Trends in Food Science & Technology 102 (2020) 203–222

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs

Colon-targeted delivery systems for nutraceuticals: A review of current vehicles, evaluation methods and future prospects

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ARTICLE INFO

Keywords:
Colon targeting
Nutraceuticals
Vehicles
Evaluation methods

ABSTRACT

Background: Advances in nutriology have suggested the colon as a superior site for nutrition absorption. Nutraceuticals, including phytochemicals, probiotics, etc., have received great attention owing to their health-promoting functionalities for colon. However, these compounds generally exhibit poor solubility or are sensitive to the harsh environment of food processing and gastrointestinal tract, thus, lowering their bioavailability and compromising their envisioned benefits. Therefore, there is a need to develop suitable delivery systems to protect active agents from these severe conditions and to maintain their functions in the colon.

Scope and approaches: Colonic delivery of nutraceuticals has emerged as a new impetus for researchers interested in developing functional foods. This review presents an overview mainly about current studies relevant to different colon-targeted vehicles for nutraceuticals. The physiological conditions of colon and the corresponding principles for constructing vehicles are first reviewed to better understand the mechanisms of different vehicles. Relevant methods for evaluating the efficiency of vehicles are also summarized. Last, current limitations and the future scope for the colonic delivery of nutraceuticals are identified and addressed.

Key findings and conclusions: Recently, significant progress has been made in colon-targeted delivery of nutraceuticals and different evaluation methods were applied to assess the efficacy of vehicles. However, advances in the colonic delivery of nutraceuticals are still in their early stages and multi-unit vehicles with great efficacy need to be further investigated. Furthermore, to fully mimic the real conditions of gastrointestinal tract, more systematic and precise *in vitro/vivo* testing should be explored to make sure that a fully function of nutraceuticals enters the colon.

1. Introduction

Advances in the nutrition and metabolism have promoted a deep understanding of the interactions between the human health and the colon. Recently, the colon has been regarded as the ideal absorption site for improving the bioavailability of functional agents due to the distinct advantages the colon presents, such as its near neutral pH, long transit time, and reduced enzymatic activity (Amidon, Brown, & Dave, 2015). In this regard, oral, colon-targeted delivery systems have been put forward that resist the chemical and enzymatic degradation taking place in the upper gastrointestinal (GI) tract and release their loaded biocomponents in the colon (Pawar, Darekar, & Saudagar, 2013). Currently, significant progress has been made in developing colon-targeted drug delivery systems (Naeem et al., 2020). Moreover, this system has been shown many advantages, including minimizing systemic side effects, improving bioavailability, and delivering the drugs in their intact forms (Kumar, Ali, Kaldhone, Shirode, & Kadam, 2010; Kumar, Chandra, & Gautam, 2013). However, the application of these advances to the food industry is still in its early stages. As is known that the bioavailability of bioactive components is the main factor that must be considered in designing functional foods. Therefore, the colonic delivery of bioactive compounds has emerged as a new goal for researchers interested in developing functional foods.

Nutraceuticals are an emerging food category defined as dietary elements that have health promoting effects beyond their basic nutritional values (Ting, Jiang, Ho, & Huang, 2014). Bioactive phytochemicals and probiotics are the two predominant nutraceuticals that have received substantial attention in the field of food industry. The

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https://doi.org/10.1016/j.tifs.2020.05.019
Received 6 September 2019; Received in revised form 22 April 2020; Accepted 21 May 2020
Available online 07 June 2020

incorporation of nutraceuticals may provide a simple way to develop functional foods that can have physiological benefits or reduce the risk of disease (Bezbradica et al., 2013). Bioactive phytochemicals, which are derived from various natural sources such as plants, vegetables and fruits, possess diverse bioactivity in the colon, including the reduction of inflammation, inhibiting colon cancer, and promoting the growth of probiotics (Prakash, Gupta, & Sharma, 2012; Sun, Zhang, Zhu, Lou, & He, 2018), Thus, they benefit colon health. However, their potential functionality has not been fully realized because they are easily degraded during storage or within the GI tract. Consequently, there is a strict requirement to develop food-grade delivery systems that encapsulate and protect active agents until they reach the colon. Additionally, microbial communities colonizing in different regions of the human colon contribute nutrients and energy to the host through the fermentation of non-digestible dietary components (Duncan & Flint, 2013). The balance of microbial species is essential for maintaining healthy metabolism and immune function. But the disturbance in this balance can have negative influence on health, resulting in inflammation and metabolic disorders that are contributory factors in inflammatory bowel disease, diabetes, and cancer (Ruan, Engevik, Spinler, & Versalovic, 2020). Probiotics are live microorganisms administered as food supplements to improve the microbial balance in the colon and to confer major health benefits such as modulation of the immune system, enhanced healing of damaged GI mucosa, improved nutrition and antagonism against pathogens (Ashraf & Shah, 2014; Olveira & González-Molero, 2016; Tejero-Sariñena, Barlow, Costabile, Gibson, & Roeland, 2012). Hence, consumption of probiotics has been a rising trend due to consumer awareness of their beneficial effects. It is noteworthy that good probiotic viability and activity are considered essential for optimal functionality. Nevertheless, survival of these probiotics during transit through the GI tract can be problematic and need to be taken into consideration since the harsh GI environment (e.g., low pH and high bile salts) can damage bacterial cells. Herein, colon-targeted delivery systems seem to be an attractive approach for delivering probiotics to address this limitation.

Recently, a significant driver in functional food innovation has been the exploration of colon-targeted delivery systems to help the nutraceuticals to resist the harsh conditions of GI tract and to fully function in the colon. However, to date, there are no reviews focused on the progress of colon-targeted delivery of nutraceuticals. Therefore, this paper provides an up-to-date overview of current studies relative to different colon-targeted vehicles for nutraceuticals. To better understand the action mechanism of different vehicles, the physiological conditions of colon and the corresponding principles for constructing the vehicles are first reviewed. Additionally, relevant methods for evaluating the efficiencies of different vehicles are summarized. Last, the limitations of current studies and the scope for future research are identified and addressed. It is hoped that the present review will provide better understanding of current progress in the area of colon targeted delivery of nutraceuticals and encourage the industry to further explore and adopt suitable techniques for the development of functional foods.

2. Anatomical and physiological characteristics

2.1. Colonic anatomy

The human GI tract is primarily divided into the stomach, the small intestine and the large intestine. Its anatomical and physical features were shown in Fig. 1(Patel, Bhatt, Patel, Patel, & Patel, 2011). The large intestine, which starts from the distal end of the ileum to the anus, is just over 1.5 m long and divided into three parts, the colon, the rectum and the anal canal. The colon, 5–7 cm in diameter, is the upper 1.5 m of the large intestine, beginning at the ileocaecal valve and ending at the rectosigmoid junction (Satheesh Madhav, Singh, & Ojha, 2012). The colon itself is composed of the caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon and the sigmoid colon.

2.2. Colonic pH

The pH of GI tract varies significantly among different regions, and can be used as an approach for constructing colon-targeted delivery system. In fact, there is a pH gradient in the upper GI tract, which ranges from pH 1.2 in the stomach to pH 6.6 in the proximal small intestine to pH 7.5 in the distal small intestine (Reddy, Malleswari, Prasad, & Pavani, 2013). The pH then decreases between the end of the small intestine and the colon due to the presence of short chain fatty acids arising from fermentation of polysaccharides by the human microbiome but then gradually increases once again in the colon (Gupta, Gnanarajan, & Kothiyal, 2012). By knowing this pH, a pH dependent colon-targeted system was investigated by researchers. The basic mechanism of this system is similar to the use of enteric coatings or employs of pH dependent polymers. Such systems exploit the generally accepted view that the pH of the human GI tract increases progressively from the stomach, small intestine at the site of digestion and then increases in the distal ileum (Singh, Sharma, Pooja, & Anju, 2014). Thus, colon-targeted delivery systems fabricating with pH dependent polymers are able to withstand the lower pH values of the stomach and of the proximal portion of the small intestine to protect the active ingredient from these acidic pH values, then break down at the neutral or slightly alkaline pH values present in the terminal ileum and release their bioactive components. In fact, the pH ranges between 1.5 and 2.0 in the stomach during fasting but the intake food results in an increase in stomach pH (Gerloff et al., 2013; Zhang, Wang, Li, Ho, Li, & Wan, 2016). Colonic pH ranges also exhibit variability between individuals due to hydration level, GI disease state, food intake, and microbial metabolism. Additionally, some polysaccharide-based bioactive components may also alter the pH of colon. Lactulose, for example, can be fermented by colonic bacteria to produce lactic acid, reducing colonic pH. The large variation of the pH values in the GI tract is well established (Patel et al., 2011). Hence, even though a pH dependent delivery system can protect an active substance in stomach and proximal small intestine, it may dissolve in the lower small intestine prior to reaching the colon, resulting in the poor site-specificity of bioactive components.

2.3. Transit time

Gastric emptying time plays an important role for colon-targeted delivery systems, especially in time-controlled delivery systems. Gastric emptying times are highly diverse and primarily depend on whether the body is fed or fasted, and the size and density of the dosage form (Kumar & Kumar, 2011). The arrival of an oral dosage form to the colon is determined by the rate of gastric emptying time and the small intestine transit time. The transit time of the small intestine is relatively constant (approximately 3–4 h) and is generally unaffected by the nature of the products (Qureshi, Momin, Rathod, Dev, & Kute, 2013). The transit times of dosage forms vary in different regions of GI tract. Colonic transit is slow and influenced by a number of factors such as diet, stress, dietary fiber content and disease. Colonic transit time in patients with ulcerative colitis was shorter (about 24 h) compared colonic transit time in a healthy body (about 52 h) (Hebden, Blackshaw, Perkins, Wilson, & Spiller, 2000). While diarrhea increases colonic transit, constipation decreases it (Krishnaiah & Khan, 2012). Human activity can also affect dosage form motility in the colon, with the inactive state of sleep delaying the colonic transit. For a colon-targeted delivery system, the lag time should equate to the time taken for the orally dosed system to reach the colon. Thus, it is usually assumed that a 5 h lag time is sufficient for colon delivery. However, the colon arrival time of dosage forms cannot be predicted accurately, since the gastric emptying time is inconsistent between individuals, resulting in poor colonic availability (Cole et al., 2002). Additionally, other

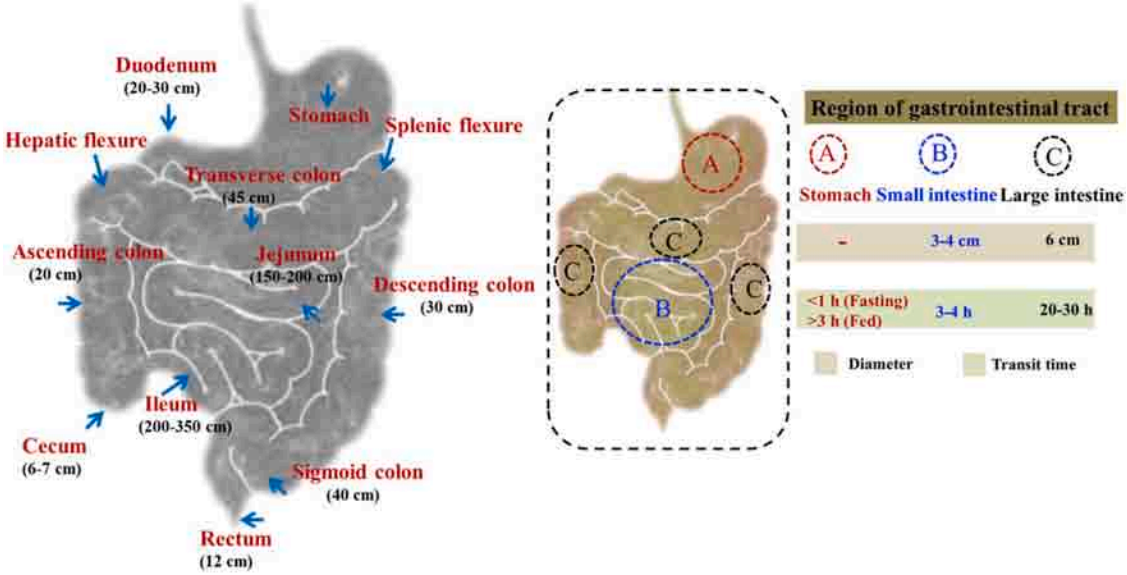


Fig. 1. Anatomical and physical features of the human GI tract.

disadvantages also exist for time-controlled colon-targeted system. First, gastric emptying time is different between different subjects and is dependent on the type and amount of food intake; Second, gastrointestinal movement, especially the peristalsis or contraction in the stomach can influence the transit time of dosage form. Third, some diseases, such as irritable bowel disease (IBD), carcinoid syndrome, diarrhea and ulcerative colitis (UC), can accelerate transit through different regions of colon (Fischer, Siva, Wo, & Fadda, 2017). Therefore, this delivery system is not ideal for colon delivery. However, the system developed by the combination of two or more different types of mechanisms might be an attractive approach to solve this problem. For example, research combining pH dependent and time-controlled systems into one dosage can overcome the variation of gastric emptying time and can improve the colon specificity, results indicate that a pH/time dependent delivery system can prevent the burst release under acidic pH conditions but show sustained release at colonic pH (Naeem et al., 2015).

2.4. Colonic microflora and enzymes

The entire human GI tract contains a large number of anaerobic and aerobic bacteria. However, the upper small intestine has relatively small amounts of bacteria (10^4 CFU/g) compared to colon (10^{11} CFU/g). Over 400 different species have been found in the colon, 20–30% of which are in the genus *Bacteroides* (Choudhury et al., 2012; Raghuvanshi, Goswami, & Kothiyal, 2014). Several hydrolytic and reductive metabolizing enzymes, which are common in the gut microbiota residing in high numbers in the colon, can play an important role in triggering the release of the bioactive compounds in the colon (Dhir, Kahlon, & Kaur, 2013). Herein, microflora activated delivery systems are based on the exploitation of the site-specific metabolic activity of microflora resident in colon. Colonic enzymes are not only capable of degrading the coating matrices, but they can also break the linkages between active agent and matrices, and thereby release active components. For example, polysaccharides (e.g., chitosan, pectin, alginate, starch, etc.) that are resistant to the gastric and intestinal enzymes but can be digested by enzymes produced by the colonic microbiota after arriving in the colon, are commonly employed as rate-controlling matrices or linkers for constructing colon-targeted delivery systems (Kotla, Gulati, Singh, & Shivapooja, 2014). When the vehicle passes through the GI tract, it remains intact in the upper GI tract where very little microbial activity is present. The colonic bacteria carry out a variety of metabolic reactions and fulfill their energy needs by fermenting various types of substrates such as disaccharides, trisaccharides, and polysaccharides (Tuck, Muir, Barrett, & Gibson, 2014). In general, this system is more site-specific than other colon-targeted delivery systems because of the presence of these enzymes only in the colon. While, this approach also has limitations since polysaccharides can dissolve or swell in an aqueous environment due to their hydrophilic properties. To address this limitation, some structural modification or other vehicle strategies are generally applied to realize the full potential of these polysaccharides for colon-targeted delivery systems (Shukla & Tiwari, 2012).

3. Current vehicles for colon-targeted delivery of nutraceuticals

Nutraceuticals need to be protected from the harsh environment of the upper GI tract and then be released in the colon to attain successful colonic delivery and elicit their functionality to improve their bioavailability. In this regard, the subsequently section provides detailed and systematic reviews of successful vehicles based on different mechanisms for the colon targeting of bioactive compounds, especially phytochemicals and probiotics that may provide a major impetus to food researchers in the development of function food.

3.1. Vehicles for colon-targeted delivery of bioactive phytochemicals

Phytochemicals have a long history of significant applications in commercial industries including cosmetics, food aids and additives. (Bourgeois et al., 2016; O'Shea, Arendt, & Gallagher, 2012). They possess numerous therapeutic benefits such as anti-obesity effects, cardiovascular effects, antioxidant activity, immune enhancement and anti-inflammatory effects. Plant-derived phytochemicals are advantageous for the treatment of colon cancer with additional benefit of improving overall health and these nutritional compounds might provide better treatment while showing few adverse effects (Clifton & Kaplowitz, 2012). Nevertheless, their applications are generally limited owing to disadvantages such as poor solubility, instability and low bioavailability (Shakeri & Sahebkar, 2016). Hence, there is a critical need to develop alternative vehicles to overcome the above limitation.

Different colon-targeted vehicles have been recently explored to improve the bioavailability and optimize the release in the GI tract of the phytochemicals, potentially promoting the health.

3.1.1. Nano-based vehicles

Nanotechnology is a promising tool in the field of food safety and nutrition and it has been shown as an efficient approach for improving the bioavailability of the bioactive components (Dima, Assadpour, Dima, & Jafari, 2019; Wang et al., 2014). There is a huge opportunity for the development of diverse products with functions because of the properties of nanomaterials such as size, shape, encapsulation efficiency, aggregation state, and solubility. Nanoparticulate can be synthesized from carbohydrates, proteins, and lipids, as well as other natural and synthetic polymers and they can exist in different forms depending on the method used for their preparation (Esfanjani, Assadpour, & Jafari, 2018; Katouzian & Jafari, 2016). In general, a scientific definition of nano-size systems in the pharmaceutical area involves particle sizes of less than 1000 nm (Assadpour & Mahdi Jafari, 2019). Moreover, Jafari, Assadpoor, He, and Bhandari (2008) also suggests that nanoparticles be defined as having dimensions below 1000 nm in the field of encapsulation. Recently, nanomaterials have been suggested as attractive vehicles for constructing colon-targeted delivery systems. They also offer other advantages including improved efficacy, reduced toxicity, and enhanced biodistribution (Manikandan, Kannan, Manavalan, & Sundresh, 2011). Nano-based vehicles can potentially overcome barriers to colon-targeted delivery of the loaded components (Lamprecht, 2010). In this case, nanoparticles are stable in the GI environment and can protect an encapsulated active substance from the harsh pH conditions and enzymatic degradation. Nano-sized carriers can accumulate active compound within a colon due to enhanced epithelial permeability and retention effects, therefore increasing the residence times at the target site and improving the bioavailability of a bioactive compound (Lei et al., 2016). To date, nano-vehicles have been extensively utilized in constructing colon-targeted delivery systems for improving the bioavailability of the loaded compounds.

Curcumin, a major active ingredient of turmeric, which belongs to the polyphenol family, shows no discernable toxicity and exerts anti-inflammatory, antioxidant, antimicrobial, and anti-hyperlipidemic activities, thus attracting the focus of many functional food researchers (Hussain et al., 2017). Curcumin has also been widely used as a functional food-derived factor in the food industry (Rafiee, Nejatian, Daeihamed, & Jafari, 2019a). Unfortunately, its low water-solubility as well as chemical instability makes curcumin difficult to incorporate into the food products (Ahmed, Li, McClements, & Xiao, 2012). Moreover, it is easily degraded and influenced by the food matrix (e.g., lipids and proteins) that can compromise its bioavailability (Zou et al., 2016). In this regard, nano-based carriers have been employed to tackle these problems. Various nanocarriers have been investigated for the encapsulate of curcumin (Rafiee, Nejatian, Daeihamed, & Jafari, 2019b). In particular, several colon-targeted nano-vehicles have been explored to improve the bioavailability of the curcumin. Beloqui et al. (2014) synthesized a polymeric pH-sensitive nanoparticle based on the PLGA and Eudragit S100 and evaluated its feasibility for the colon targeting of curcumin. *In vitro* studies on encapsulated curcumin demonstrated enhanced curcumin permeation across Caco-2 cell monolayers as compared to curcumin in suspension, thus, significantly increasing the bioavailability of curcumin. *In vivo* studies showed that myeloperoxidase (MPO) activity and tumor necrosis factor-α (TNF-α) secretion was reduced. These nanoparticles appear to provide specific curcumin delivery to the colon. Similarly, colon-targeted delivery systems for other bioactive phytochemicals are presented in Table 1. Challenges in fabricating functional foods incorporated with bioactive compounds lie in stabilizing these in food processing and within the GI tract. Recently, Liu and his co-workers constructed a colon-targeted nanocapsule based on self-aggregates of octenylsuccinate oat *β*-glucan and systemically verified the workability of this system by evaluating the thermal stabilities, *in vitro* stabilities, release profiles, and *in vivo* bioavailability of the loaded curcumin (Liu et al., 2017). Results demonstrated that curcumin in the nanocapsule showed better stability in storage and under thermal treatment than in its free form. Moreover, curcumin was tightly accommodated in the capsule through the upper GI tract, while it rapidly escaped as it reached the colon. The loaded curcumin generated higher values of peak concentration (C_{max}) and area under the curve than its free form, illustrating that this nanocapsule was a promising vehicle for stabilizing the bioactive compound in food processing and storage, facilitating their colon-targeted delivery and enhancing their bioavailability.

Additionally, apart from nanoparticles, there are other types of nanocarriers used for constructing colon-targeted delivery system. For instance, nanofibers fabricated by electrospinning have attracted increasing attention on encapsulating and delivering bioactive compounds (micromolecular as well as macromolecular ingredients) in recent years (Feng et al., 2017; Wen, Zong, Linhardt, Feng, & Wu, 2017). Electrospun fibers provide proper protection of the bioactive compounds due to its excellent properties, such as large surface area to volume ratio, and high porosity. Furthermore, electrospinning can be able to directly encapsulate the bioactive compounds into the electrospun fibers under the mild conditions, thus, making it an especially suitable technique for encapsulating the labile and sensitive compounds. Recently, in order to verify the feasibility of developing a microflora activated delivery system for bioactive compounds by electrospinning, a novel core-shell structured nanofilm for the delivery of protein to the colon was developed by coaxial electrospinning using bovine serum albumin (BSA) as a model (Wen, Feng, et al., 2017). First, the BSA was incorporated into the chitosan nanoparticle prepared by ionic gelation, and then the coaxial nanofilm was fabricated using alginate as shell layer and the BSA-loaded chitosan nanoparticle as core layer. Results demonstrated that 75% of BSA was released in the stimulated colonic fluid, moreover the electrospinning condition had no significant effect of the structure of BSA. Therefore, electrospinning represents a promising microflora activated colon-targeted delivery system for bioactive compounds. In the following studies, Wen and her co-workers investigated the feasibility of this system for the micromolecular (quercetin) and macromolecular (phycocyanin) bioactive compounds (Wen et al., 2019; Wen, Zong, Hu, Li, & Wu, 2018) (Fig. 2B). They found that the core-shell nanofiber could release most of the bioactive compounds in the colon with the retention of their bioactivity. In addition, triaxial electrospinning has recently emerged as a new technique in the field of encapsulation and controlled release. The schematic of the tri-axial electrospinning devices is shown in Fig. 2B, it can be seen that the fibers obtained had one additional layer than the fibers prepared by coaxial electrospinning, which may provide an extra protective layer for the loaded bioactive compounds to resist the harsh environmental conditions. Therefore, future studies could be carried out to develop high-efficiency colon-targeted delivery systems though this technique and thus promote the application of electrospinning in the functional food industry.

3.1.2. Micro-based vehicles

Microencapsulation has been proposed as a promising technology for entrapping and delivering bioactive compounds in the field of food science (Corrêa-Filho, Moldão-Martins, & Alves, 2019). Micro-vehicles ranging in diameter from 1 to 1000 μm, including microparticles, microspheres, microcapsules and microbeads, have been investigated for constructing colon-targeted delivery systems. These vehicles have great advantages for use in delivery systems, such as for protecting the active substance from degradation, realizing sustained/controlled release, and reducing toxicity and side effects (Nidhi et al., 2016). Microparticulate delivery systems developed based on different mechanisms, have been investigated for colon-targeted delivery of bioactive compounds.

Madhavi, Madhavi, and Jithan (2012) developed the colon-targeted

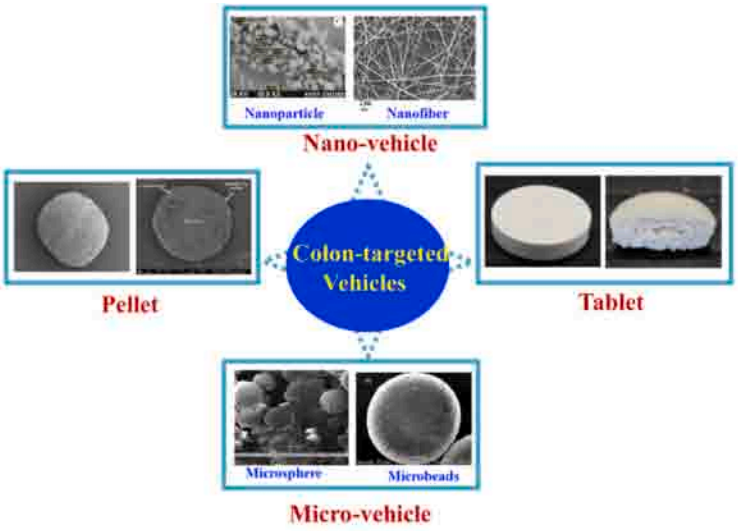
Table 1
Nanoparticulate delivery systems evaluated for colon-targeted delivery of phytochemicals.

Carrier material	Active ingredient	Average size (nm)	Result	Reference
Eudragit S 100 (ES)	Curcumin (CUR)	< 135	➢ Objective was to enhance the CUR bioavailability simultaneously reducing the required dose by selective targeting to colon. ES was chosen since it dissolves at colonic pH, resulting in selective colonic release of entrapped drug. MTT assay demonstrated a nearly 2-fold increased inhibition of the cancer compared to CUR alone.	Prajakta et al. (2009)
Chitosan (CSN)	CUR	214 ± 1.0	➢ Encapsulated CUR shows enhanced adsorption of mucin due to H-bonding and π-π interactions between CUR and mucin. Nanoparticles (NPs) ensure sustainable nanoparticulate retention along the colon mucosa and this vehicle promotes mucoadhesion and delivery of CUR at the colon.	Chuah, Billa, Roberts, Burley, and Manickam (2011)
Amorphous chitin	Paclitaxel	200 ± 50	➢ *In vitro* studies showed a sustained release of paclitaxel, preliminary results indicated the potential of these NPs in drug delivery for colon cancer.	Smitha et al. (2012)
CSN, ES	CUR	236 ± 3.2	➢ ES coating on the ES-CSN-NPs-CUR minimizes the release of CUR in upper gastrointestinal tract while maximizing release of CUR in simulated colonic fluids of pH 6.8. May be useful as potential delivery system for treatment of colon cancer.	Khatik et al. (2013)
Polyacrylamide-grafted-xanthan gum (PAAm-g-XG)	CUR	425	➢ CUR was better absorbed systemically in nanoparticulate form with increased Cm_{ax} (~3 fold) and area under the curve (AUC) (~2.5 fold) than when delivered as free CUR. Grafted co-polymeric NPs containing drug were suitable for colon targeting.	Mutalik et al. (2016)
Monomethoxyl poly(ethylene glycol)-polylactide (m PEG-PLA)	CUR	118–149	➢ *In vitro* studies showed CUR/gemcitabine exhibit greater synergy than free combinations of CUR/gemcitabine. In vivo studies showed better antitumor effects and reduced systemic toxicity in a murine xenograft model. This study suggests such nanoparticle may be useful in colon cancer therapy.	Tan, Luo, and Tian (2014)
Polylactic-glycolic acid (PLGA), poly(vinyl alcohol) CSN	Camptothecin (CPT), CUR	193–224	➢ The combined delivery of camptothecin and CUR in a single NP enhanced synergistic effects. The study represents the first report of combinational application of CPT and CUR with a one-step–fabricated co-delivery system for effective colon cancer combination chemotherapy.	Xiao, Si, Han, et al. (2015)
CSN, pectinate	CUR	206.0 ± 6.6	➢ Nanoparticle mucoadhesiveness was higher at alkaline pH than at acidic pH. More than 80% of CUR release was achieved in pectinase-enriched medium (pH 6.4) as opposed to negligible release in acidic and enzyme-restricted media (pH 6.8). The results suggest that this system could be applied for colon-targeted mucoadhesive CUR delivery.	Alkhader, Billa, and Roberts (2016)
PLGA	CUR	181.5–206.9	➢ *In vitro* cellular uptake studies with HT-29 cells showed that the optimized CUR loaded PLGA NPs exhibited a much higher cellular uptake of CUR (7.01 ± 0.33 mg/10^6 cells) than a native CUR solution (3.74 ± 0.56 mg/10^6 cells). Stability studies showed that all vehicles were stable at least for 2 months. Optimized CUR-loaded PLGA nanoparticle vehicle (C-PNP9) had potential use for the development of an efficient oral, colon-targeted drug delivery system.	Akl, Kartal-Hodzic, Oksanen, and Viitala (2016)
Pectin, $ZnCl_2$, CSN, PEG	Resveratrol	399 ± 18	➢ More than 63% of the resveratrol was encapsulated into the developed NPs. Low levels of resveratrol were released during one month in simulated juice model (pH 4.0) and the remaining resveratrol in NPs (~49%) was released in simulated colon fluid in the presence of pectinase. Nanoparticles might be used in the successful colon delivery of resveratrol in a fruit juice matrix.	Andishmand, Tabibiazar, Mohammadifar, and Hamishehkar (2017)
CSN, Nutriose, Polyethylene glycol	quercetin	132 ± 6	➢ A delayed, enzyme-sensitive delivery system was developed by the combination of phospholipid vesicle nanotechnology and a polysaccharide-starch complex. The gastric resistance of the vehicle was improved by coating with the chitosan and nutriose. The coated vesicle has a promising ability to protect the quercetin during its transit through the upper gastrointestinal tract and allow its release in the colonic region.	Castangia et al. (2014)

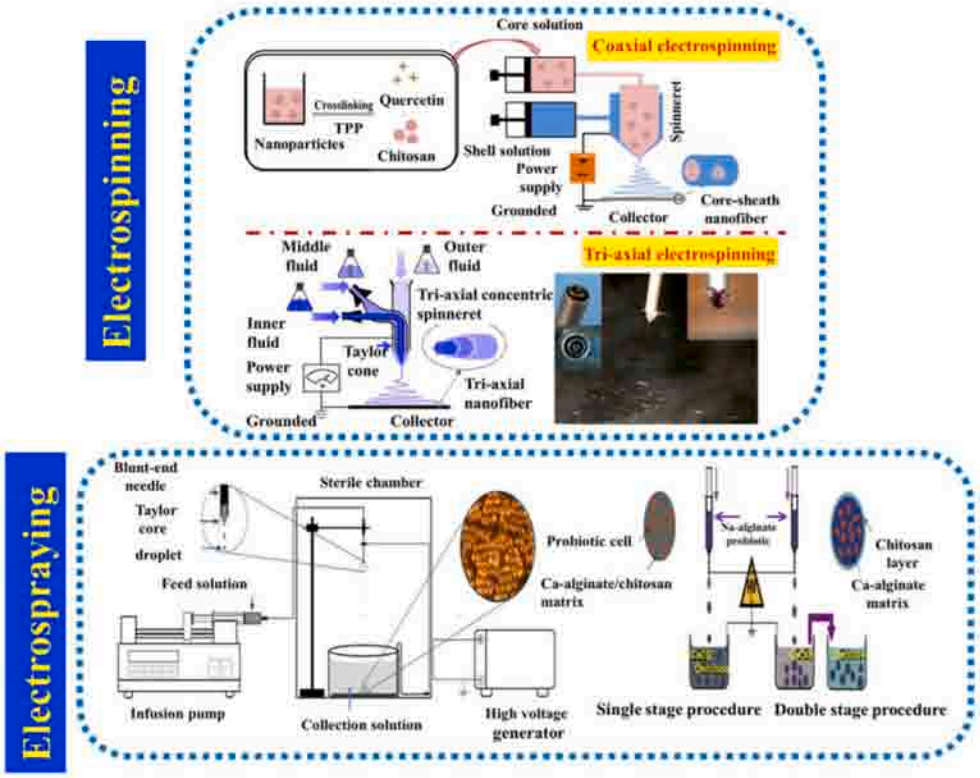
(*continued on next page*)

Table 1 (*continued*)

Carrier material	Active ingredient	Average size (nm)	Result	Reference
Ginger	6-gingerol and 6-shogaol	230	➢ The nanoparticles derived from edible ginger is demonstrated as a novel colon-targeted carrier and represent as an effective therapeutic strategy for preventing and treating IBD and CAC.	Zhang, Viennois, et al. (2016) and Zhang, Wang, et al. (2016)
CSN, pectinate	CUR	178 ± 0.896	➢ An orally curcumin-containing mucoadhesive nanoparticulate system was developed and it potential to be applied as a colon-targeted system has been confirmed. The vehicle could survive acidic milieu, but most of the CUR (up to 68%) release in cecal medium over 24 h.	Sabra, Billa, and Roberts (2018)
ES100, PVA	quercetin	66.8	➢ The polymeric nanoparticle has a pH-specific mechanism and could achieve a colon-specific delivery of quercetin. In vitro release study showed a delay release in acidic pH, but complete release at pH 7.2 within 2 h.	Sunoqrot and Abujamous (2019)
PLGA, Hyaluronan	CUR	200–300	➢ HA-functionalized polymeric hybrid nanoconjugate system provides an alternative strategy for colon targeting of CUR. The CUR could be released in the colonic region in a prolonged manner, thus improving it bioavailability.	Kotla, Burke, Pandit, and Rochev (2019)
CSN, pectinate	CUR	218.1–291.7	➢ A colon-targeted CUR-containing modified pectinate-CSN nanoparticle was developed to deliver the CUR to the colon for exhibiting its bioactivity locally. Additionally, the contact time of the carrier with the cancer cells was prolonged due to its good mucoadhesive properties.	Sabra, Robert, & Billa, (2019)
PLGA, CSN, wheat germ agglutinin (WGA), GE11peptide	CUR	209–252	➢ Three different CUR-loaded particles were prepared by coating the PLGA particles coated with CSN, WGA and GE11, respectively. Stability studies showed that the coated particles had a good colloidal stability in synthetic gastrointestinal fluids. *In vivo* studies also revealed that the WGA-coated nanoparticles could efficiently accumulate in the colon.	Akl et al. (2019)
Gellan gum, pectin	resveratrol	330	➢ Mucoadhesive nanoparticle containing gellan gum and pectin was developed for colon-targeting resveratrol. *Ex-vivo* studies indicated that there was a low permeability and high retention of resveratrol from the nano-vehicle in rat intestinal tissue, suggesting it is a promising carrier for controlled delivery of resveratrol at the colon.	Prezotti et al. (2020)
konjac glucomannan octenyl succinate	CUR	94.2 ± 4.1	➢ After encapsulation of CUR in the particle, its stability and release rate were significantly lower that of the free CUR samples in SGF and SIF. *In vivo* study also revealed that this nano-carrier has great potential for colon-targeted delivery of CUR.	Meng et al. (2020)
β-lactoglobulin,	mangiferin	89 ± 10	➢ A *β*-lactoglobulin nanoparticle was fabricated to encapsulate the mangiferin to improve its bioavailability. It was observed that approximately 80% of the encapsulated mangiferin released in the colon fluid. Both of the release mechanism analysis and time dependency study demonstrated that this nanoparticle is ideal for colon oral delivery.	Samadarsi and Dutta (2019)
stearic acid, CSN	Resveratrol	174 ± 5	➢ The efficacy of a CSN coated solid lipid nanoparticle for encapsulation of resveratrol and its colon cancer targeting property was evaluated. It was found that the nanoparticle exhibited a good stability under acidic condition and may be a beneficial biomaterial for targeted delivery and treatment of colon cancer.	Kumar et al. (2020)



(A)



(B)

Fig. 2. A) Different vehicles used for colon-targeted of nutraceuticals; **B)** Schematic illustration of electrospinning (coaxial and tri-axial) and electrospraying for constructing colon-targeted vehicles (Wen, Zong, Hu, Li. & Wu, 2018; Yu et al., 2015; Zaeim et al., 2017).

curcumin microspheres employing the Eudragit S100 as a pH dependent polymer and evaluated the *in vitro* and *in vivo* properties of this system. Results of the *in vitro* release studies revealed that the optimized vehicle showed an 8-fold enhancement of curcumin aqueous solubility. Curcumin exhibited sustained released into the systemic circulation after oral administration of the optimized vehicle. Moreover, the microspheres delivered most of loaded curcumin (79%) to the colon and could be used effectively for colon-targeted curcumin delivery. Other

similar microparticulate carriers used for colon-targeted curcumin delivery have been reported (Gogu & Jithan, 2010; Hwang & Shin, 2018; Jyoti et al., 2016; Karade & Jadhavb, 2018; Pereira et al., 2013; Sareen, Jain, Rajkumari, & Dhar, 2016; Sharma, Khan, Singh, & Bhatnagar, 2013; Singh, 2011; Xiao, Si, Zhang, & Merlin, 2015). Resveratrol, a polyphenol naturally occurring in a number of fruits and other food products, has been extensively studied and approved for its potential in promoting the colon health and for its beneficial properties, including anti-inflammatory, anti-obesity and anti-carcinogenic effects (Sebastià, Montoro, León, & Soriano, 2017). However, resveratrol can be rapidly absorbed through the upper gastro-intestinal tract after administration and only a small amount of resveratrol can reach the colon, resulting in a low bioavailability. Considering this, a colon-targeted delivery system is a great option to improve its bioavailability. A pectin-based microparticle was designed by using the zinc ions and chitosan as the cross-linking agent for colonic-specific delivery of resveratrol (Das, Ng, & Ho, 2011). This microparticle was designed by using colonic microflora as a triggering mechanism since the pectinolytic enzymes of colonic microflora can selectively degrade pectin. Indeed, one limitation is that solubility of pectin in upper GI fluids makes it unsuitable as a colon-targeted carrier. In this aspect, divalent cations, such as Ca^{2+} and Zn^{2+}, can be used to produce stronger and more water-resistant gels. Here, chitosan was utilized to interact with pectin through electrostatic and hydrogen bonding to form a polyelectrolyte complex. *In vivo* results indicated that colonic microflora activated microparticles, prepared under optimized vehicle conditions, afford the colon-targeted delivery.

To our knowledge, however, most colon-targeted delivery systems developed using a single mechanism have achieved limited success. In contrast, systems based multiple mechanisms show fewer adverse effects and can be better suited for delivering the bioactive compounds to the colon. Zhang et al. (2011) developed a Eudragit S100 coated calcium pectinate microsphere by the combination of pH dependent and microflora activated system and investigated it as a colon specific delivery for curcumin. *In vitro* release studies indicated that this microsphere could effectively protect curcumin in the upper GI tract, and the curcumin was released specifically in the colon. Similarly, coating chitin microspheres with ethyl cellulose could further decrease the release of anthocyanins in the GI tract, achieving the release of most of the loaded anthocyanins in the colon (Wang, Li, & Li, 2017). Likewise, other bioactive ingredients such as bovine lactoferrin (Balabushevich et al., 2014), kenaf seed oil (Chew, Tan, Long, & Nyam, 2015), fish oil (Chatterjee & Judeh, 2015), icariin (Wang, Wang, Zhou, Gao, & Cui, 2016), lappaconitine (Xu, Zhong, Liu, Xu, & Gao, 2011), and folic acid (Ahmad, Qureshi, Maqsood, Gani, & Masoodi, 2017) could be protected during their passage through GI tract using various microparticulate carriers.

Hydrogel beads represent another alternative micro-sized dosage form that has been widely investigated as a carrier system to encapsulate, protect and release the bioactive compounds. These are generally formed by two steps, the formation of biopolymer and the cross-linking of the biopolymers (Mcclements, 2017). For encapsulation, hydrophilic nutraceuticals are mixed with the biopolymer solution prior to formation of the hydrogel beads, whereas the hydrophobic nutraceuticals rely on the opposite approach. Different particle-formation methods have been used to fabricate hydrogel beads, including injection, emulsion templating, and electrostatic complexation. The most commonly applied biopolymers for preparing hydrogels are polysaccharides and proteins. Many polysaccharides, including alginate, pectin, carrageenan, gum and cellulose, are dietary fibers and not degraded in the upper GI tract. These biopolymers are commonly utilized to prepare colon-targeted hydrogel beads, which remain intact in the upper GI tract but disintegrate in the colon releasing loaded ingredients (Bannikova, Rasumova, Evteev, Evdokimov, & Kasapis, 2017; Keppeler, Ellis, & Jacquier, 2009; Kumar, Rijo, & Sabitha, 2018; Olukman, Oya, & Solak, 2012; Sookkasem, Chatpun, Yuenyongsawad, Sangsen, & Wiwattanapatapee, 2017). However, one similar limitation that also exists is that swelling or premature degradation of beads in the upper GI tract tends to adversely influence the efficiency of the colonic delivery system when hydrogel beads designed by using one single polysaccharide. An important approach that has been popularly adapted to address this challenge is to add a second polymer. Kumar, Bhatt, and Sharma (2016) designed and evaluated an oral, colon-targeted delivery based on the biodegradable sodium alginate. However, sodium alginate hydrogel beads showed low entrapment efficiency and burst release of the loaded compounds. Guar gum was included with the alginate matrix together with a cross-linking agent to address the above-mentioned problems. They found that presence of guar gum and glutaraldehyde increased the entrapment efficiency and prevented the rapid dissolution of alginate at the higher pH of the intestine, ensuring the expected colon-targeted release. Hydrogel beads based on one or more polymers can also serve as carrier systems for the target release of other phytochemicals, including anthocyanins, resveratrol, mango seed kernel extract, cherry laurel polyphenol extracts and ginger extract (Das & Ng, 2010; Lotfipour, Mirzaeei, & Maghsoodi, 2012; Nithitanakool, Pithayanukul, Bourgeois, Fessi, & Bavovada, 2013; Oehme, Valotis, Krammer, Zimmermann, & Schreier, 2011; Prezotti et al., 2018; Çakır & Gülseren, 2017). Besides the aforementioned approach, other microbased vehicles, which were designed by combining different mechanisms or different dosage vehicles, have been reported. For example, a multi-particulate system designed by the combination of the microflora activated and pH dependent mechanisms was shown to be workable for colon-targeted ginger extract delivery (Deol & Kaur, 2013). *In vitro* and *in vivo* studies showed that the alginate beads coated with Eudragit S100 could successfully avoid the release of entrapped ginger extract in the upper GI tract since Eudragit S100 dissolves at pH values above 7.0. Hence, these beads were a more suitable and effective dosage form to target release the Ginger extract to colon. Other research also found that curcumin-loaded, colon-targeted microbeads prepared by the combination of chitosan and Eudragit S100 could successfully deliver curcumin to colon and notably enhance the bioavailability of curcumin (7-fold), which demonstrated the superiority of vehicles combining different mechanisms (Karade & Jadhavb, 2018).

3.1.3. Pellets

Pellets are multiple-unit solid dosage forms commonly characterized by a spherical or pseudo-spherical shape and a smooth surface (Bipin & Jagdish, 2017). The techniques for producing pellets describe a size-enlargement process and currently include direct pelletization (by high shear mixer of fluidized bed), hot melt extrusion (HME) or wet extrusion (extrusion/spheronization) (Palugan, Cerea, Zema, Gazzaniga, & Maroni, 2015). Pellets find the specific application in preparation of modified release oral dosage forms when formulated as either matrix system or coated reservoirs. Matrix systems are composed of an active compound closely dispersed in inert or swellable excipients and exhibiting controlled release. The reservoir system contains the bioactive ingredient in its core and then was coated with one or more layers that are able to better control the release kinetics. Thus, the release profiles are attributed to the thickness and other properties of the coating. Pellets coated with layers based on different mechanisms have been developed and their potential applications in colon targeting have been extensively evaluated. For instance, double coated pellets, loaded with caffeine, were constructed based on the pH sensitive polymers (Eudragit FS and Eudragit RL) for colon-targeted delivery and the Eudragit FS coated pellets were also prepared for comparison. Results demonstrate that the double-coated pellets could ensure a prolonged release of caffeine in the distal small intestine and the colon (Bott et al., 2004). In another similar study, apigenin, a plant flavonoid, was also encapsulated in a pH sensitive pellet for colon-targeted delivery (Pápay et al., 2017). Additionally, pellets with a time dependent film coating were also designed and examined as a colon-targeted delivery system. In this case, a lag phase, which corresponds to the brief intestinal transit time, is essential for a successfully colon-targeted delivery. However,

because of the unpredictable residence time of solid substrates in the stomach, the coating needs to be shielded form gastric fluid. It is also particular important that their performance should be not affected by physiological variables and enzymatic breakdown. Hence, several attempts have been made to overcome these issues. For example, pellets coated with rupturable, erodible or permeable layers shown an intrinsic delayed release (Del Curto et al., 2014; Yadav, Survase, & Kumar, 2011). Furthermore, naturally occurring polysaccharides (pectin, alginate, chitosan, guar gum and amylose) are generally utilized as a microflora activating pellet coating for colon-targeted delivery of phytochemicals. Such polysaccharides have remarkable advantages, including renewability, good biocompatibility, low toxicity, and biodegradability. Among these, pectin is one of the widely studied coating materials for the designing pellets. But the solubility and swelling properties in aqueous is a major disadvantage that hinder the application of pectin as a colon-targeting biopolymer. Therefore, a considerable thickness of coating layer is often used. A rate controlling polymer, high molecular weight hydroxypropyl methylcellulose (HPMC), has also been employed as a coating layer to control the release of curcumin. Results demonstrated that the ideal vehicle exhibited a minimum release of curcumin at pH 1.2 and maximum release at pH 6.8, and an increased amount of curcumin appeared in the blood stream when compared with the use of pure curcumin, illustrating that this type of pellet could be a good candidate for colonic delivery of bioactive curcumin (Sureshkumar et al., 2009). Hiorth, Versland, Heikkilä, Tho, & Sande (2010) developed a pellet using a combination of chitosan and pectin for colon-targeted delivery of riboflavin. The coating, containing chitosan, was capable of hindering the release of the active ingredient in an enzyme-free fluid (pH 6.8). In addition, pectin can also be replaced with alginate and, thus, further improve coating performance. In pellets based on chitosan, designated for colonic delivery, it is necessary to apply a protective coating, since chitosan is soluble in an acidic medium. In this aspect, the colon-targeted pellet was fabricated by combining chitosan with natural biopolymers such as alginic acid and its salts or other polysaccharides, instead of using methacrylic acid copolymers or semisynthetic cellulose derivatives. The results of this study illustrated that pellets coated with alginate and chitosan exhibited a lower amount of rutin dissolution in the upper GI tract when compared with that in the colon (12–14%, 87–89%, respectively), demonstrating that this pellet could be a promising carrier for colon-targeted delivery of a natural product (Rabišková et al., 2011). Besides pectin and chitosan, other natural or modified polysaccharides, such as amylose and starch acetate, have also been established as a microflora activated colon-targeted delivery system (Li, Liu, Chen, & Yu, 2011; Pu et al., 2011). Tamarind seed polysaccharide, which is extracted from the kernel of seeds of *Tamarindus indica*, has been investigated to develop a colon-targeted delivery system. Kshirsagar and Pandit (2017) reported that pellets prepared by carboxymethyl tamarin seed polysaccharide could be used successfully for colon-targeted delivery of curcumin, and in this case, a solid dispersion was used to increase the dissolution of curcumin. Results indicate that the dissolution and absorption of curcumin could be increased by 1.5- and 2-fold, respectively, and, thus, an improved oral bioavailability of curcumin was obtained.

3.1.4. Tablets

Tablets, which are commonly prepared by wet granulation methods, have also been employed for developing colonic delivery systems. Taking tablets as a colon-targeted delivery system exhibits several advantages, such as simple manufacturing methods, industrial relevance, and convenience (Newton & Lakshmanan, 2014). Several types of tablets based on different mechanisms or combined with other vehicles have been proposed. Tablets based on single mechanism may have limited success in colon targeting, while the microflora activated delivery system seems to be more site-specific than vehicles based on other mechanisms (Ilango et al., 2010). Regarding this problem, a great deal of research has been devoted to design the microflora activated colonic delivery systems by applying different polysaccharides. But colon-targeted delivery systems, developed by applying one polysaccharide, have poor efficacy. For example, tablets of curcumin have been investigated by employing sodium alginate and hydroxypropyl methylcellulose (HPMC) as a carrier. Tablets with sodium alginate as a compression coat in the absence of HPMC K15M were not able to retard the curcumin release in stimulated gastric and intestinal fluids (Modasiya & Patel, 2012). Similar systems prepared by the combination of alginate and Eudragit L100 or pectin and Eudragit S100 were applied to deliver the curcumin to the colon (Butte, Momin, & Deshmukh, 2015; Kumar et al., 2018). Furthermore, other efforts have also been made to obtain a better colon-targeted delivery system by the combination of different trigging mechanisms. Caddeo et al. (2014) designed the chitosan/xanthan gum/Eudragit L tablets for quercetin based on pH dependent and microflora activated delivery mechanisms. The quercetin-loaded microparticles were compressed into the tablets, coated with pH sensitive polymer. Results showed that the microparticle tablets exhibited resistance to acidic condition, allowing a complete release of quercetin in colonic environment. This study also indicated that the tablets prepared by the combination of different trigging mechanisms or vehicles were a promising, easy, reproducible and cost-effective oral dosage form for the targeted and sustained delivery of quercetin to the colon.

3.2. Vehicles for colon-targeted delivery of probiotics

It is well known that the desired effect of probiotic can only be conferred when a minimum level of 10^6 -10^7 CFU/g of food product be eaten in sufficient amounts to afford a daily intake of 10^8–10^9 CFU (Modzelews-kakapituła, Kłebukowska, & Kornacki, 2007). There has been a rising interest in producing functional foods containing encapsulated probiotics, like cheese, yogurt, ice cream as well as chocolate in the recent years. However, the shelf life of most probiotic products is short even though they are stored at low temperature. In regard to this problem, encapsulation technologies have emerged as promising prospects for introducing the viable probiotic cells into foods (Terpou et al., 2019). Given that encapsulation matrix can provide a barrier to protect living probiotics against the harsh environmental conditions during processing, storage and GI passage, various encapsulated vehicles have been developed to improve the viability of the probiotic cells and deliver the living cells to the target site, consequently promoting the health.

3.2.1. Nano-based vehicles

Nanocarriers have been suggested as a promising alternative in encapsulating micromolecular compounds because of their inherent advantages. However, their application in bacterial encapsulation is less well explored since the microbial cells are quite large (1–4 μm) (Huq, Khan, Khan, Riedl, & Lacroix, 2013). Two strategies are currently successfully used to encapsulate the probiotics that apply a nanosized polymer matrix.

First, a Layer-by-Layer (LbL) technique, initially introduced in 1990s, represents a versatile procedure involving the absorption of oppositely charged polyelectrolytes on surfaces. LbL has been introduced for the formation of nanocages on living microorganisms. Diaspro, Silvano, Krol, Cavalleri, and Gliozzi (2002) investigated the feasibility of encapsulating living cells using the LbL method. In addition, researchers also reported that *Lactobacillus acidophilus,* coated by the self-assembled polymers, could resist adverse conditions, such as low pH, bile salts and digestive enzymes (pepsin, pancreatin) (Priya, Vijayalakshmi, & Raichur, 2011). In another study, the encapsulation of *Lactobacillus delbrueckii subsp. bulgaricus* CIDCA 333 was examined using block-copolymers of poly(acrylic acid) and pluronic as the coating materials. The survivability of encapsulated cells in different conditions, such as freeze drying, storage in stimulated gastric and

intestinal fluid were also evaluated, and the results demonstrated that the coated microorganisms were well-protected against these adverse conditions (Quintana et al., 2017). Unlike other methods, in this approach the bacterial cell was coated sequentially in suspension. Another special characteristic of LbL is that the encapsulation exhibits a permeability to molecules of size smaller than 5 nm, such as monosaccharides, disaccharides, amino acids and dipeptides or tripeptides, which can provide the main source of carbon and energy for the growth of the loaded probiotic cells. However, the encapsulation should also prevent bacteriophage, bacteriocins or harmful enzymes from permeating. In summary, the LbL technique is a promising method to enhance the viability of loaded cells during processing, storage, and transit through the GI tract.

In addition to the LbL technique, electrospinning has also been proposed as a feasible route to encapsulate bacterial cells and even virus particles (Amna, Hassan, Pandeya, Khil, & Hwang, 2013; Klein et al., 2009). It is noteworthy that the electrospinning process has no significant influence on the viability of the loaded cells by virtue of the mild processing conditions and the stability of the loaded cells are generally enhanced (Feng et al., 2018). The encapsulation of probiotic cells often leads to beaded nanofibers as the result of the widening of the nanofibers due to the relatively larger size of loaded cells. The confocal image also showed that the probiotic cells were successfully encapsulated in the nanofibers. Electrospinning has been successfully investigated as an efficient colon-targeted delivery system and exhibited good colon-specific properties. A novel double-layered vehicle was fabricated by coaxial electrospinning that was capable of improving the resistance of encapsulated probiotic bacterial cells against the low pH and bile salt conditions (Feng et al., 2020). Hence, it is foreseeable that the incorporation of probiotic cells into nanofibers will offer an effective means of delivery of living probiotic cells in appropriate levels to the colon and maintain their viability in simulated gastric intestinal juice, thus, modulating the balance of intestinal flora and promoting good health.

3.2.2. Micro-based vehicles

Microparticles are an attractive vehicle has been extensively explored for protecting probiotics from the harsh conditions and improving their survivability (Teoh, Mirhosseini, Shuhaimi, & Manap, 2011). Recently, the protection efficiency of the encapsulated *B. longum,* prepared by using extrusion and emulsion techniques, against the sequential exposure to simulated gastric and intestinal juices, refrigeration storage and heat treatment was evaluated. In this case, *Eleutherine americana* was used as an encapsulation agent since the *E. ameracana* and the related oligosaccharide extract showed resistance to low pH and partial tolerance to human α-amylase. They also found that the encapsulated cells prepared by extrusion method, survived better under the adverse conditions than those protected by the emulsion technique. Moreover, the viability of the encapsulated cells was better than free cells held at 65 °C for 15 min. This work substantiated the microencapsulated probiotic cells with *E. americana* offers an effective delivery of probiotics to the colon and maintains their survival in food products (Phoem, Chanthachum, & Voravuthikunchai, 2015). Additional micro-vehicles utilized for encapsulating and colonic-targeting of probiotics using polysaccharides and proteins are summarized in Table 2. It is noteworthy that electrospraying has received considerable interest as a method for encapsulating probiotics (Fig. 2B) (Gomez-Mascaraque, Morfin, Pérez-Masiá, Sanchez, & Lopez-Rubio, 2016; Zaeim et al., 2017; Librán, Castro, & Lagaron, 2017). Since other technologies, such as extrusion, emulsification, and spray drying, usually involve the use of polymer cross-linking or high temperatures and cell viability can be compromised. In contrast, the electrospraying can produce microcapsules without excessive use of heat, thereby producing microcapsules possessing high cell loading with good cell viability. Electrospraying can also be employed to produce core-shell microcapsules that can maximize the protection of encapsulated microorganisms. For example, alginate-zein core-shell microcapsules helped to improve the survival of encapsulated probiotics in stimulated gastric fluid up to 5-fold (Laelorspoen, Wongsasulak, Yoovidhya, & Devahastin, 2014). In regard to this technique, probiotic loaded microvehicles could be prepared in either a single step or in two steps (Fig. 2B) (Zaeim et al., 2017). Hence, this technology provides a potential alternative for delivering viable bacterial cells to the colon and helps in preserving their survival during transit of the gastric and intestinal tract.

3.2.3. Pellets

In recent years, many attempts have been made to explore different microencapsulation vehicles to enhance the survivability of the loaded probiotic cells in the harsh environmental conditions. Most encapsulation techniques, including drying, extrusion, and emulsion/interfacial polymerization, provide a physical barrier allowing encapsulated bacterial cells to resist adverse conditions. However, some significant issues still exist in terms of the currently available techniques for probiotic encapsulation. For instance, microorganisms may come in contact with aqueous and/or organic solvents or be exposed to high temperatures during the fabrication processes and this can compromise the cell viability of the final products. However, pellets, designed based on a dry polymer powder coating technique, has been used to encapsulate several bioactive components. However, the use of pellets for encapsulating probiotic cells is somewhat less explored. Pellets have been successfully used to encapsulate the *L. acidophilus* and *B. animalis* by taking hydroxypropyl methylcellulose acetate succinate (HPMCAS) as a coating material. A markedly higher survival rate of the loaded probiotic cells in the acidic medium and during storage were observed compared to free cells and marketed products prepared by a conventional enteric coating process (Park, Lee, Jun, Son, Choi, et al., 2016). In another study, probiotic cells containing powders were first compressed into a pellet, and then coated with a combination of sodium alginate and HPMCAS. The results demonstrated that the survivability of encapsulated cells in these pellets was significantly improved (10^5–10^6 fold) compared to free cells. Furthermore, an *in vitro* study showed that this system could be used in colon-targeted delivery of probiotic cells (Lone, Dhole, & Borhade, 2013).

3.2.4. Tablets

Tablets are another promising dosage form for probiotic encapsulation and have been employed to improve the stability and survival of the entrapped bacterial cells. Tablets employ different functional polymers, and are attractive due to their ease of production and administration, good acceptance, stability on storage and large-scare production properties. Furthermore, the effects of vehicle and processing parameters, including compression force, matrix-forming excipients on the bacterial viability have been investigated. Klayraung, Viernstein, and Okonogi (2009) reported that the proportion of matrix forming excipients in tablets and the compressing force both affected the tensile strength and disintegration as well as the survival of the bacterial. Tablets produced with high compression force exhibited high bacterial cell viability. Chan's group demonstrated that bacterial viability decreased when the compression pressure reached 90 MPa (Chan & Zhang, 2002). Silva et al. (2013) demonstrated that there was no significant influence of the detrimental effects for compaction forces higher than 9.8 kN ($P > 0.05$). Tablets are commonly fabricated through two strategies, either directly compressing the probiotic cells with polymer matrix or incorporating the probiotic cells loaded particles inside the tablet. In the first approach, the process simply carried out by compressing the probiotic cells with one or more matrix forming components. The tablet obtained improves bacterial stability during storage as well as in gastric fluid. Some reports also confirm that pellet coated with the polymers exhibit desirable properties including gastric protection of probiotic cells and their delivery to the colon. For example, Calinescu and Mateescu (2008) described a hydrophilic tablet

Table 2
Different microparticulate vehicles investigated for colon-targeted delivery of probiotics.

Encapsulating material	Probiotic strain	Vehicle	Result	Reference
• Alginate (ALG), Chitosan (CSN)	*E. coli* DH 5	Microcapsule	➢ Alginate-chitosan-alginate (ALG-CSN-ALG) microcapsules remain intact and stable in simulated gastrointestinal fluid and entrapped bacteria survived and grew normally. These results reinforce the potential of ALG-CSN-ALG microcapsules for the therapeutic oral delivery of live bacterial cells.	Lin et al. (2008)
• CSN, ALG	*Lactobacillus casei*	Microparticle	➢ The microencapsulation method and vehicle of microencapsulated *L. casei* shows potential for effective preservation and targeted release of viable cells in the colon.	Ivanovska et al. (2014)
• ALG, CSN	*Bifidobacterium breve*	Microcapsule	➢ Coating with chitosan increases the survival of *B. breve* in simulated gastric fluid prolong release upon exposure to intestinal pH.	Cook, Tzortzis, Charalampopoulos, and Khutoryanskiy (2011)
• ALG, Resistant starch	*Lactobacillus plantarum* PTCC 1058	Microcapsule	➢ Encapsulated *L. plantarum* reached the colon with a viable count of 6.48 and 7.23 log CFU/ml live cells, respectively, in the presence and absence of bile salts in the intestinal fluid. Free bacteria reached the colon with 4.6 log CFU/ml live cells, insufficient for probiotic function.	Shafiei (2012)
• ALG, CSN Thiolated CSN	*L. reuteri* DPC16	Microcapsule	➢ The coated system was demonstrated on HT29-MTX colonic epithelial monolayer to deliver markedly higher amount of probiotic bacteria to the *in vitro* model of colonic mucosa.	Chen, Cao, Ferguson, Shu, and Garg (2012)
• Whey protein (WP), ALG	*L. casei*	Microparticle	➢ The probiotic load in the microparticles after incubation for 3 h in simulated gastric juice containing pepsin was significantly higher (6.20–9.77 $\log_{10}$ CFU/g) than that of free cells (2.68 $\log_{10}$ CFU/g).	Smilkov et al. (2014)
• ALG, Carrageenan, CSN	*Lactobacillus rhamnosus* GG	Microcapsule	➢ Chitosan-coated ALG capsules served as a suitable delivery system for biofilm-like probiotics, owing primarily to their excellent release profile and storage viability.	Cheow and Hadinoto (2013)
• ALG	*L. casei*-01, *Lactobacillus paracasei* L26, *Lactobacillus acidophilus* KI and *Bifidobacterium animalis* BB-12	Microparticle	➢ *B. animalis* BB-12 was the most resistant probiotic strain, to both the microencapsulation process and to simulated GI tract conditions. Sometimes microencapsulation is not synonymous of cell protection. Further studies exploring coating systems can increase the resistance of microcapsule/microspheres. Cryoprotectants or co-polymers can be used with alginate without comprising the cell viability.	Sousa et al. (2013)
• ALG, Locust bean (LB) gums, Xanthan (XT) gum, CSN	*Lactobacillus rhamnosus* GG	Microcapsule	➢ LB and XT gums added to alginate (ALG) capsules improve cell release profiles. Compared to the ALG-only capsules, the ALG-LB capsules exhibit improved stress tolerance. ALG-XT capsules only improve the acid tolerance. The ALG-LB capsules possess the optimal cell release profile releasing more cells in the simulated intestinal juice than in gastric juice.	Cheow, Kiew, and Hadinoto (2014)
• ALG, Na polyacrylate	*L. plantarum* MA2	Microcapsule	➢ Probiotic encapsulated in ALG:Na polyacrylate (PAAs) (1:2) microcapsule survived better than that in ALG microcapsule both in small intestine (5.30 log CFU/mL) and large intestine (2.14 log CFU/mL) after 24 h. This might prove an effective microcapsule matrix in probiotic delivery	Liu, Sun, Sun, Rehman, and Wang (2016)
ALG, Silica	*L. rhamnosus* GG	Microparticle	➢ Encapsulation of probiotics in the core-shell ALG-silica microparticle could efficiently protect the probiotic cells from the low gastric pH. The developed vehicle allowed for a better colonization of colon compared with free cells.	Haffner, Van de Wiele, and Pasc (2017)
Pectin, Starch	*L. plantarum*	Microsphere	➢ A novel food-grade hydrogel particle and its efficacy for probiotic colon delivery were highlighted in this study. Results revealed that the viability of encapsulated cells in simulated gastric and bile salt solutions were significantly higher when compared to free cells.	Dafe Etemadi, Dimaghani, & Mahdavnia (2017)
ALG, Antacids	*B. pseudocatenulatum* G7	Microgel	➢ Microgels containing antacid ($CaCO_3$) was able to protect the encapsulated cells from the destruction of the hash conditions in the upper GI tract. It is supposed as a promising carrier for the probiotics to survive the adverse conditions and colonize the colon.	Gu et al. (2019)
ALG, CSN, WP	*B. bifidum*	Microbeads	➢ Probiotics were encapsulated into the CSN/ALG microbeads, which were double coated with WP. GIT assay showed the coated microbeads were proven to have the higher survival when incubated in the simulated conditions of the stomach and intestine.	Iqbal, Zahoor, Huma, Jamil, and Ünlü (2019)

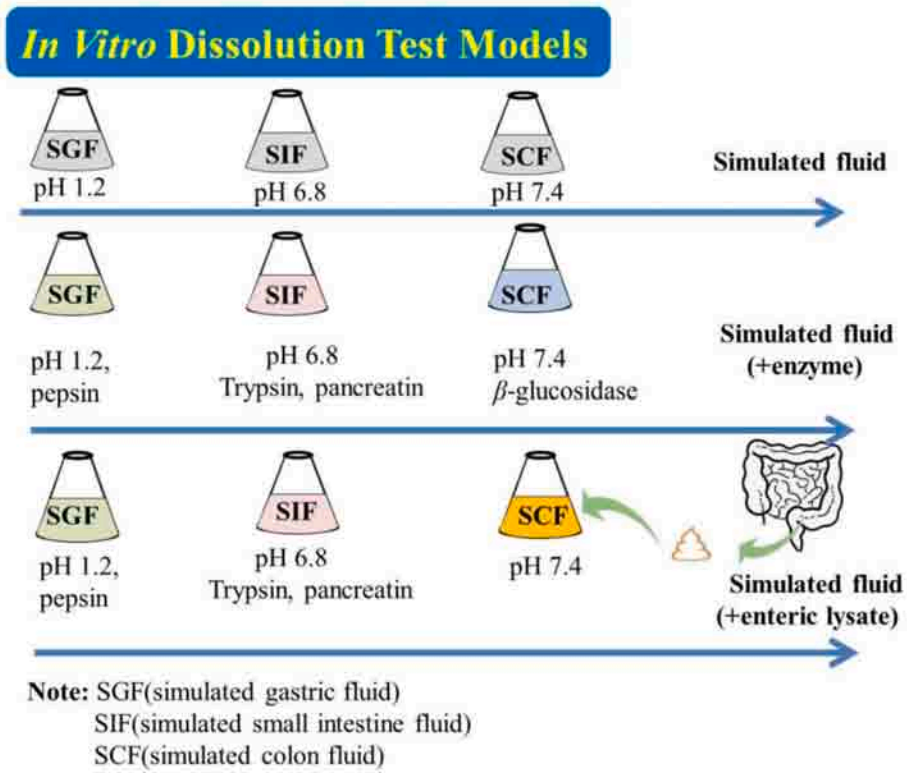


Fig. 3. Schematics of different *in vitro* simulated media to assess the release behaviors of obtained vehicles.

employing a carboxylated (carboxymethyl high amylose starch, CM-HAS) and an amino excipient (chitosan) for probiotic colon delivery. This system relies on two mechanisms to obtain a desirable release profile of the loaded probiotic. First, the tablet has a compact structure in the gastric acidity, since CM-HAS (Na^+) changes the cation for a proton, enhancing water uptake and generating the polymeric swelling and matrix dissolution. The fast dissolution of the matrix makes it impossible to achieve the colon-targeted delivery. In this case, Calinescu and the co-workers reported that the association of chitosan with CM-HAS can be used to address this limitation. Chitosan is a linear polysaccharide that is widely used for delayed liberation of active agents in colon since it can resistant the enzymes in duodenum and the lower intestinal tract, but be degraded by the colonic bacterial enzymes. However, chitosan can dissolve in gastric medium owing to the protonation of its amino groups. Hence, the CM-HAS/chitosan tablet was further coated with CM-HAS polymer to assure a good stability and cell viability in the gastric medium, allowing *Lactobacillus rhamnosus* to be delivered to the colon. Succinylated β-lactoglobulin, a novel functional tablet excipient, was examined in another study for protection the acid-sensitive bacteria during transit in the upper gastro-intestinal tract (Poulin, Caillard, & Subirade, 2011). A tablet made of native β-lactoglobulin did not ensure the cell survival in the gastric medium. However, grafting the carboxylic acids by succinylation modified the protein's physico-chemical properties, and this tablet made of β-lactoglobulin could result in survival of up to 10^7 CFU after 2 h in the gastric medium and a good stability over a period of 3 months (4 °C). This study demonstrated the potential of succinylated food proteins as novel excipient-carriers for probiotics to be delivered alive and in high numbers in the lower GI tract.

A desirable strategy involves tablets prepared by combination of two different vehicle approaches to further enhance the stability and viability of the embedded cells. For example, microparticle embedded tablets have been proposed for colonic delivery and have been applied to encapsulate probiotics. Silva and co-workers first encapsulated the probiotic (*Lactobacillus paracasei* L26) in whey protein microparticles and then these microparticles were incorporated in a tablet. This vehicle showed the potential of tablets for the colonic delivery of viable *L. paracasei* L26 cells in simulated gastric fluids with a very good percentage of cell survival (Silva et al., 2013). In another study, a multiple-unit tablet was developed and the improvement of storage stability, acid tolerance and *in vivo* intestinal protective effect was investigated. They first prepared probiotic-loaded pellets with hydroxypropyl methylcellulose acetate succinate, and explored the optimized preparation conditions, then compressed the pellet into the tablet. They found that this multiple-unit tablet showed significantly improved storage stability under ambient conditions over 6 months and a stronger resistance to acid medium compared to the native pellet. *In vivo* studies in rats also illustrate that repeated intake of this multiple-unit tablet exhibited superior properties when compared to unformulated probiotics or marketed products in rats (Park, Lee, Jun, Son, & Kang, 2016). Therefore, this multiple-unit tablet is an excellent alternative vehicle for delivering viable cells and benefiting the human health.

4. Evaluation of colon-targeted delivery system

A successful colon-targeted delivery system is one that can be capable of maintaining the integrity and activity of the bioactive compounds in the physiological environment of stomach and small intestine, but releases the active ingredients in the colon. To verify the colonic efficiency of the vehicles, various *in vitro/in vivo* evaluations studies have been proposed to investigate the release mechanisms, transit behavior of the dosage forms as well as the physiological action of the encapsulated bioactive compounds.

4.1. In vitro evaluation methods

Currently, there are no standardized evaluation techniques for *in vitro* assessment of colon-targeted delivery systems, since an ideal *in vitro* model should possess the conditions of GI tact, including pH, volume, stirring, pressure, bacteria, enzymes and other food components. Furthermore, these conditions are easily affected by several factors (e.g., diet, physical stress, disease, etc.), making it more difficult to design a standard *in vitro* evaluation model. In the past years, several *in vitro* models, while less than ideal, have been applied and are presented in Fig. 3.

4.1.1. In vitro dissolution tests

The dissolution test is probably the simplest and widely used method for evaluating oral release delivery systems including the colon-targeted delivery systems. This method is considered reproducible, scientifically justifiable and biorelevant. Generally, four types of dissolution apparatus are recommended in the USP to evaluate different dosage forms: basket, paddle method, reciprocating and flow-through cell (Emami, 2006). Dissolution tests of colon-targeted vehicles in various media simulating physiological conditions (e.g., pH conditions and transmit times) at various locations in the GI tract have been reported. For example, pH 1.0 for 2 h simulate gastric conditions, pH 6.8 for 3 h to simulate the jejunal region of the small intestine, and pH 7.4 to simulate the large intestine (Barba, Dalmoro, D'Amore, & Lamberti, 2013). In addition, kinetic studies have been conducted to investigate the release mechanisms of the bioactive agents loaded in different colon-targeted vehicles. The corresponding equations and principles of five mathematical models, including zero-order model, first-order model, Higuchi model, Ritger–Peppas model and Weibull model, are shown in Table 3 (Dodov et al., 2009; Sinha, Ubaidulla, & Nayak, 2015). Regression analysis is then conducted for the release data in different simulated fluids and the model with the highest correlation coefficient (r) is considered the best fitting.

4.1.2. Modified in vitro dissolution tests (containing enzyme)

For several *in vitro* tests, the simulating solutions simply consist of buffers with different pH values (Petrovic et al., 2013). However, these may not accurately reflect the true release performance in the human GI tract. Some researchers have carried out *in vitro* release studies in buffer medium containing enzymes, such as pepsin, trypsin, pancreatin and β-glucosidase to evaluate the release profiles of embedded components (Bokkhim, Bansal, Grondahl, & Bhandari, 2015; Liu, Ye, Liu, Liu, & Singh, 2013; Wen, Wen, Huang, Zong, & Wu, 2017). The amount released over a period of time is typically viewed as directly proportional to the rate of carrier polymer degradation. The release amount of the loaded bioactive compounds in enzyme-enriched media is generally higher than that in buffers without enzymes. The addition of β-glucosidase serves to mimic the enzymes generated by the microorganisms present in the colon, hence, the enzyme enriched simulation media are often viewed as an effective way of evaluating the release profiles of different colon targeted vehicles, especially for those based on microflora activated mechanisms.

4.1.3. Modified in vitro dissolution tests (containing enteric lysate)

The GI tract is very complex so that simulated media cannot accurately represent the real conditions even with the presence related enzymes. Hence, besides the above-mentioned *in vitro* dissolution tests and *in vitro* dissolution test (enzyme), researchers often directly carry out release studies by adding the animal cecal contents (Rajyalakshmi & Muzib, 2015) or human fecal slurries (Vieira et al., 2013) into the release medium. Ilango et al. (2010) developed a colon-targeted tablet using okra polysaccharide as a microbially triggered material. These *in vitro* release studies were carried out in dissolution medium containing rat cecal contents. A group without rat cecal contents was used as a control. In this study, the cecal contents were obtained from the rats pretreated with okra dispersion for 7 days to induce enzymes acting on okra polysaccharide. These researchers found that the maximum release was 98% at 10 h with rat cecal matter, but only 47% without rat cecal matter after 10 h. Therefore, the composition of the stimulated release medium had a significant influence on the release of the loaded bioactive compounds, particularly in microbially triggered delivery systems. The result was similar to that of another study conducted by Zhang et al. (2011). This study compared the release behaviors in the media only containing enzymes. The results showed that the cumulative amount of curcumin released from the microsphere in the presence of 1% rat cecal contents after 24 h was about 90%, while only 84% in the media with pectinase and 80% without cecal content and pectinase. These results also demonstrate that it is crucial for researchers to select a suitable medium to accurately evaluate the release profiles of the bioactive compounds in the colon-targeted vehicles.

4.1.4. Cell studies

The use of cell-based *in vitro* models allows the evaluation of bioactive ingredients permeability under conditions close to the *in vivo* or the cellular uptake properties of the loaded components (Li, Cui, Ngadi, & Ma, 2015; Zhang et al., 2012). For example, a bioactive protein, ovalbumin, was entrapped in three different polymeric nanoparticles, pH-dependent nanoparticles, bioadhesive nanoparticles, and PLGA based nanoparticles (Coco et al., 2013). The transepithelial transport of these different nanoparticles was investigated using Caco-2 monolayers mimicking an inflamed colon. Results showed that different delivery strategies had various degrees of success for the local delivery of orally administered proteins to inflamed colon. This study also illustrates the application prospect of the colon-targeted systems designed by the blending of different colon delivery strategies.

Table 3
Different release models commonly applied for characterizing the release profile of the bioactive compounds.[A]

Mechanisms	Equations	Application	Release Mechanisms
First order	$Q = 1\text{-}\exp(kt)$	One release mechanism	≻ Dissolution
Higuchi	$Q = kt^{1/2}$	One release mechanism	≻ Fick diffusion mechanism
Weibull	$Q = 1\text{-}\exp(-at^b)$[B]	More than one release mechanism	≻ $b < 0.75$, Fick diffusion mechanism; $0.75 \leq b \leq 1$, Case II transport; $b > 1$, Complex release mechanism
Ritger-Peppas	$Q = kt^n$	More than one release mechanism	≻ $n < 0.45$, Fick diffusion release; $0.45 \leq n \leq 0.89$, anomalous (non-Fickian) transport; $n = 0.89$, zero-order (case II) release; $n > 0.89$, super case II transport
Peppas-Sahlin	$Q = k_1t^{1/2} + k_2t$[C]	Quantify the contributions of erosion mechanism and diffusion mechanism	≻ $K_1/k_2 < 1$, erosion predominates; $K_1/k_2 = 1$, diffusion equates erosion; $K_1/k_2 > 1$, diffusion predominates

Notes.
[A] $Q = M_t/M_\infty$, M_t and M_∞ represent the cumulative amount of the bioactive compounds released at time t and the total amount of bioactive compounds loaded in the vehicles, respectively; k, the release rate constant.
[b] a, scale parameter; b, shape parameter.
[C] k_1 and k_2 are the diffusion and erosion terms, respectively.

4.2. In vivo evaluation methods

In vivo studies are usually conducted to evaluate site specific and the relevant physiological efficacy of the delivered bioactive compounds and to prove the workability of the resultant dosage forms. Different animals such as rats, dogs, pigs, guinea pigs and rabbits have been used to evaluate the delivery behavior since their anatomical and physiological conditions as well as the microflora are similar to those of the human GI tract. Different imaging techniques were employed to clearly examine the delivery of the vehicles and the release behavior of bioactive compounds. Additionally, an *ex vivo* study was also carried out to verify the distribution of bioactive ingredients in different GI tissues, which can in other parts to further illustrate the workability of the designed vehicles.

4.2.1. In vivo imaging

The aim of the colon-targeted system is to deliver the bioactive compounds into the absorption or function site. Vehicles based on different mechanisms have been proposed and evaluated by just carrying out *in vitro* studies but these cannot lead to an accurate understanding of the delivery and disintegration behaviors of these systems. In such cases, several imaging techniques have been applied to observe the movement of the delivery vehicles.

4.2.1.1. X-rays. X-ray imaging is the most commonly used technique for pinpointing visually various stages of the delivery vehicles throughout the GI tract of humans as well as animals. Yassin et al. (2010) designed a tablet-based colon targeted delivery system, and extensively examined the resistivity of the system to the stomach and small intestine environment and the selective disintegration of the system inside the large bowel. They observed the complete disintegration of the tablets after 10 h post administration (Fig. 4A), and similar results were also reported by Omar' group (Omar, Aldosari, Refai, & Gohary, 2007). In another report, X-ray was also used the to monitor the site specificity of the movement, location and the integrity of the vehicles in the rabbit (Ilango et al., 2010). Nandy, Verma, Dey, and Mazumder (2014) also substantiated the feasibility of X-ray to monitor the changes of the colon-targeted microspheres. Results of the X-ray images showed that the swelling layer eroded from the outer surface and a size reduction was seen after reaching the site of colon (6 h). Hence, X-ray is considered as a suitable technique for revealing the location, the swelling, intactness or otherwise of the colonic delivery vehicles in the GT tact.

4.2.1.2. γ-Scinitigraphy. Gamma scintigraphy is another utilized technique for observing the *in vivo* fate of the vehicles with respect to the GI resistance and matrix integrity in the body. Asghar and Chandran (2011) reported that the vehicles maintained intact when pass through the GI tact and colon, and the imaging results showed that a mean gastrin emptying of 1.87 ± 0.55 h, small intestinal transit of 3.1 ± 1.3 h, and the colon residence time of 16.67 ± 1.6 h, respectively. The colon arrival time was around 5.0 ± 1.52 h, which substantiate a good correlation between *in vitro* release profiles and *in vivo* transit times. Meanwhile, γ-scintigraphy was also utilized by other researchers to verify the workability of the designed colon targeted delivery system as shown in Fig. 4B and C (Cole et al., 2002; Marvola et al., 2008).

4.2.1.3. Fluorescent imaging. In addition to the above-mentioned imaging techniques, Bie, Chen, Li, and Li (2016) labeled the microcapsules with FITC and the *in vivo* colon targeted delivery of vehicles was observed by fluorescence imaging with a fluorescence image analyzer. As shown in Fig. 4D, the intensity of fluorescence in the colon weakened as a function of transit time, indicating that the microcapsules might be excreted from the body of nude mouse. A similar study was carried out to monitor the delivery behaviors of the alginate-chitosan microspheres labeled with FITC. The results demonstrated that the retention time in colon was more than 12 h (Wang et al., 2016).

4.2.2. Ex vivo tests

Nutraceuticals, especially phytochemicals or probiotics, possess various functions. One of the widely studied characteristics is their anti-inflammatory activity, thus, much research has been conducted in the design of colon-targeted delivery systems to protect these bioactive compounds and improve their bioavailability. An *ex vivo* test was proposed to observe the tissue sections and evaluate the efficacy of the colon-targeted system. These tests are mostly performed to investigate the mucoadhesive properties of the vehicles or for evaluating the impact of the loaded bioactive compounds on colonitis. For instance, Rameshand co-workers investigated the mucoadhesive properties of the tablet made of pectin and PVP by determining their *ex vivo* mucoadhesive strength (Ramesh, Rubeena, Sai, Srikar, & Anil, 2015). As a number of studies reported, many probiotic including *Lactobacillus casei* 01 have anti-inflammatory activities. Researchers have developed a probiotic loaded chitosan-Ca-Alginate microparticles to deliver the probiotic cells to the colon. From the results of the tissue test, it was clear that synbiotic microparticles showed significantly higher effectiveness in reduction of inflammation parameters, probably because of the improved viability and bioavailability of the probiotic cells (Ivanovska et al., 2017) (Fig. 5A). In addition, *ex vivo* studies were also performed to determine the distribution of the bioactive compounds in different tissue sections (gastric, small intestine and the colon epithelial tissue) by fluorescence labeling (Fig. 5B) thus estimating the colonic targeting capacity of the vehicles (Situ, Li, Liu, & Chen, 2015).

5. Current limitations and future trends

Recently, oral, colon-targeted delivery systems have been proven to be effective in the field of pharmacy due to the special character of the colon. Nevertheless, their application progress in the functional food industry lags. Bioactive components, which have physiological benefits or reduce risk of diseases, have currently attracted growing attention among food researchers. The incorporation of these bioactive compounds in a food system has been recommended as a simple way to develop novel functional foods. Thus, the protection of such bioactive food compounds and the improvement of their physiological benefits in the GI tract have led to numerous attempts to develop food-grade controlled release systems. A great number of studies have been carried out to design and evaluate colon-targeted delivery systems for the active ingredients based on various mechanisms and vehicles. However, there still remain obstacles that prevent the application of colon-targeted delivery systems in the food industry.

The mostly studied colon-targeted delivery systems mainly depend on approaches like pH sensitive systems, time dependent systems, microflora-activated systems etc. Moreover, various vehicles developed based on these mechanisms have been evaluated for their workability in colon targeting. Based on the review of relevant research, we found that some vehicles, especially those based on one single mechanism or polymer, often cannot perform well in targeted release of the bioactive compounds since it is difficult to precisely control the release of bioactive component in the human digestive system. Generally, this limitation can be addressed by combining multiple mechanisms (e.g., pH sensitive mechanism and microbial triggered mechanism) or multiple dosage forms (e.g., microparticle inside the tablet, nanoparticle inside the nanofiber) for successful colon-targeted delivery.

A second challenge is associated with the selection of the appropriate polymers. For oral, colon-targeted systems, the polymers applied need to be edible and have no adverse effect on health. In this case, natural polymers, such as polysaccharides and proteins, may be the best option due to their bio-friendly properties. Several studies developed the colon-targeted delivery systems by utilizing the modified

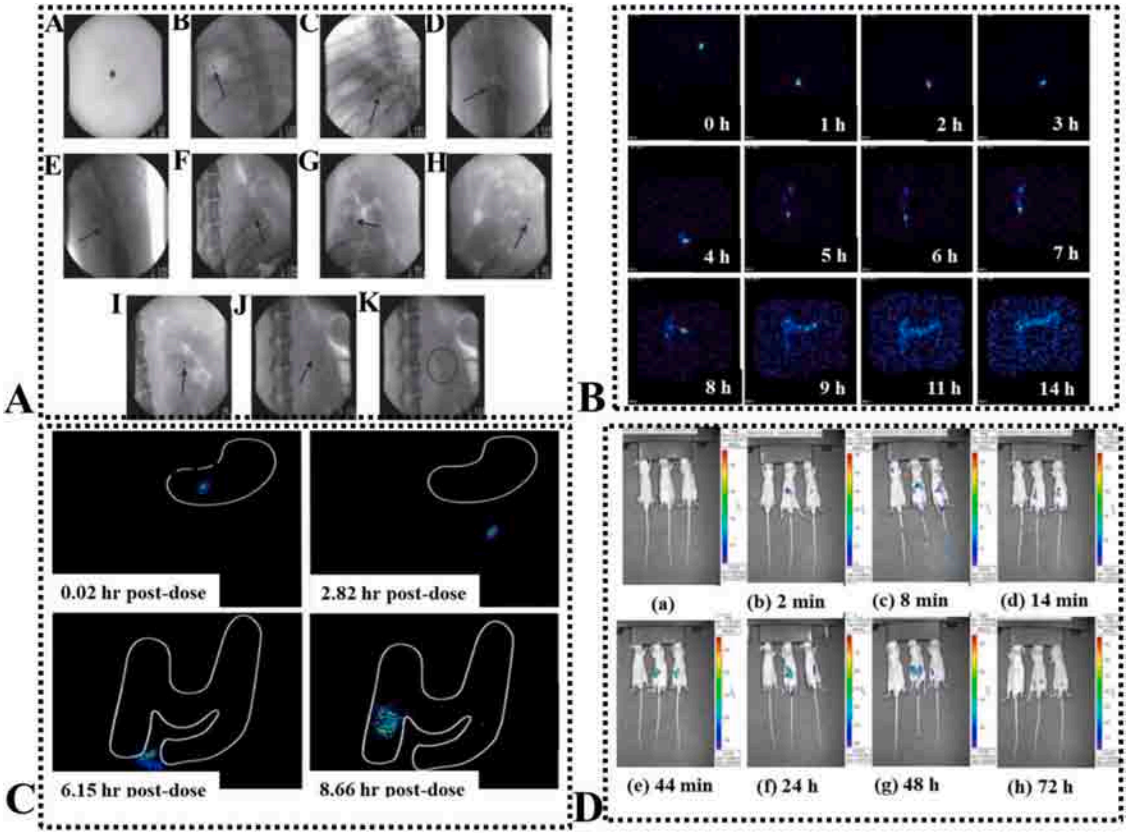


Fig. 4. Different *in vivo* imaging techniques used for monitoring the delivery behaviors of different colon targeted vehicles. **A)** X-ray imaging (A, coated tablet; B, control image (stomach); C, 0.5 h (stomach); D, 2.5 h (proximal small intestine); E, 4 h (distal small intestine); F, 5 h (colon); G, 6 h (large intestine); H, 7 h (large intestine); I, 8 h (large intestine); J, 9 h (large intestine); K, 10 h (large intestine)) (Yassin et al., 2010); **B)** and **C)**: Gamma scintigraphic imaging (Cole et al., 2002; Marvola et al., 2008); **D)** Fluorescent imaging (from left to right are the blank group and two Con A−RSA film-coated microparticle groups) (Bie et al., 2016).

polysaccharide to further improve the colonic targeting capacity of the vehicles. Nevertheless, some solvents or synthetic polymer additives are often needed in fabricating colon-targeted delivery systems. Thus, toxicity studies of residual solvents and synthetic polymers as well as their biological fate following digestion and absorption must be undertaken. Other issues concern encapsulation efficiency, distribution, and initial burst release of incorporated compounds in the vehicles also needed to be considered. Apart from this, the bioactivity of the loaded components both in the vehicles and release medium should be verified since the bioactivity is the key factor for function. The impact of the biopolymer-bioactive ingredients interactions in the targeted area on the absorption also needs to be investigated.

Future researchers should consider multifunctional colon-targeted delivery systems. Prebiotics are non-digested food compounds that can improve the growth and/or activity of the probiotics. The co-encapsulation of probiotic and prebiotic can significantly improve the survivability of the encapsulated cells when exposed to a harsh environment. In addition, the improved physiology activity of the loaded active agents can also be achieved by co-encapsulation of probiotics. Hence, the combination of prebiotics, probiotics and bioactive ingredients in one colon targeted delivery system maybe an attractive way to preferably promote the health; meanwhile, the underlying mechanisms should be extensively explored.

A more reliable and comprehensive evaluation system is required to estimate the colonic targeting capability of the designed vehicles. In fact, most studies about the release profiles of colon-targeted delivery systems are only conducted in the stimulated medium with different pH values. However, several studies have confirmed that the addition of the enzymes in the stimulated medium can have a significant impact on the release behavior of the loaded components. Therefore, the improved release medium (e.g., medium contains fecal contents, medium contains enzymes and microorganisms) should be applied to more accurately evaluate the release properties of the bioactive compounds in the future studies. In addition, efficient biological models, like cell models, mimicking the uptake of the released bioactive compounds also need to be adopted. Although *in vivo* studies are carried out in some instances, these only obtained some physiological indexes of the tested animals. Imaging techniques should be employed to clearly understand the transit behavior and biodegradation characteristics of vehicles in the GT tract. Further research is required to develop not only a better correlation between the *in vitro* and *in vivo* models and accurate scaling factors should take into account interspecies variations to accurately predict human oral bioavailability.

Last but not least, it is foreseeable that the colon-targeted delivery vehicles could be applied in the food industry and provides an alternative way to develop novel functional foods. Nevertheless, challenges in fabricating functional foods incorporated with bioactive compounds lie in stabilizing them in food processing and the GI tract. Several studies successfully developed protective vehicles to encapsulate and protect the loaded bioactive compounds, like phytochemicals and probiotics, by employing some food grade materials and both of these are powerful vehicle ingredients for stabilizing the bioactive compounds over food processing, storage and digestive fluids, thus realizing their colonic delivery. However, in regard of developing functional food for colon-targeting, colon-targeted delivery vehicles should be introduced into the food matrix, which may influence the structure of the

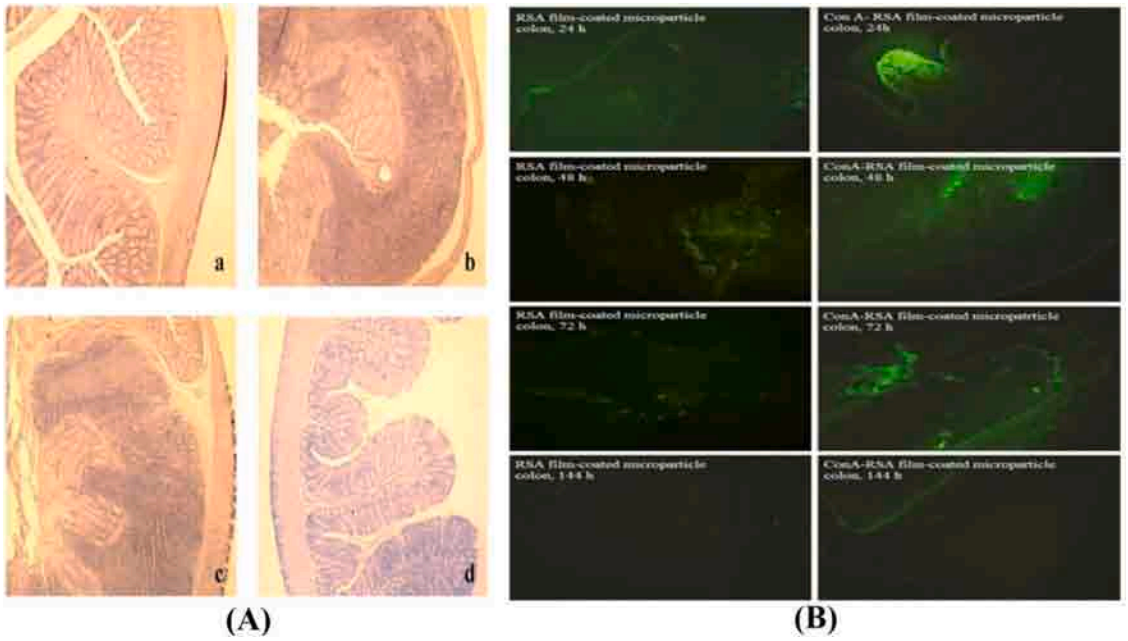


Fig. 5. A) Effect of probiotic loaded microparticle on the colitic rat's colon segments. (a, non-colitic rats; b, colitic rats; c, colitic rats treated with non-encapsulated probiotic/synbiotic; d, colitic rats treated with synbiotic microparticles) (Ivanovska et al., 2017); **B)** The fluorescence distribution after oral administration of fluorescein isothiocyanate (FITC)-labeled microcapsules coated with RSA film (left) and coated with Con A-conjugated RSA film (right) in the colon epithelial tissue of mouse at different time (Bie et al., 2016).

vehicle, compromising the bioactivity of the loaded active ingredients. Hence, it is essential to investigate the impact of the food processing (e.g., temperature, pressure) as well as the food matrix (e.g., type of food consumed, quality of food, acidity or alkalinity of food) on the structure of the vehicle, the release behavior as well as the bioactivity of the delivered active compounds. Also, additional work should be performed to examine the effect of the addition of colonic delivery vehicles on the sensory characteristics of the products.

6. Conclusions

Nowadays, colon has been suggested as a particular important site for constructing colon-targeted delivery systems due to its special properties. Much progress has been made in colon-targeted delivery of drugs in recent years. However, the colon-targeted delivery system is still in its early stage in the field of food science. Currently, with the increasing concerns on the health and nutrition of colon, colon-targeted delivery of bioactive compounds has emerged as an impetus for researchers to construct functional foods. Hence, it is necessary to review various colon-targeted vehicles used in the current research, especially those for the colon targeting of nutraceuticals, phytochemicals, and probiotics. Herein, this paper systematically summarizes information on the physiological properties of the GI tract, different colonic delivery vehicles, evaluation techniques as well as the current challenges. The issues encountered with the colon-targeted systems suggest future studies should be carried out to prepare vehicles that combine different polymers, mechanisms and/or vehicles. Also, multifunctional colonic delivery systems are an important and interesting alternative for delivering the functional bioactive compounds to the colon. Mechanistic insights into the relations between the carrier materials and bioactive compounds should be extensively investigated and should provide the theoretical basis for its industrialized application as well as promote the development of the functional industry.

Acknowledgements

This work was financially supported by the Science and Technology Project of Guangzhou City (201804010151), the National Natural Science Foundation of China (31671852), the Natural Science Foundation of Guangdong Province (2017A030313148), and the Collaborative Innovation Center for Sports of Guangdong Province (2019B110210004).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tifs.2020.05.019.

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