5) and remained more than 8 log $CFU.g^{-1}$. The viability of encapsulated form of *L. bulgaricus* in 1% bile salt solution showed a reduction from 9.98 log $CFU.g^{-1}$ to 9.24 and 8.48 log $CFU.g^{-1}$ microspheres after incubation for 1 and 2 h, respectively (Shi, Li, Li et al. 2013). In the 2% bile salt solution, these reductions were 1.3 and 2.1 log $CFU.g^{-1}$ microspheres after 1 and 2 h incubation, respectively. It was also stated that full survivability of encapsulated *L. bulgaricus* was achieved after 30 days of storage at 4 °C. Therefore, the encapsulation of *L. bulgaricus* in alginate-milk microspheres could be an efficient technique against adverse environmental situations (Shi, Li, Li et al. 2013). Moreover, it has been reported that the regular consumption of probiotic-based functional/synbiotic foods should be ~100 g per day (~10^9 viable cells), which could provide a daily dose of 10^6–10^8 $CFU.mL^{-1}$/$CFU.g^{-1}$ (Hill et al. 2014). Therefore, the protection activity of encapsulation systems should be able to provide these minimum concentrations of the viable probiotic cells into the colon. In fact, encapsulation systems could potentially reduce regular daily consumption of such functional foods with the same daily delivery of viable probiotic cells, if they are well-engineered for evading probiotic-losing situations.

3. Prebiotics: Types and health benefits

The term prebiotics was first introduced by Gibson and Roberfroid (1995) and was defined as "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon and thus attempt to improve host health". The foremost function of these materials is to profoundly boost the existing metabolic mechanism inside the colon (Coussement 1996). It has been well-documented that prebiotics are often comparatively short-chained and low-molecular-weight carbohydrates that can penetrate easily through the large intestine (i.e., colon) and are able to act as substrates for the endogenous colonic bacterial population. Generally, they are obtained from plant polysaccharides, for instance, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), isomalto-oligosaccharides (IMO), xylo-oligosaccharides (XOS), as well as the cell wall polysaccharides originated from different parts of plants. In general, the beneficial prebiotics are classified into three main leading categories; oligosaccharides, polyol (sugar alcohols), and soluble fibers, all of which exhibit paramount significant health-promoting benefits including their effects against acute gastroenteritis, constipation, diabetics, various types of cancer, and immune diseases (Ashwini et al. 2019; Yahfoufi et al. 2018). It is known that the consumers who regularly take a reasonable concentration of prebiotics from numerous categories of vegetables (e.g., garlic, onion, asparagus, chicory, leeks, Jerusalem artichokes, etc.) and fruits (e.g., bananas, berries, tomatoes, mangoes, dragon fruits, etc.), substantially benefit in terms of various health effects (Crittenden and Payne 2008; Khuituan et al. 2019). Table 2 summarizes the recent information on the classification, sources, and health benefits of prebiotics, as well as their health-promoting benefits.

Prebiotics partake a unique antagonistic effect against pathogenic microorganisms by restraining their proliferation. Thus, they have a strong potential to boost the metabolism, survival, growth, and meaningful health-promoting activities of probiotics (as the beneficial bacteria) in the digestive surroundings (Sekhon and Jairath 2010). Thanks to their excellent bioactivities, prebiotics are being used as energy sources, particularly, for those bacteria present inside the colon. Several investigations have successfully reported the diverse features of prebiotics in food applications including encapsulation technology (Dawood et al. 2017; Ganguly et al. 2013; Song et al. 2014). Application of prebiotics as active ingredients has become a recent trend for enhancing the capability and sustainability of probiotic live organisms through the co-encapsulation process. It has been documented that the application of prebiotics for entrapment and safe delivery of probiotics, as well as the co-delivery of prebiotics and probiotics toward the colon, are recognized as two of the most effective delivery approaches. This will be further elaborated in Section 5.

4. Co-encapsulation of probiotics and prebiotics (PRO-PRE co-encapsulation)

As it was discussed earlier, there has been a number of approaches (e.g. immobilization and encapsulation) adopted as physical barriers against adverse conditions for improving the survival of probiotics in both food and GIT already, yet only some limited success has been achieved (Gardiner et al. 2002; O'riordan et al. 2001; Prevost, Divies, and Rousseau 1985; Ying et al. 2007). Encapsulation of live organisms such as probiotics is a comparatively new approach which is currently receiving a lot of attention and interest in both academia and industry. This approach is based on the entrapment of the bioactive organisms (i.e., bacteria) within a polymeric material, in order to protect the organism from undesirable environmental conditions, with no deleterious effects on the physiological properties of the live bacteria (Chang 1999). Among several encapsulation and entrapment techniques suggested for oral delivery of probiotics, a successful system would only meet the requirement if it can protect the bacteria considering different substantial parameters such as type of the bacteria and the living conditions, carrier size, wall material (and its safety), carrier stability, polymer coating, mass transfer, and mechanism of release in

Table 2. Classification, sources, and health benefits of prebiotics.

Classification	Prebiotics types	Sources	Health benefits	References
Oligosaccharides	Galacto-oligosaccharides	Human milk, cow milk	• Beneficial effect on LDL-cholesterol and total cholesterol level of infants. • Relapse of Clostridium difficile associated with diarrhea.	Alander et al. (2001); Alliet et al. (2007)
	Raffinose oligosaccharides	Chickpeas, seeds of legumes, mustard, peas, and mallow composite	• Strong anti-constipation potential. • Stimulation of the growth of bifidobacteria and lactobacilli. • Decreasing the growth of Clostridium perfringens in mice as well as in human.	Adamberg et al. (2018); Johansen, Glitsø, and Bach Knudsen (1996)
	Fructo-oligosaccharides (FOS)	Sugar beet, wheat, tomato, garlic, banana, onion, asparagus, honey, rye	• Simulation of the growth of lactobacilli and bifidobacteria. • Increasing short-chain fatty acids levels in the large intestine. • Decreasing the damage of ulcerative colitis.	Lewis et al. (2005); Sangeetha, Ramesh, and Prapulla (2005)
	Xylo-oligosaccharides	Wheat bran, fruits, honey, bamboo shoots, milk	• Improving the bifidogenic potential. • Enhancement of the level of short chain fatty acids in the feces.	Vazquez et al. (2000)
	Inulins	Garlic, wheat, chicory, onion, artichoke	• Lessening distal colitis. • Stimulation of intestinal Ca and Mg absorption.	Demigné et al. (2008)
	Isomalto-oligosaccharides	Sauce, miso, sake, starchy food, soy	• Boosting the general performance of weaned pigs through strengthening immune function and intestinal health.	Kaneko et al. (1994); Wu et al. (2017)
	Arabinoxylo oligosaccharides	Wheat bran	• Improvement of the bifidogenic effects. • Decrease of the body weight and fat mass, associated with attenuated plasma leptin levels in mice.	Eeckhaut et al. (2008); Neyrinck et al. (2018)
Polyols (sugar alcohols)	Lactulose, lactilol, sorbitol, mannitol, and xylitol	Lactose (milk)	• Promotion of the beneficial cecal fermentation in rats.	Juśkiewicz, Klewicki, and Zduńczyk (2006)
Fibers	Pectins, inulin type fructans, cellulose, waxes, dextrins, and lignins	Potatoes, grains, fruits, legumes, vegetables	• Reduction of the intestinal transit time and upsurge stools bulk. • Boosting the fermentation by colonic microbiota. • Decrease of the total and/or LDL cholesterol levels. • Minimizing the post-prandial blood glucose as well as insulin levels.	Delzenne et al. (2020)

the gut. Most importantly, such encapsulation techniques must be able to deliver viable bacteria to the gut without negatively affecting their physiological properties.

One of the most important reasons for the low success rate for protection (encapsulation) of probiotics is their low viability inside the vesicle (capsule) environment. Thus, among the different techniques used for the immobilization of prebiotic bacteria, co-encapsulation (co-entrapment/co-delivery) of these bacteria with prebiotics has promised more success in terms of viability and stability of these living microorganisms. Some researchers have suggested that prebiotics may improve the survival of probiotics during passage through the upper part of the GIT, and accordingly, enhance their biological effects in the large intestine (Fooks, Fuller, and Gibson 1999; Roberfroid 2000). Iyer and Kailasapathy (2005) studied the addition of a resistant starch (as the co-encapsulant) with chitosan on the viability of protected probiotics (*Lactobacillus acidophilus* CSCC 2400 or CSCC 2409). It was reported that Hi-maize could significantly improve the survival of the encapsulated bacteria either under the in vitro acidic conditions or in yogurt (Iyer and Kailasapathy 2005).

There are several technologies reported for PRO-PRE co-encapsulation. These include high-temperature processes (e.g., spray drying) and low-temperature processes (e.g., spray chilling, freeze-drying, emulsification, extrusion, coacervation, gelation, and electro-hydrodynamic atomization). In this section, co-encapsulation technologies, the corresponding conditions, and the materials used for such co-encapsulation techniques are discussed.

4.1. Spray drying

One of the widely-used economical technologies for PRO-PRE co-encapsulation is spray drying. In this technology, the bioactive ingredients (i.e., prebiotic and probiotic) are dispersed in the solution containing the carrier and then the dispersion is injected to the atomizer in a heated-air chamber. This technology is based on the rapid removal of solvent from the dispersion in the heated-air chamber, after which the dried porous spherical particles containing the bioactive ingredients incorporated in wall material are obtained. The encapsulation efficiency and size of the manufactured dried particles depend on different factors such as spray drying conditions (e.g., flow rate, atomizer type, humidity of the chamber, inlet and outlet temperatures of the chamber) and dispersion properties (e.g., the properties of bioactive ingredients as well as those of the carrier/wall material, solution viscosity, and so on) (Jafari et al. 2008). This drying method is a fast process (the material is exposed

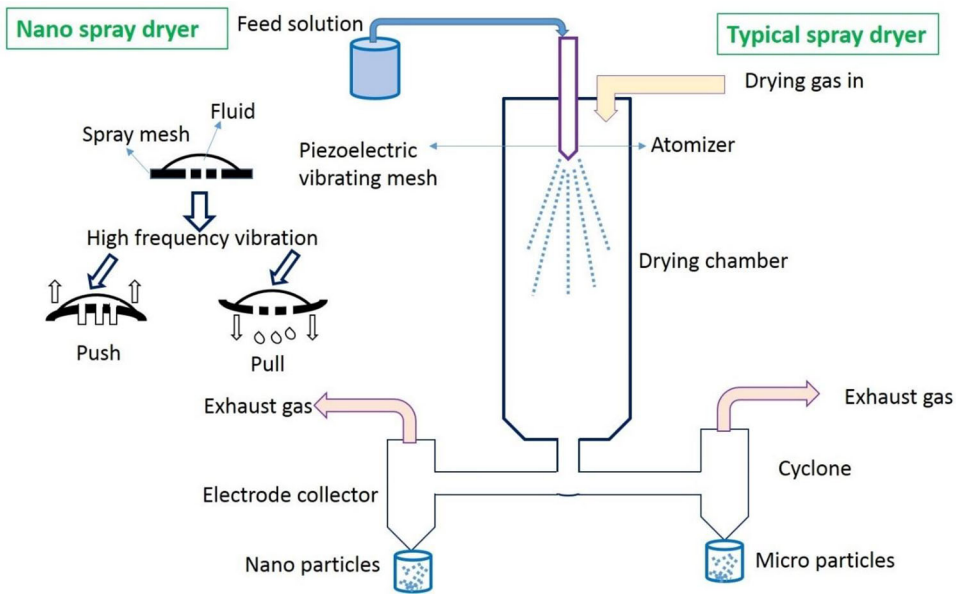

Figure 1. Schematic representation of a typical spray dryer and nanospray dryer. Modified from Arpagaus et al. (2018) and Assadpour & Jafari (2019).

to the high temperature for only a few seconds); therefore, heat-sensitive ingredients such as probiotics can be efficiently encapsulated using spray drying (Di Battista et al. 2017). However, due to the high temperature applied in the air chamber, the use of thermostable carriers is recommended while the encapsulation of probiotics is practiced using this process.

Recently, the studies about co-encapsulation of prebiotics and probiotic by spray drying have been increasing and the stability and viability of probiotics have been improved significantly in all cases (Colín-Cruz et al. 2019; Pinto et al. 2019; Tao et al. 2019). As an example, Tao et al. (2019) studied the co-encapsulation of *Lactobacillus paracasei* Lpc-37 within different polysaccharides by spray drying and indicated that the addition of polysaccharides enhanced the cell viability during storage and decreased the viability loss of probiotics lower than 0.3 log CFU/g after 8 weeks in refrigerated storage (Tao et al. 2019). Moreover, the co-encapsulation of probiotic bacteria and bioactive compounds from blackberry juice using different biopolymers (gum Arabic, maltodextrin and whey protein concentrate) by spray drying maintained cell viability higher than 6 log CFU/g after two weeks at 20 °C (Colín-Cruz et al. 2019).

In terms of the size of particles that are produced due to the spray drying process, there are two types of spray dryers; a) typical spray dryer that produces particles in micron size, and b) nano spray dryer that produces nano-scale particles. Typical spray dryers use atomizer and cyclone collectors in their structure while nano spray dryers use a piezoelectric vibrating mesh, where they contain electrode collectors instead of cyclone collectors, as shown in Figure 1 (Arpagaus et al. 2018; Assadpour and Jafari 2019). The piezoelectric vibrating mesh works with ultrasonic frequency and causes upward and downward vibrating and converts the fluid into nanoscale particles (Assadpour and Jafari 2019; Fathi, Martin, and McClements 2014). The main advantage of the nanospray drying process, in comparison to typical spray drying, is the production of nanoscale particles with higher bioavailability that are suitable for delivery of bioactive ingredients (Arpagaus et al. 2018). Nevertheless, nanospray drying cannot be used for PRO-PRE co-encapsulation due to the large size of probiotic cells.

4.2. Spray chilling

Spray chilling, also known as spray cooling and spray congealing, is very similar to spray drying with the difference that the dispersion matrix of the bioactive ingredient(s) and carrier is atomized in a cold air chamber or liquid nitrogen (the temperature of the chamber is below the melting point of the carrier and bioactive ingredients) (Ilić et al. 2009). Okuro et al. (2013) used spray chilling technology for co-encapsulation of *Lactobacillus acidophilus* with prebiotics (inulin or polydextrose) to improve the stability of *Lactobacillus acidophilus* against gastric and intestinal fluids. Due to the use of low temperatures, this technology is cost-effective and therefore, is easy to scale up. However, in comparison with spray drying, the encapsulation efficiency is lower.

4.3. Freeze-drying

Freeze-drying is used to produce probiotic powders and can also be used for the PRO-PRE co-encapsulation. This technology is based on the sublimation of frozen solution or dispersion of probiotics, prebiotics, and the carrier materials under high-vacuum conditions. Because of the low temperature that is used in freeze-drying, the survival rate of probiotic bacteria is higher in comparison with the spray drying method (Wang, Yu, and Chou 2004). However, the formation of extracellular ice crystals, which are formed during the freezing process, results in some damage to the probiotic cell wall. This problem can be tackled by interacting the bound water of probiotics with some cryoprotectants, in order to stabilize the cell wall and prevent the cell wall damage. Cryoprotectants are divided into two

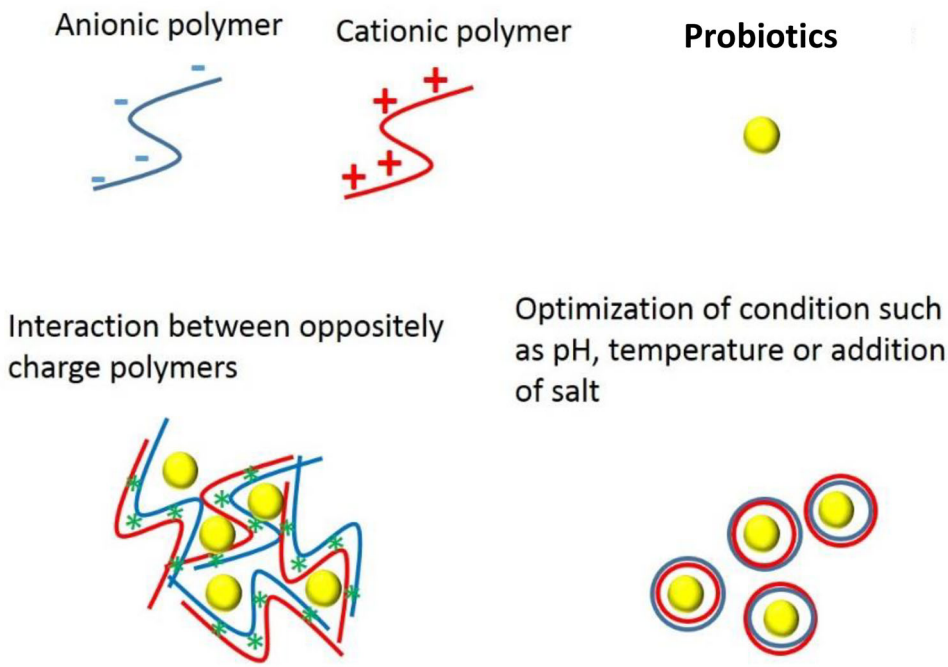

Figure 2. Schematic representation of complex coacervation for co-encapsulation of probiotics and prebiotics.

groups of low and high molecular weight materials. Low-molecular-weight protectants are mainly different sugars such as glucose, trehalose, lactose, sorbitol, and mannose, among which, trehalose is more effective than others. Low-molecular-weight sugars can react with the phospholipids of the cell wall of probiotics and prevent cell damage (Santivarangkna, Higl, and Foerst 2008). High-molecular-weight protectants, on the other hands, are mainly polysaccharides and proteins (e.g., alginate, whey proteins, gelatin, xanthan gum, maltodextrin, etc.), which are adsorbed on the surface of probiotics and form a viscous layer that can prevent the growth of ice crystals (Carvalho et al. 2004; Liu et al. 2019).

Freeze-drying can be done in two forms; direct freeze-drying and indirect freeze-drying. For the first method, the probiotic bacteria can be mixed with the cryoprotectant solution and then directly freeze-dried. During indirect freeze-drying, the probiotic bacteria are first maintained in the polymer matrix to form probiotic beads and then are freeze-dried for the removal of water. There are four patterns for indirect freeze-drying, including extrusion, impinging aerosol technique, enzyme gelation methods, and emulsion technique, which are extensively explained by Liu et al. (2019).

Poletto, Fonseca et al. (2019) investigated the viability of probiotics after co-encapsulation with different prebiotic agents (e.g., rice bran, inulin, and Hi-maize) by indirect freeze-drying (external ionic gelation method followed by freeze-drying). Their results showed that prebiotics had a protective effect for probiotics against the gastrointestinal conditions (Poletto, Fonseca et al. 2019).

4.4. Emulsification

Emulsification is one of the low-temperature encapsulation technologies that can be used for PRO-PRE co-encapsulation. This technique is easy to scale up and enhances the survival rate of the probiotics significantly. The main defect of this procedure is the large range of the size and shape of the obtained carriers, even though their size can be changed by variation of the water/oil ratio and agitation speed (Kasipathy Kailasapathy 2009). Generally, emulsions contain at least one immiscible phase dispersed into another continuous phase with a surfactant or emulsifier (Rezaei, Fathi, and Jafari 2019). Vos and Poortinga (2011) introduced a method for manufacturing stable W/O/W emulsion formulations which can be useful for PRO-PRE co-encapsulation. In addition, it is advantageous in the term that masks the flavors of the aqueous components of the inner water phase.

There are three methods of emulsification for encapsulation of probiotic cells: a) emulsification and ionic gelation; b) emulsification and enzymatic gelation; c) emulsification and interfacial polymerization (Burgain et al. 2011).

a. Emulsification and ionic gelation: in brief, in this method, the discontinuous phase (the probiotic cells with prebiotic and polymer suspension) interacts with the continuous phase (e.g., vegetable oil) and emulsifier to form a water/oil emulsion. After this, a solidifying agent such as calcium chloride is needed to insolubilize the water-soluble polymer and form gel particles. The obtained particles can be coated with a second polymer to enhance the protection of the cells in the GIT conditions (Gaudreau et al. 2016). Gaudreau et al. (2016) investigated the co-encapsulation of probiotic cells with green tea extract using an emulsification/internal gelation process. Green tea extract showed positive effects on the viability of probiotic cells in food products and gastrointestinal conditions (Gaudreau et al. 2016).

b. Emulsification and enzymatic gelation: in some countries, the use of special hydrocolloids such as xanthan, gellan-gum, alginate, and κ-carrageenan is not allowed in dairy products (the main synbiotic/functional foods containing encapsulated probiotics). To overcome this limitation, milk proteins are used for the encapsulation of probiotics in dairy products using enzymatically-induced gelation (e.g., rennet-gelation) (Heidebach, Först, and Kulozik 2009). Milk proteins have high gelation properties and can produce water-insoluble particles after enzymatic gelation (Yousefi and Jafari 2019). These materials can be used for the fabrication of an emulsion containing both probiotics and prebiotics, after which the enzymatic gelation can be carried out. For enzymatic gelation, where a polymer such as chitosan is required, the pH is increased from a low pH (where chitosan has a good solubility) to an alkaline high pH to induce the gelation mechanism.
c. Emulsification and interfacial polymerization: in this method, an emulsion containing probiotic cells as discontinuous phase and an organic solvent as a continuous phase is formed and then a biocompatible agent, which is soluble in the continuous phase, is added to the emulsion to induce the interfacial polymerization. The probiotic cells are encapsulated in a strong membrane and their viability is enhanced (Jennifer Burgain et al. 2011).

4.5. Extrusion

Extrusion can be used for co-encapsulation of probiotics and prebiotics to protect and enhance the viability of probiotic cells. Extrusion is a simple and low-cost method that is done in gentle condition and therefore is suitable for encapsulation of probiotic cells. In this method, at first a hydrocolloid solution of probiotic and prebiotic is prepared and then is injected into a hardening solution using a syringe nozzle. The obtained beads are finally dried. Alginate is the most commonly used material in this method and a solution containing divalent cations such as $CaCl_2$ solution is used as hardening solution (Liu et al. 2019).

Phoem et al. (2019) encapsulated *Lactobacillus plantarum TISTR1465* with sodium alginate and *Eleutherine americana* oligosaccharide extract as prebiotic using extrusion method. The viability of encapsulated probiotic cells was higher than free cells at weeks 2 and 4. The acidification of encapsulated probiotic cells was lower than free cells during refrigerated storage and therefore can be used as food additive in yoghurt (Phoem et al. 2019).

4.6. Coacervation

Coacervation is based on the electrostatic interactions between oppositely-charged biopolymers (Ghasemi et al. 2017). There are two types of coacervation; simple coacervation and complex coacervation. In simple coacervation, the electrostatic interaction occurs between a charged bioactive compound (prebiotic or probiotic) and an oppositely-charged biopolymer as the carrier. In complex coacervation, the electrostatic interaction is between two biopolymers with opposite charges as the carrier, and the bioactive ingredients (i.e., prebiotic and probiotic) are encapsulated into the carrier (Fathi, Martin, and McClements 2014), as shown in Figure 2. Drying process (e.g., oven drying, spray drying, freeze-drying, or vacuum drying) may be done after the formation of the complex coacervates to obtain powder capsules. Spray drying and freeze-drying have more applications in comparison to other drying techniques (Timilsena et al. 2019).

The surface charge of the carrier material has an important effect on the functional properties of the produced capsules. This depends on the pH, polymers concentration, molecular weight of biopolymers, ionic strength, the ratio of biopolymers, the degree of homogenization, and temperature. These parameters should be optimized to obtain suitable capsules for encapsulation of probiotics. Protein and polysaccharide pairs with opposite charges are usually used for formation of complex coacervation (Ghasemi et al. 2018). Frequently-used proteins for the coacervation method are gelatin, whey protein, albumin, β-lactoglobulin, and various plant proteins (e.g., those from soy and pea). The most-used polysaccharides are chitosan, gum Arabic, alginate, pectin, carrageenan, xanthan gum, and carboxymethyl cellulose (Eratte et al. 2018). Gelatin-gum Arabic is the most usable complex coacervation, because the charge density of gelatin can be changed with variation of pH. In addition, the colloidal structures of gelatin and gum Arabic makes them suitable for maintaining sufficient charges on their chains to avoid precipitation (Ducel et al. 2004). Whey protein isolate–gum Arabic complex coacervates were used for co-encapsulation of probiotic bacteria and omega-3 fatty acids. The viability of probiotic bacteria increased significantly in the potent of omega-3 fatty acids (Eratte et al. 2015). Whey protein isolate–gum arabic complex coacervates were used for co-encapsulation of probiotic bacteria and Omega-3 fatty acids. The viability of probiotic bacteria increased significantly in the potent of omega-3 fatty acids (Eratte et al. 2015).

4.7. Gelation

Probiotics and prebiotics can be co-encapsulated within different polymers such as alginate, sodium carboxymethyl cellulose, and carrageenan using external or internal gelation methods. In the external gelation for alginate, the bioactives are mixed with alginate solution and then form a water/oil emulsion by suspending in an oil containing emulsifier. After adding $CaCl_2$ solution, the emulsion is broken, and alginate beads are obtained (similar to Section 4.4). In the case of internal gelation, first, the alginate solution containing $CaCO_3$ is prepared and then water/oil emulsion is prepared. Alginate gel is obtained after the addition of an organic acid to the emulsion and releasing of calcium ions (Liu et al. 2019). Serrano-Casas et al. (2017) used alginate ionotropic gel matrix for co-encapsulation of lactic acid bacteria and prebiotics (apple marc, cactus pear peel flour, and inulin) and enhanced the resistance of lactic acid bacteria to the acidic conditions (Serrano-Casas et al. 2017). Serrano-Casas et al. (2017) used alginate ionotropic gel matrix for co-encapsulation of lactic

acid bacteria and prebiotics (apple marc, cactus pear peel flour, and inulin) and enhanced the resistance of lactic acid bacteria to the acidic conditions (Serrano-Casas et al. 2017). In the case of gelation process for carrageenan, it starts by dissolving carrageenan at 60-90 °C and then the bioactive ingredients are added to the solution at 40-45 °C. Gelation takes place by cooling to room temperature to form the beads. K^+ is added as a cross-linker to stabilize the gel structure (Miles, Morris, and Carroll 1984). For sodium carboxymethyl cellulose, Al^{3+} is used as a cross-linker (Chitprasert, Sudsai, and Rodklongtan 2012).

Hydrogels that have hydrophilic structure and organogels that possess hydrophobic structure are three-dimensional porous structures that are produced by chemical (usually, between monomer or polymer precursors) or physical (usually, between polymer precursor) cross-linking (Rezaei, Fathi, and Jafari 2019). Different polysaccharides such as alginate, pectin, chitosan, cellulose, cyclodextrin, starch, dextran, hyaluronic acid, heparin, and pullulan and proteins such as milk proteins, whey protein, and soy protein can be used to produce organogels or hydrogels (Abaee, Mohammadian, and Jafari 2017; Debele, Mekuria, and Tsai 2016).

4.8. Electro-hydrodynamic processes

The electro-hydrodynamic process has been recently attracted much attention for the encapsulation of various bioactives and heat-sensitive compounds (Khoshnoudi-Nia, Sharif, and Jafari 2020). This process includes electrospraying (also known as electro-hydrodynamic atomization) and electrospinning technologies that are simple, efficient, cost-effective, and scalable to produce particles and fibers (Hoseyni et al. 2020). Electro-hydrodynamic process is based on applying an electrostatic force to spray a polymer solution into micro or nanodroplets that are known as electrospraying (Soleimanifar, Jafari, and Assadpour 2020) or to spin a polymer solution into ultrafine fibers that is known as electrospinning (Rostami et al. 2019). Different parameters such as process parameters (e.g., applied voltage, flow rate of the polymer solution, the distance between needle and collector), solution parameters (e.g., viscosity, concentration, surface tension, polymer molecular weight, solution conductivity), and ambient conditions (e.g., humidity and temperature) have substantial effects on the properties of obtained fibers and/or particles (Rezaei, Nasirpour, and Fathi 2015).

There are different electrospinning methods to produce fibers; blend electrospinning, emulsion electrospinning and coaxial electrospinning. In the case of blend electrospinning, the bioactive ingredient is dissolved or dispersed in the polymer solution. The solution is pumped to the needle and after applying the high voltage, a Tylor cone will form at the tip of the needle. After stretching the droplets, ultrafine fibers will form and be thrown out on the collector. The bioactive ingredient may distribute throughout or on the surface of the fibers. In coaxial electrospinning, a concentric double needle is applied in electrospinning set up and core-sell fibers produce. In this process, the separate injection of the bioactive compound and polymer solution result in more protection of bioactive compound. In emulsion electrospinning, the bioactive compound is emulsified into the polymer solution using a surfactant to form a water in oil (W/O) emulsion or oil in water (O/W) emulsion. In this method, the bioactive compound may distribute throughout the fibers like blend electrospinning or encapsulate in core-sell structure of fibers similar to coaxial electrospinning (Rezaei, Fathi, and Jafari 2019). Lastly, in the case of electrospraying, the process is similar to electrospinning and in both of them, a high voltage is needed to form a jet flow of the solution. However, in this case (i.e., electrospraying), the jet flow breaks to ultrafine droplets while in electrospinning the jet flow turns to ultrafine fibers. Usually, the solution used in electrospinning has a higher viscosity than the solution used in electrospraying (Rezaei, Nasirpour, and Fathi 2015).

Zaeim et al. (2019) used electro-hydrodynamic atomization for co-encapsulation of probiotics (*Lactobacillus plantarum* and *Bifidobacterium lactis*) and prebiotics (inulin or resistant starch) in Ca-alginate/chitosan microcapsules. Their results indicated that the stability and resistance of the probiotics in gastrointestinal conditions enhanced after co-encapsulation with prebiotics in Ca-alginate/chitosan microcapsules using electro-hydrodynamic atomization (Zaeim et al. 2019). In a recent study (Alehosseini et al. 2019), *Lactobacillus casei* was co-encapsulated with high-resistant whey protein through both methods of electrohydrodynamic atomization and freeze-drying technique (as the control method). The findings revealed a higher encapsulation efficiency as well as a greater viability for the probiotic bacteria co-encapsulated using electrospraying, compared to the values of the freeze drying co-encapsulation. In addition, the electrosprayed capsules showed better protection during the storage (120 days), in contrast to freeze-dried structures (Ali Alehosseini et al. 2019).

5. Various wall materials (carriers) for co-encapsulation purposes

As it has been well-described in several previous reports (Rehman, Tong et al. 2019; Singh et al. 2018; Zaeim et al. 2019), the biocompatible and food-grade wall materials are those shells (also known as coatings, carriers, and/or membranes) or a mix of these materials that can act as barriers for the entrapment of bioactive ingredients and their protection against harsh environments (i.e., food and digestive tract). The availability of suitable edible delivery systems can improve the effectiveness of probiotics at improving the human health and wellbeing, resulting from the creation of a healthier gut microbiome (Yao et al. 2020). The main food-grade wall materials used for the encapsulation of probiotics are presented in Table 3. In this section, polysaccharides, proteins, polymers, and lipids, which are used as wall materials for PRO-PRE co-encapsulation, are briefly discussed.

5.1. Polysaccharides

Polysaccharides are being widely used as encapsulating materials for the entrapment of bioactive ingredients because of their enormous capabilities to produce amorphous glassy entities which offer fundamental support to the wall materials

Table 3. Application of different wall materials for co-encapsulation of probiotics and prebiotics.

Wall materials	Co-encapsulation elements		Encapsulating system	Results	Reference
	Prebiotics	Probiotics			
Alginate	Inulin, rice bran, and resistant starch (Hi-maize)	*Lactobacillus acidophilus*	Microparticles	• Prepared microcapsules presented higher protection for probiotics as introduced into the simulated GIT juice, compared to the free culture. • At 25 °C, microcapsules containing prebiotics maintained viable probiotics for 4 months, and at -18 °C, only inulin-treated formulation found to be more stable (even after 4 months storage).	Poletto, Raddatz et al. (2019)
Goat whey concentrates	Inulin	*Bifidobacterium animalis*	Microcapsules	*Bifidobacterium animalis* entrapped into microcapsule fabricated with goat whey concentrates and inulin increased the stability of the bacteria during the storage, although whey concentrates and inulin were recognized as promising wall materials too.	de Liz et al. (2020)
Calcium alginate and chitosan	Inulin or resistant starch	*Lactobacillus plantarum* and *Bifidobacterium lactis*	Microparticles	Inulin-coated microcapsules were able to hinder the viability loss of *Lactobacillus plantarum*.	Zaeim et al. (2019)
Pea protein isolate and alginate	Fructo-oligosacchardes	*Bifidobacterium adolescentis*	Capsules	All formulations presented noteworthy protection to the encapsulated *Bifidobacterium adolescentis* throughout experimentations and also exhibited controlled- and prolonged-release inside the SIF.	Klemmer et al. (2011)
Sodium alginate and chitosan	Inulin and Jerusalem artichoke	*Lactobacillus acidophilus* TISTR 1338	Microcapsules	Viability of the encapsulated cells was improved by double-coating microcapsules with chitosan which improved their survivalability in terms of probiotic count after freeze-dry process.	Jantarathin et al. (2017)
Whey protein concentrate	Inulin	*Bifidobacterium* BB-12	Microcapsules	• Results demonstrated a substantial concentration of bifidobacteria, lower water contents, and minor water activity during the storage of three months at either 4oC or -20oC. • The addition of prebiotics could be more effective for the stability enhancement of the microcapsules.	Pinto, Fritzen-Freire et al. (2015)
Carboxymethyl cellulose and chitosan	Cyclodextrins	*Lactobacillus rhamnosus* GG	Microparticles	Viability count of the prebiotic-treated formulations was even realistically high after 30 days of storage at room temperature.	Singh et al. (2018)
Sodium alginate, fenugreek gum, and locust bean gum	Fructo-oligosaccharides, lactulose and maltodextrin	*Pediococcus pentosaceus, Lactobacillus plantarum, Lactobacillus fermentum, and Lactobacillus helveticus*	Microcapsules	• Incorporation of all strains of lactic acid bacteria into sodium alginate, fenugreek gum, and locust bean gum (AFL) matrix tolerated GIT conditiond efficiently. • Bacterial cells retained higher viability during freeze-drying condition and subsequent storage for 3 months at 4 °C.	Damodharan, Palaniyandi, Yang, and Suh (2017)
Alginate	Arabinoxylan	*Latobacillus plantarum*	Microspheres	• Incorporation of prebiotic arabinoxylan into the alginate-based microspheres considerably upgraded the encapsulation efficiency, bile salt resistance, gastric stability. • The storage stability of Lactobacillus plantarum was enhanced.	Wu and Zhang (2018)
Alginate	Inulin and apple marc	Lactic acid bacteria	Microcapsules	• Lactic acid bacteria viability was enhanced through co-encapsulation with prebiotics. • Resistance of lactic acid bacteria to the acidic environment was improved.	Serrano-Casas, Pérez-Chabela, Cortés-Barberena, and Totosaus (2017)
Alginate and xanthan gum	Inulin	*Lactobacillus acidophilus*	Matrix	Co-encapsulation protected *L. acidophilus* from exposure to simulated gastric circumstances.	Nazzaro et al. (2009)
Lipid carrier (palm and palm kernel oil)	Inulin	*Lactobacillus acidophilus*	Solid lipid microparticles	All produced microcapsules significantly enhanced the survival rate of *Lactobacillus acidophilus* exposed to SGF and SIF, when compared with the free probiotic cells.	Okuro et al. (2013)

(*continued*)

Table 3. Continued.

Wall materials	Co-encapsulation elements		Encapsulating system	Results	Reference
	Prebiotics	Probiotics			
Sweet whey (by-product of dairy industry)	Inulin and polydextrose	*Bifidobacterium BB-12*	Microcapsules	Combination of sweet whey and prebiotics coated microcapsules were found to be the most effective during exposure to GIT conditions and heat treatments in maintaining the viability of bacteria after spray drying.	Pinto, Verruck et al. (2015)
Canola vegetable oil and caseinate	Fructo-oligosaccharides	*Bifidobacterium infantis Bb-02*	Microcapsules	This novel encapsulant incorporated prebiotics and substantially protected the bacterium during non-refrigerated storage and GIT transit and rapidly released the bacteria in SIF.	Crittenden, Weerakkody, Sanguansri, and Augustin (2006)
Full-fat goat milk	Inulin and oligofructose	*Bifidobacterium BB-12*	Microcapsules	• All carrier agents improved the survival of the Bifidobacterium BB-12 after thermal treatments. • The highest viability count (9.58 log CFU g − 1) and encapsulation yield (97.43%) were obtained for the microcapsules produced with full-fat goat milk only.	Verruck et al. (2017)
Alginate and chitosan	Galacto-oligosaccharides (GOS) and inulin	*Lactobacillus acidophilus 5* and *Lactobacillus casei 01*	Beads	• GOS delivered a virtuous protection to the encapsulated probiotics in the simulated digestive system. • Desirable number of the entrapped probiotics containing GOS were found in both yogurt and orange juice during and after storage.	Krasaekoopt and Watcharapoka (2014)

of the conveyance structure. Their capability to entrap the bioactives is an interesting feature for the use in the food industry, due to their multiplicity, inexpensive, and prevalent usage in this area (Rehman, Tong et al. 2019). They are comprised of several monosaccharide units interlinked with glycosidic bonds; however, their chemical configurations vary among each other which deliver different physiochemical characteristics such as digestibility, water holding capacity, emulsification aptitude, and solubility (Fathi, Martin, and McClements 2014; Rehman, Ahmad et al. 2019). Due to the possessing of the surface groups such as amino, carboxyl, and hydroxyl, polysaccharides can be merely improved either chemically or biochemically, resulting in several functional derivatives. On the whole, these derivable groups play an effective role in the non-covalent bonds with biological tissues including mucous membranes and epithelia, resulting in bioadhesion (Liu et al. 2008).

For example, polysaccharides such as chitosan, pectin, carrageenan, gums, starch, and alginate are fundamentally recognized as tremendous bioadhesive matrices. Probiotics-prebiotics co-encapsulated systems equipped through bioadhesive polysaccharides could intensify the residence time as well as the cellular absorbance/uptake of both probiotics and prebiotics. All these accumulated facts about the biological and physiochemical features of polysaccharides are considered and they have an encouraging prospect as biomaterials (Peredo et al. 2016; Sathyabama et al. 2014). As an example, Peredo et al. (2016) conducted an experiment on the co-encapsulation of probiotic strains including *Lactobacillus casei Shirota* (Lc) and two strains of *Lactobacillus plantarum* (Lp33 and Lp17) and prebiotics (potato starch, inulin, and Plantago psyllium) by using alginate as the wall material, in order to explore the influence of prebiotics on the viability of the entrapped probiotics. It was concluded that carriers containing Plantago psyllium exhibited a higher encapsulation efficiency (94%) as compared to those containing inulin (78%). Furthermore, fabricated carriers exhibited spherical shape and excellent flow properties, and Plantago psyllium-based carriers showed higher viability during storage at 4 °C, which also presented the best resistance throughout the GIT (Peredo et al. 2016). In another work, Jerusalem artichoke and inulin (as prebiotics) were separately co-encapsulated with a probiotic (*Lactobacillus acidophilus* TISTR 133) inside sodium alginate shell that was further coated by chitosan. The results showed that the double-layered microcapsules significantly enhanced the viability of the entrapped cells, and they enhanced the resistance time in the case of probiotic counts after the freeze-drying process. It was reported that the microcapsules containing 3% alginate, 0.8% chitosan, and 3% prebiotic showed higher survivability throughout heating process, whereas non-encapsulated cells were found to be destroyed (Jantarathin, Borompichaichartkul, and Sanguandeekul 2017).

Yao et al. (2017) incorporated *Lactobacillus salivarious Li01* into either alginate or alginate-gelatin microgels and found that such an encapsulation greatly enhanced the survival rates of this bacteria when exposed to the factors such as long-term storage, heat, and the simulated gastrointestinal conditions. The manufactured microgels made of alginate/gelatin could effectively protect the probiotics more than alginate-microgels. The authors speculated that this could be due to the differences in the properties (both physicochemical and structural) of the interiors (Yao et al. 2017).

5.2. Proteins

Proteins, as well as their derived isolates, are amphiphilic in nature, and consequently, have excellent emulsifying abilities. Furthermore, their gelation, film-forming, and putative foaming abilities, as well as their capacity to self-associate

into complexes, make them meaningful encapsulating materials (Rehman, Tong et al. 2019). Owing to their remarkable competencies such as bio-based origin, abundant renewable sources, GRAS (Generally Recognized As Safe), and water holding capabilities, proteins have gained more popularity as wall materials for encapsulation of bioactive compounds such as prebiotics, fatty acids, oils, flavors, fats, and specifically bioactive organisms (i.e., probiotics) (Pathakoti, Manubolu, and Hwang 2017). Proteins are universally obtained from animal sources (e.g., collagen, silk protein, caseins, gelatin, albumin, elastin, whey proteins) or plant sources (e.g., gliadin, cereal proteins, soy proteins, zein proteins, pulse proteins).

Proteins have been widely used for co-encapsulation of different prebiotics and probiotics (Klemmer et al. 2011; Riaz et al. 2019). For instance, Klemmer et al. (2011) used pea protein isolate and alginate as wall materials to co-encapsulate *Bifidobacterium adolescentis* and fructoligosaccharides. They analyzed the swelling, probiotic survival, size, and efficiency of the fabricated carriers within SGF and accessed their releasing properties inside the SIF. It was reported that all formulations presented noteworthy protection to the encapsulated *Bifidobacterium adolescentis* throughout experimentations and also exhibited controlled- and prolonged-release inside the SIF (Klemmer et al. 2011). In another investigation, Pinto, Fritzen-Freire et al. (2015) fabricated microcapsules containing probiotic (*Bifidobacterium BB-12*) by using whey concentrate and inulin as carriers/wall materials. The findings demonstrated a substantial concentration of *bifidobacteria*, lower water contents, and minor water activity during the storage of three months at either 4 °C or −20 °C. It was also found that the addition of prebiotics could be more effective for the stability enhancement of the microcapsules (Pinto, Fritzen-Freire et al. 2015). The above-mentioned investigations indicate that proteins could be used as suitable food-grade wall materials for PRO-PRE co-encapsulation, although there is still a need for exploration of the interactions between these wall materials and the co-encapsulated ingredients.

5.3. Lipids

Lipids (i.e., oils and fats), which are categorized into two main classes including polar lipids (e.g., monoglycerides and phospholipids) and non-polar lipids (e.g., cholesterol and triglycerides) (Mandal et al. 2013; Rehman, Tong et al. 2019) and are enormously available in nature, can be excellent wall materials for PRO-PRE co-encapsulation. These materials are nontoxic, offer a strong emulsification functionality, and hold a strong capability to produce intermingled micelles which are useful for encapsulation of bioactive ingredients (Fathi et al. 2013). Polar lipids (particularly, phospholipids) are safe and biocompatible polymers with outstanding surface-active attributes, confirming their further suitability for the maintenance, defence, and specific conveyance of the encapsulated bioactive materials. Phospholipids (natural amphiphiles), for example, possess some distinctive characteristics including emulsifying capacity, wettability, and self-assembly, which make them more vital candidates for the entrapment of bioactives (Rehman, Tong et al. 2019). As a result, lipid-engineered encapsulation methods such as emulsions and solid-lipid microparticles are exploited for PRO-PRE co-encapsulation. For example, both palm and palm kernel oil were successfully used as wall materials to produce solid lipid microparticles, in which probiotics (*Lactobacillus acidophilus*) and prebiotics (inulin) were co-encapsulated to assess their resistance inside the SGF and SIF. It was found that all produced microcapsules significantly enhanced the survival rate of *Lactobacillus acidophilus* exposed to SGF/SIF, when compared with the free probiotic cells during storage for four months at −18, 7, and 22 °C (Okuro et al. 2013).

5.4. Minerals

Yao et al. (2018) studied the behavior of a model probiotic (*Pediococcus pentosaceus Li05*) after its encapsulation in an alginate-gelatin microgels in the absence or presence of magnesium oxide (MgO). They found that the bacteria encapsulated in microgels in the presence of MgO were more stable than those in microgels in the absence of MgO. Additionally, the addition of MgO nanoparticles could enhance the viability of bacteria through filling the pores inside the microgels. The MgO nanoparticles decreased the acid-induced degradation of probiotics by neutralizing the hydrogen ions in the gastric fluids (Yao et al. 2018). In another research (Gu et al. 2019), anaerobic *Bifidobacterium pseudocatenulatum G7* (BPG7) was encapsulated in alginate microgels containing antacid agents, in order to control their internal pH within the stomach in a simulated gastrointestinal tract. The results indicated that in the presence of CaCO3 (as an antacid), alginate microgels were more efficient at protecting the probiotic bacteria during passage through the upper GIT.

6. The stability/survival of the co-encapsulated probiotics in synbiotic/functional dairy foods

Dairy foods are exquisite carriers for probiotic bacteria such as *Lactobacillus acidophilus* and *Bifidobacterium* species. Most dairy foods contain lactose, which is a prominent requirement for probiotics growth in the intestinal tract, as well as providing other nutrients required for the growth and survival of the bacteria over the storage period (Caballero, Trugo, and Finglas 2003; Jafari, Masoudi, and Bahrami 2019). The survival of incorporated probiotics into dairy products during the storage is a fundamental factor that has been a major challenge for the incorporation of probiotics into dairy foods. Type of the probiotic strain, packaging, storage conditions, and physicochemical properties of the fortified dairy products (e.g., moisture content, pH, buffering capacity, oxygen scavengers, osmotic pressure, and overrun) are the main factors which have significant effects on the stability of probiotics over time.

According to the regulations, synbiotic/functional dairy products must contain a certain claimed number of live probiotic bacteria when they are reached to the consumers, and therefore, the protection of probiotics is a necessity.

Table 4. A summary of the recent studies on co-encapsulation of probiotics and prebiotics, the encapsulation systems, and their applications in dairy products.

Probiotic(s)	Prebiotic(s)	Encapsulation system(s)	Symbiotic/ functional food	Main results	References
Lactobacillus plantarum	Eleutherin Americana polysaccharide	Extrusion technique by sodium alginate solution	Yoghurt	*L. plantarum* TISTR1465 encapsulated with E. Americana oligosaccharide extract was more effective than the free cells, after sequential exposure to the SGF and SIF and refrigerated storage in yoghurt.	Phoem et al. (2019)
Lactobacillus plantarum LS5 and *Helianthus tuberosus*	Inulin	Alginate beads	Doogh	Microencapsulation, besides the addition of inulin, increased the survival of probiotics during storage of Doogh.	Hashemi, Shahidi, Mortazavi, Milani, and Eshaghi (2015)
Sacharomyces boulardii	Inulin	Sodium alginate and cactus mucilage	Cheese	Microencapsulation and the addition of inulin improved the survival of probiotics during storage of cheese.	Zamora-Vega et al. (2013)
Lactobacillus rhamnosus	β-glucan	Emulsification	Reduced-fat cream cheese	*L. rhamnosus* significantly increased diacetyl compounds in the cheese product.	Ningtyas et al. (2019)
Lactobacillus rhamnosus GG	Resistant and waxy starches	Alginate-gum microcapsules	Soymilk	The modified waxy starch increased the freeze-drying, thermal, and storage durability of the probiotic microcapsules, with no effect on the initial cell density.	Cheow, Kiew, and Hadinoto (2016)
Bifidobacterium lactis	NutrioseFB	Spray drying	Gouda-type cheese	The counts of microencapsulated cells were above 10^{10} $CFU.g^{-1}$ in probiotic powder and above 10^{10} $CFU.g^{-1}$ in cheese, confirming their viability after storage.	Borrás-Enríquez et al. (2018)

Basically, there are two main barriers which lead to the restrictions of adding probiotics into fermented milk products. These two include their slow growth in milk and their low survival during the process and storage of the synbiotic products (Karimi, Mortazavian, and Da Cruz 2011). PRO-PRE co-encapsulation has recently received considerable interest in the fortification of various dairy foods to produce synbiotic/functional products. Such an approach can provide several advantages; increasing the durability of the target live microbial strains in the GIT, and other health advantages such as antimicrobial, immune-stimulating, anticancer, and anti-allergic properties (Fazilah et al. 2018). Accordingly, there have been numerous efforts implemented for minimizing the vulnerability of probiotics to the environmental conditions (e.g., during the manufacture and storage of the food) and uncontrolled release of probiotics from functional dairy foods during the GIT digestion.

As presented in Table 4, the recent studies show that both the viability and growth of probiotics are increased when they are co-encapsulated with prebiotics. Although dairy food is an ideal delivery vehicle for probiotics and prebiotics, some main factors must be considered when co-encapsulated probiotics and prebiotics are incorporated into this type of food product. First and foremost, it is vital that co-encapsulated materials do not exhibit any adverse effects on the sensorial (e.g., flavor, texture, color) and/or physiochemical properties of the synbiotic dairy foods. Therefore, compatibility of the encapsulation systems containing probiotics and prebiotics with the food formulation is a primary factor in producing any possible synbiotic product. Along these lines, the interactions of the encapsulation systems with other components of dairy products (e.g., proteins, fats, carbohydrates, minerals) must be noticed. Because, such interactions may not only decrease the functionality of both probiotics and prebiotics, but may also result in undesirable properties of the final dairy product. The stability of co-encapsulated probiotic and prebiotic during the process and storage of the synbiotic dairy products is another significant factor for the incorporation of co-encapsulated live organisms and prebiotics (Borrás-Enríquez et al. 2018; Champagne and Fustier 2007). In this section, some of the main dairy products, that have been used as delivery vehicles for co-encapsulated probiotics and prebiotics, will be discussed.

6.1. Yogurt

Starter cultures (mainly lactic acid bacteria) are one of the most important factors responsible for the shelf life, flavors, and textures of yogurt. However, recently, researchers have been looking for advancing healthy functions of yogurts in addition to their traditional functions by using probiotic bacteria (Phoem et al. 2019; Sodini et al. 2004; Zaeim et al. 2019). Thus, probiotics have been used with prebiotics to produce healthy synbiotic yogurt products through new emerging processes such as co-encapsulation systems, with the main goal being improving the survival of probiotics in the yogurt formulations. Silva, Cezarino et al. (2018) co-encapsulated *Lactobacillus acidophilus* with fructooligosaccharides (FOS) in alginate-gelatin (AG) and alginate-gelatin-fructooligosaccharides (AGF) microbeads through external gelation; then the co-encapsulation systems were added into yogurt. Their results showed that higher stability of the probiotics was obtained during GIT passage and storage of the yogurt, due to the co-encapsulation of *Lactobacillus acidophilus* with FOS, compared to non-encapsulated probiotics. Such an increase in the stability of incorporated bacteria was attributed to the increase in the AG network and the creation of small pores in the matrix of AG when FOS was added, compared to encapsulated *Lactobacillus acidophilus* without FOS. Capela, Hay, and Shah (2006) evaluated the effect of microencapsulation and the addition of prebiotics on the viability of the species such as *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, and *Bifidobacteriumspp* in a normal yogurt product and a freeze-dried yogurt. These researchers found that, when the prebiotic *Raftilose P95* was added, the microencapsulation with alginate showed positive effects on the viability of probiotic organisms (by 0.31 log) in the freeze-dried yogurt during four weeks of storage (21 °C).

In another study by Fazilah et al. (2019), yogurt was fortified with microencapsulated *Lactococcus lactis* through spray-drying with a complex of gum Arabic and *Synsepalum dulcificum*, which provided higher viability for *Lactococcus lactis* compared to their free form in yogurt formulation. The addition of *Synsepalum dulcificum* (a plant extract/prebiotic agent) improved the stability of *L. lactis* during yogurt processing and increased its functionality when it was loaded into the yogurt formulation (Fazilah et al. 2019). Inulin is another prebiotic that has been popularly used in the formulation of the encapsulated probiotics. A functional yogurt was fortified by encapsulated *Bifidobacterium longum* LMG 13197 in Vegetal BM 297 inulin by freeze-drying (Amakiri and Thantsha 2016). According to this study, vegetal-inulin co-encapsulation provided adequate protection of probiotics against GIT fluids with some negligible effects on the sensorial properties of yogurt. Krasaekoopt and Watcharapoka (2014) co-encapsulated *Lactobacillus acidophilus* 5 and *Lactobacillus casei* 01 with galactooligosaccharides (GOS) and inulin as prebiotics in alginate beads coated with chitosan; then the produced particles were transferred into commercial yogurt matrix. The encapsulation system containing GOS provided better protection for probiotics and increased their growth in the simulated GIT. It is known that prebiotics provide some major nutrients such as nitrogen and carbon, which result in a faster proliferation of organisms in the large intestine, resulting in some health benefits to the host.

6.2. Cheese

Advanced synbiotic cheeses containing co-encapsulated probiotics and prebiotics have been developed in the recent years. For this reason, various probiotics and prebiotics have been incorporated into a few cheese products. For example, Borrás-Enríquez et al. (2018) formulated a ripened Gouda-type cheese with an encapsulation system containing *Bifidobacterium* (as the probiotic) and Nutriose®FB (a soluble dietary fiber/as the prebiotic) produced by spray drying of the mixture of β-cyclodextrin-Arabic gum (BC-AG). They observed that the incorporated probiotics into cheese were resistant against GIT conditions, while the encapsulation system did not show any adverse effects on the physicochemical properties of the functional cheese.

The conditions of processing, cooking method, the aerobic conditions, ripening, and storage temperatures have major effects on the viability of the incorporated probiotics into the products such as cheese during their storage period. In this regard, Ningtyas et al. (2019) evaluated the survival of *L. rhamnosus* in cream cheese over time. Probiotic cream cheese with β-glucan and phytosterol emulsion showed a low decrease in *L. rhamnosus* viable counts after 35 days of the refrigerated storage, which could be related to the ability of β-glucan to enhance the growth and adherence of probiotics such as *Lactobacillus* and *Bifidobacterium*, due to the high fermentability of β-glucans by the intestinal microbiota in the cecum and colon.

Schoina et al. (2018) encapsulated *Lactobacillus casei* ATCC 393 into *P. terebinthus* resin matrix (a plant material used as the prebiotic) to fortify Mizithra cheese. *P. terebinthus* not only improved the viability of *L. casei* during the storage, but also provided antimicrobial effects, which increased the shelf life of the cheese. In a study by Zamora-Vega et al. (2013), *Sacharomyces boulardii* was co-encapsulated with inulin using sodium alginate and cactus mucilage, and the encapsulated product was used for the manufacture of a synbiotic cheese. When compared to their free form, the encapsulated microorganisms showed higher stability during the storage, without negatively influencing the chemical composition of cheese and even improving the organoleptic properties of the cheese product. The use of prebiotics with probiotics in the cheese formulation can also improve the sensory properties. For example, Ningtyas et al. (2019) formulated a low-fat cream cheese by adding a delivery system containing β-glucan, phytosterols, and *L. rhamnosus* produced by the aerosol spraying technique. The diacetyl compounds (buttery flavor) was increased by adding *L. rhamnosus*. Fatty acid compounds were dominant in cream cheese with phytosterols ester, and the new flavors agents (e.g., aldehydes and ketones) were developed in the cream cheese enriched with phytosterols emulsion. It was concluded that probiotics were a good candidate for promotion of the flavor of low-fat dairy foods, since they produced a pleasant buttery flavor resulted from the compounds such as diacetyl.

6.3. Ice-cream

The application of the co-encapsulated probiotics and prebiotics in ice cream and frozen desserts has also received a special interest, as co-encapsulation can protect probiotics against stresses (resulting from the cold conditions of ice milk), which leads to a decrease in their effect on sensory properties of the final product. For instance, the fortification of ice cream by microencapsulated *Lactobacillus casei* (Lc-01) and *Bifidobacterium lactis* (Bb-12) with alginate and Hi-maize resistant starch (as a prebiotic) did not have any undesirable effects on the sensorial properties of the manufactured ice-cream product (Homayouni et al. 2008). Therefore, using multiple encapsulated probiotics and prebiotics in the formulation of ice cream is more beneficial than the addition of the encapsulated probiotics without prebiotics. Co-encapsulation systems containing probiotics with prebiotics such as inulin can help with their survival during the storage of ice cream, besides their stability during the encapsulation process (Spigno et al. 2015).

The culture medium is a significant factor regarding the viability of probiotics in ice-cream. For instance, a primary challenge in the ice cream freezing process is the formation of ice crystals in the environment or inside the cell, which leads to the damage of cell walls and/or rupture of their membranes. However, this may be avoided to some degree by the implication of rapid freezing; it can still produce a small size of ice crystals, but that is a decrease in the cell-damages (Park et al. 2015). Furthermore, ice cream is a whipped product in which oxygen is loaded in high amounts and this is toxic for the anaerobic bacteria such as *Bifidobacterium* spp.

6.4. Other dairy products

Production of various synbiotic dairy products such as fermented milk, dairy desserts, and sauces has been expanding due to their advanced health functions. For instance, a fermented milk product was formulated by the incorporation of *Lactobacillus (Lb) plantarum* B-4496 and *Bifidobacterium (Bif.) animalis* B-41405 co-encapsulated with beetroot or ginger aqueous extract (as prebiotics) through the extrusion microencapsulation method using alginate and chitosan. The fortified fermented milk with chitosan-coated beads containing mentioned extracts increased the stability of probiotics during the storage and processing, while it also improved the acceptability of the fermented milk (El-Abd et al. 2018).

Dairy powders fortified with probiotics such as skimmed milk powders, whole milk powder, and buttermilk powder are also receiving considerable attention in the food industry. As explained in Section 4, spray drying is a fast, flexible, and economical process for the manufacture of the encapsulated probiotics while this method can also be used for the manufacture of dairy powders as well. Although the high temperature of spray drying process is the main challenge against the survival of probiotics, this can be overcome by adding probiotics in the encapsulation systems containing prebiotics (Tafti, Peighambardoust et al. 2013; Tafti, Peighardoust et al. 2013). In this regard, during the production of probiotic dairy powders, the type of the carrier significantly affects the stability of the probiotics as well as the psychophysical properties of powders. Evaluation of the effect of full-fat goat's milk and/or inulin and/or oligofructose on the stability of *Bifidobacterium* BB-12 and powder properties produced by spray-drying showed that the full-fat goat's milk combined with or without inulin provided a higher stability of probiotics with the powders containing appropriate characteristics. On the other hand, some cracks were observed in the case of powder particles produced by only oligofructose.

7. Release and fate of the co-encapsulated probiotics in the GIT

7.1. The role of GIT in probiotic digestion

The human GIT by itself is a highly complex ecosystem, in which, various types and populations of bacteria exist from the mouth to the colon (Hooper et al. 2001). Albeit, there has been an enormous research advances in the understanding of this complex ecosystem and its microbial ecology; however, understanding of the microbial interactions in the GIT is still limited. In effect, the diversity of the bacteria present in the large intestine is so vast (about 500 different species of bacteria) that a great majority is yet to be identified (Tannock 2001). Although the microbial colonization in the GIT occurs instantly after birth, significant changes occurring in the flora profile, especially in the intestines, due to weaning and ageing, which leads to an established profile of microflora within few days after birth (Mitsuoka 1992; Te Biesebeke et al. 2004). Such an established ecosystem will not remain unchanged, however, as different factors (e.g., age, diet, health, stress level, hormonal functions, and drugs) can modulate this intestinal microflora substantially (Gibson and Wang 1994; Goldin and Gorbach 1984).

There is no doubt about the importance of intestinal microflora for the maintenance of human's health in terms of the major physiological functions such as the maintenance of mucosal health, production of nutrients, barrier function restoration, stimulation of bowel motility, secretion of antimicrobial substances, immune stimulation, and improved bioavailability (Holzapfel et al. 1998; Shanahan 2002). Generally speaking, and with respect to the host's health, there are three major groups of bacteria found in the gut microflora. These include beneficial (health-promoting), potentially pathogenic, and neutral bacteria. Apart from the predominance of harmful bacteria in the GIT, which can predispose the host to different diseases and disorders (e.g., ulcerative colitis, inflammatory diseases, and cancer) either directly or indirectly (i.e., making the host more susceptible to different deleterious conditions such as infections) (Ellmerich et al. 2000; Huycke and Gaskins 2004), there are some general beneficial effects associated with the health-promoting bacteria such as *lactobacilli* and *bifidobacteria*. Because, these bacteria can provide a vital barrier against the antigens, the pathogenic microorganisms, and the harmful compounds from different origin (Blumberg and Strober 2001; Gill and Guarner 2004; Reid et al. 2003).

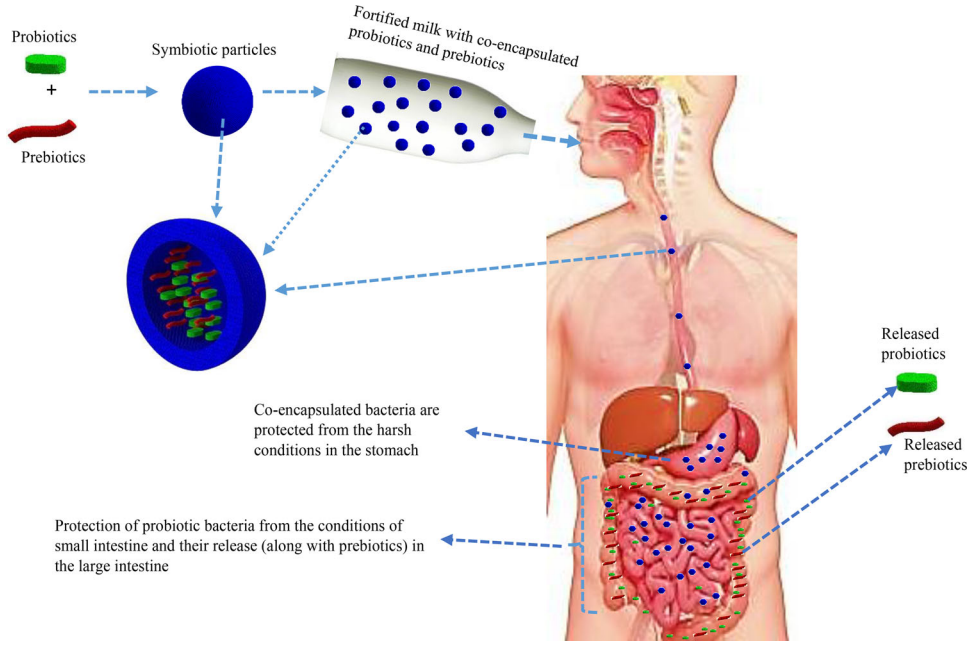

Figure 3. The fate of co-encapsulated probiotics and prebiotics in the gastrointestinal tract.

7.2. Survival and release of probiotics in the GIT

The survival of different species of probiotics in the GIT is affected by a range of factors associated with the functional product containing these organisms. These include pH, post-acidification during products fermentation, production of hydrogen peroxide, and the storage conditions of the food, in particular, temperature (Fávaro-Trindade, Heinemann, and Pedroso 2011). In this regard, providing probiotics with an encapsulant barrier will result in their protection against adverse conditions in stomach and their controlled-release in the later part of GIT, while their co-encapsulation with prebiotics will also add further protection. Nevertheless, there remain several challenges in regard to the controlled-release of probiotics in the GIT, mainly because the mechanisms of such a release are yet to be adequately known.

There have been research attempts made to study the release of the content of the microcapsules, development of symbiotic microcapsules, the design of cost-effective enteric polymer microcapsules, and conferring thermal stability to probiotic cultures (Lee et al. 2019; Zhou et al. 1998). For example, it is known that hydrophilic encapsulants release probiotic cells when they become in contact with water during digestion process; lipid-based capsules release probiotics when they melt (due to the higher temperature in the GIT than their melting point) or when they are digested by lipase; and enteric polymers, which are insoluble in acidic condition of stomach, release the encapsulated microorganisms when they solubilize in basic medium of the intestine (Fávaro-Trindade, Heinemann, and Pedroso 2011). Considering the delivery methods for probiotics, the encapsulation techniques such as spray drying, freeze-drying, or fluidized bed drying are known to have limitations, since the capsules made using these techniques release most of the cells into the product (during processing and/or storage) or within the upper parts of GIT (Gbassi and Vandamme 2012).

7.3. The importance of co-encapsulation in the context of probiotic survival in the GIT

The major objective of the co-encapsulation of probiotics is controlling their release in the GIT especially, their protection against harsh conditions of the stomach, which promotes their performances in the later parts of GIT. Generally, dissolution, partitioning, erosion, swelling, diffusion, and osmosis are the main mechanisms for the release of bioactive compounds from the encapsulation systems (Jafari et al. 2017). When probiotics are incorporated into carriers with prebiotics through co-encapsulation systems, their release can be controlled by wall materials; therefore, wall materials have an important role in the targeted release of probiotics. For example, multiple-layer walls can provide long-time release of probiotics. When the performance of probiotics is high, they can release in the large intestine (Banerjee, Chowdhury, and Bhattacharya 2017).

As shown in Figure 3, when the fortified dairy products via co-encapsulated probiotics and prebiotics are ingested, the first section of the body that has the adverse condition for probiotics is the stomach, in which the acidic condition destroys the probiotics. Thus, these live organisms can be protected from the harmful conditions of the stomach by being loaded into appropriate carriers. The encapsulated probiotics can survive in the small intestine containing pancreatin and bile with the pH close to neutral, but this is still not the ideal place for the release of probiotic bacteria. Finally, probiotics which reach the large intestine (colon) can be released in an ideal condition, which helps them by attaching onto mucus for their further proliferation in this part of the gut. Besides, as more prebiotics release from the carriers into the large intestine, their growth is promoted (Albadran et al. 2018; Banerjee, Chowdhury, and Bhattacharya 2017). Therefore, these advantages make the co-encapsulation approach as the most popular method to

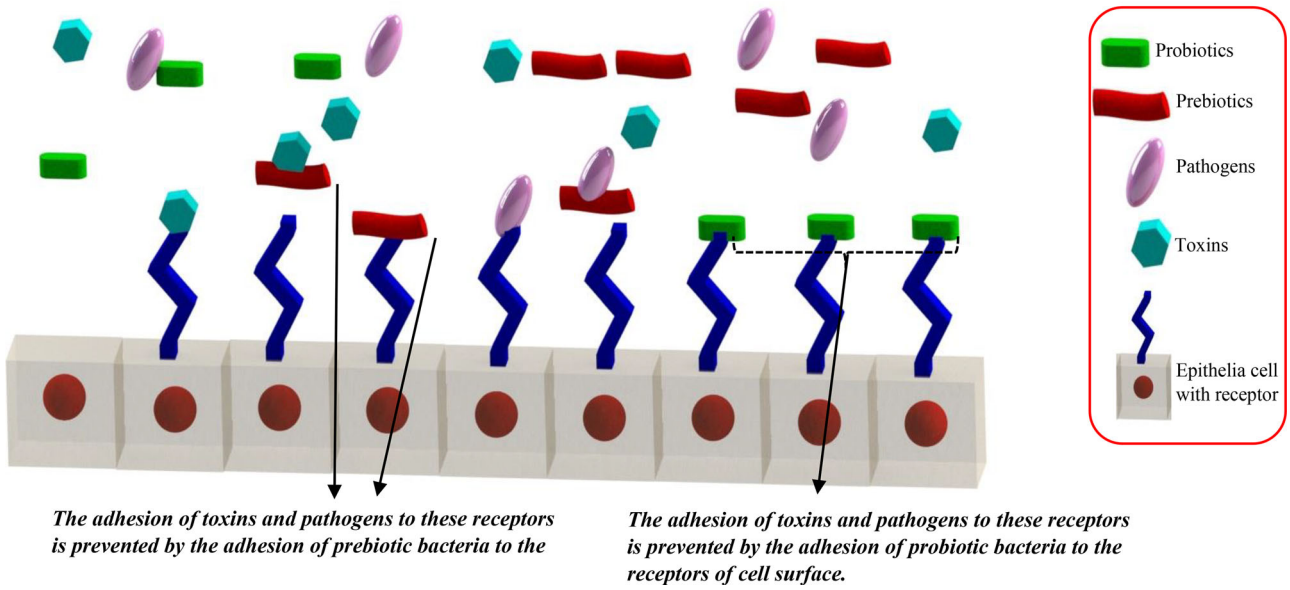

Figure 4. Antiadhesive mechanisms of the co-encapsulated probiotics and prebiotics released from the carriers into the large intestine.

enhance the stability, viability, and correspondingly, the bioavailability of probiotics.

Lactobacillus acidophilus was encapsulated using a system composed of alginate-inulin-xanthan gum (Nazzaro et al. 2009), and it was observed that such encapsulation protected *L. acidophilus* against simulated gastric conditions, with some negligible changes in the viability after its incubation in pancreatic juice for 60 min. Banerjee, Chowdhury, and Bhattacharya (2017) showed that the synbiotic microcapsules were an effective delivery system for *Lactobacillus casei,* where this organism was protected against the conditions of the stomach and the small intestine. They proposed a "burst release" mechanism for probiotics in the large intestine, which was proved in the simulated conditions. In these conditions, *probiotic10* cells were released after 50 min when 1 g synbiotic microcapsules were initially suspended in 10 mL of simulated large intestinal juice (Banerjee, Chowdhury, and Bhattacharya 2017). A new synbiotic microcapsule was formulated using PLGA (poly(lactic-co-glycolic acid)) particles, *bifidobacterium,* gum Arabic, and alginate. This microencapsulation system provided a high protection of *bifidobacterium* against the simulated gastric solution.

As shown in Figure 4, the released probiotic bacteria from the carriers into the large intestine have a noticeable adhesion ability, which can prevent the adherence of pathogens by competition for host cell attaching place. This inhibition can be elevated by the presence of prebiotic compounds in the large intestine, which is also released from the carriers by direct interactions with pathogens (Monteagudo-Mera et al. 2019).

8. Conclusion and future perspectives

Dairy foods are the main delivery vehicle for the co-encapsulated probiotics and prebiotics. However, the viability of probiotic cells during manufacture, processing, and storage of dairy foods is critical and without such viability being maintained, the incorporation of these bacteria into the food may not be as beneficial. This is due to the poor survival of probiotics in the food environment and the GIT, which has been widely reported. The concept of co-encapsulation with prebiotics appears to be an efficient method of delivery for probiotic live cells with a promising potential to increase the survival efficacy of the probiotics during encapsulation process and the manufacture and storage of the food, as well as throughout the GIT.

Co-encapsulation can be a useful technique toward modification of the intestinal microbiota for the achievement, restore, and maintenance of a positive balance in the GIT ecosystem, by introducing more of the resistant probiotic microorganisms. Numerous reports confirm the tolerance of the co-encapsulated probiotic live organisms to the acidic environment of the stomach in the presence of prebiotics. Since most of the available research has been carried out in the simulated digestion, future studies are to be carried out to systematically investigate the efficacy of the co-encapsulation approach on the survival of the bacteria in the gut using animal models (in vivo tests). In regard to the delivery of probiotics and their effect on the human health, it appears that this is an exciting time as we have entered the era of the microbiome science, where the contributions of microbiota to human health and disease are only at the beginning of the revelation path. This means that over the next few years, more research will be focused on the delivery of probiotics using co-encapsulation technology, and the interaction of the co-encapsulated probiotics to the human host, as well as in the synbiotic products. The future research should aim to increase the survival of probiotics in vivo, and more examples of the functional foods containing these ingredients are to be developed and tested.

Role of authors

A. Rashidinejad proposed the topic, managed the teamwork and compilation of the sections, wrote Sections 1 to 3 and 8, finalized the 1st draft, and revised the next drafts.

A. Bahrami wrote Section 6 and draw some of the images.

A. Rehman wrote Section 5 and created some of the Tables.

A. Rezaei wrote Section 4 and some Tables.

A. Babazadeh wrote Section 7 and draw some images.

Harjinder Singh revised the 1st draft and further enriched it.

Seid Mahdi Jafari designed the framework and contents of the text, revised the 1st draft, finalized the manuscript, and took responsibility of submissions and publishing stages.

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