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Mucoadhesive carriers for oral drug delivery

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Abstract

Among the various dosage forms, oral medicine has extensive benefits including ease of administration and patients' compliance, over injectable, suppositories, ocular and nasal. Despite of extensive demand and emerging advantages, over 50% of therapeutic molecules are not available in oral form due to their physicochemical properties. More importantly, most of the biologics, proteins, peptide, and large molecular drugs are mostly available in injectable form. Conventional oral drug delivery system has limitation such as degradation and lack of stability within stomach due to presence of highly acidic gastric fluid, hinders their therapeutic efficacy and demand more frequent and higher dosing. Hence, formulation for controlled, sustained, and targeted drug delivery, need to be designed with feasibility to target the specific region of gastrointestinal (GI) tract such as stomach, small intestine, intestine lymphatic, and colon is challenging. Among various oral delivery approaches, mucoadhesive vehicles are promising and has potential for improving oral drug retention and controlled absorption to treat local diseases within the GI tract, as well systemic diseases. This review provides the overview about the challenges and opportunities to design mucoadhesive formulation for oral delivery of therapeutics in a way to target the specific region of the GI tract. Finally, we have concluded with future perspective and potential of mucoadhesive formulations for oral local and systemic delivery.

Keywords

Oral medicine; Oral delivery; Mucoadhesive polymer; Gastric cancer; Inflammatory bowel disease

1. Introduction

Patients greatly prefer oral dosage form over injections and millions of individuals skipped their medications due to needle phobia and associated pain. However, most of

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the macromolecules are not stable in gastric environment and not absorptive due to low permeability. For instances orally administered drug faces extreme obstacles due to various conditions such as lack of stability in the acidic stomach fluids, negligible solubility, and bioavailability due to barrier associated with mucus. These limitations and obstacles make the oral delivery of bio-macromolecules impossible.

Recent advances in nanotechnology-based formulation made tremendous progress in delivery science including oral delivery (Fig. 1) [1]. Nanomaterials with size below 1000 nm can pass through the biological barriers in the intestine. Among the various nano-platforms, polymer-based nanoparticulate drug delivery system has several advantages that include flexibility of formulating various types of delivery systems (micelle, liposome, layer-by-layer, and hybrid), surface functionalization, higher payload, and protection of loaded therapeutic molecules from biological barriers [2]. Additionally, the polymer-based delivery system facilitates further coating with desired materials that may result in longer retention of the drug payload and facilitate release upon reaching to the site of action. Surface functionalization provide specificity to enhance binding ability with the targeted cell. Surface functionalization has even potential to improve cellular internalization of the nanoparticles and release the payload which offer higher therapeutic effect [3,4]. However, regarding treatment of local diseases within GI (Gastrointestinal) tract, the formulation should adhere on the intestinal lumen and retain for adequate duration for achieving effective therapy. Mucoadhesiveness is a unique property of a polymer that are promising because of their strong interaction with mucin lining within the intestinal duct. In oral delivery, mucoadhesive activity of polymeric formulation enhances the retention time in GI tract and facilitate controlled releases of drug for extended time [5].

In the last 20 years polymer mucoadhesive oral delivery have been growing due to their interesting physicochemical properties. Among the mucoadhesive oral delivery mucoadhesive polymeric oral delivery is a most promising candidate. We have extensively reviewed the literature about polymeric mucoadhesive oral delivery. We have conducted literature search with term “mucoadhesive oral delivery” and “oral delivery mucoadhesive” and type of articles “Review articles” and publication dated range from 2015 – till date in google scholar. From the search results, we have collected the articles titles included terms “mucoadhesive”, “oral” and “polymer”. In following table, we have summarized the review articles published. Best of our knowledge we observed that, there is a space to draft a comprehensive review article focused on mucoadhesive polymers and their range of formulation for oral delivery application. More interestingly targeted delivery to stomach, small intestine, intestinal lymphatic and colon is not documented well.

From the Table 1, it is concluded that there is now publication focused on most promising mucoadhesive polymers, and their different types of formulations range from nanoparticles to composite. More interestingly, we also discussed the targeted delivery of formulation to desire site of diseases such as stomach, small intestine, intestinal lymphatic, and colon. We have discussed extensive literature comprehensively documents.

This article reviews the barriers for oral drug delivery and promising role that the mucoadhesive polymers can offer to overcome several biological barriers. We have

extensively reviewed hundreds of key articles related to chitosan, alginate, pectin, poly (acrylic acid) (PAA), β-glucan, and carboxymethyl cellulose (CMC). We have demonstrated the role and mechanism of mucoadhesive polymeric formulation in oral drug delivery system to target specific region of the GI tract to improve treatment of the related diseases. This article also provides the insight about gastric cancer and drug delivery system for treatment of gastric cancer (GC) and inflammatory bowel disease (IBD) using mucoadhesive polymeric system. Finally, we have concluded with further perspectives and expert opinion.

2. Major gastrointestinal diseases

2.1. Helicobacter pylori

Globally 50% of population affected by *H. pylori* and it is the most recalcitrant bacteria. It is a microaerophilic bacterium which reduce acidity. The treatment to clear *H. pylori* improved recovery of gastric ulcers and inhibits recurrence. Urease, cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VasA) are the biochemicals involved in *H. pylori* pathogenesis [16]. Currently antibiotics such as metronidazole, clarithromycin, and amoxicillin are the available treatment options. However, at serious condition antibiotics not effective. Maximum antibiotics consumption may lead gastric ulcers [17].

2.2. Gastric cancer

Gastric cancer is a major cancer around the globe. In 2018, 1 million new cases and 783 thousand deaths were reported. Gastric cancer is the firth most diagnosed and third leading mortality cancer [17]. The gastric cancer incidence rate high in Eastern Asia and Eastern Europe. Overall, the treatment available gastric cancer is poor and survival rate is very low. The major pathways for gastric cancer are such as gene mutations, epigenetic changes, and dysfunction of molecular signaling [18]. Currently available treatments for gastric cancers are such as Trastuzumab, Apatinib, Perbrolizumab, Ramucirumab, TAS-102, and Napabucasin. Lapatinib, Pertuzumab, Nimotuzumab are targeting to HER2/EGFR. Subitinib, Regorafenib, and Bevacizumab are targeting to VEGF/VEGER targeting. Nivolumab are targeting to PD-1/PD-L1 and Ever-olimus is targeting mTOR. miR-1179, miR-198, miR-623 and MiRNA used MiRNA treatment gastric cancer. LSD1 shRNA, Pin1 shRNA, PRSS23 shRNA, and GHET1 shRNA are used for gene therapy for gastric cancer [19].

2.3. Inflammatory bowel diseases

Inflammatory bowel disease is two types such as ulcerative colitis and Crohn’s disease. Crohn’s disease was first observed by German surgeon Wilhelm Fabry in 1623 and later described by and named US physician Burril B Crohn [20]. Ulcerative colitis first described by British physician Sir Samuel Wilks in 1859 [21]. High rate of IBD located in northern Europe, UK, and North America. IBD is also associated with race and ethnic origin. In North America, Crohn’s disease in Hispanic 4.1 per 100,000, in Asian 5.6 per 100,000, whereas in white 43.6 per 100,000 and African American 29.8 per 100,000 [22]. The treatment of IBD depends on other health issues, intense of disease, and patients’ tolerance of drugs. The most common drugs are anti-inflammatory and immunosuppressive agents such as 5-aminosalicylates and corticosteroids [23]

2.4. Colon cancer

Colon cancer or colorectal cancer is the third most common malignancy. It has high morbidity and mortality. Duo to development of colonoscopy, which is approved in 2014, colon cancer can be diagnosed even in early stage of colon cancer [24]. World Health Organization (WHO) report, 2018 informed that 1.80 million new cases of CRC were diagnosed, and 862,000 patients died worldwide. In US 145,600 cases diagnosis and 50,000 patients' death was reported [25]. The major risk factors are environmental and genetic. Other factors are high body weight, modern lifestyle, smoking, alcohol intake, fat diet, insulin resistance, acromegaly, renal transplantation, and MMR gene mutation [26]. The common treatment strategy available is surgery. Adjuvant chemotherapy is standard care for stage III patients. Chemotherapy also improves quality of life. However, the efficacy of these strategies is less, and chemotherapy has several side effects [27]. So targeted delivery needs to be developed.

2.5. Diabetics

Diabetics is Diabetes is a chronic health issue which affects process of converting food into energy. The hormone insulin moves sugar from the blood into your cells to be stored or used for energy. With diabetes, your body either doesn't make enough insulin or can't effectively use the insulin it does make [28,29]. According to 2019 report, 37.3 million Americans had diabetes. Nearly 1.9 million Americans have type 1 diabetes, including about 244,000 children and adolescents. 1.4 million Americans are diagnosed with diabetes every year [30]. Common medications are insulin, insulin aspart, insulin gluilisine, insulin lispro, Tresiba, Levemir, Lantus, Toujeo [31]. However, intense and combination insulin therapy for diabetics initially not guarantee of prevention to late effects. The mechanism of glucose also contributes the diabetics which are not well understand yet [32]. So, there is no medication developed. Advanced technologies and extensive and long-term impacts need to be investigated.

There is other gastrointestinal disease such as Celiac Disease, Irritable Bowel Syndrome (IBS), Lactose Intolerance, Chronic Diarrhea, Constipation, Gastroesophageal Reflux Disease (GERD), Peptic Ulcer Disease, Crohn's Disease, Ulcerative Colitis, Gallstones, Acute and Chronic Pancreatitis, Liver Disease, and Diverticulitis which are not prominent compared to above discussed diseases.

3. Oral drug delivery

Mucoadhesive polymeric oral drug delivery system can be designed sophistically to target a particular region within the GI tract such as stomach, small intestine, intestine lymphatic, and colon. Targeting mucoadhesive polymeric drug delivery to site of diseases enable higher absorption, higher concentration of the drug within the site of interest, and localized therapy. However, designing of the localized targeting delivery depend on various factors that includes pH value, length and surface area of the region, and enzyme activity. The physiological features of human GI tract summarized in Table 2 [33].

3.1. Oral delivery system to target stomach

Stomach targeting mediated local drug delivery gained great attention due to importance of development of effective therapy for *H. pylori*. *H. pylori* infection affects 50% of population worldwide and 20% of infection result in developing gastric diseases such as gastric ulcers [34]. The major challenges in stomach targeting are gastric retention, protecting the drug molecules from acidic gastric juice, and facilitating of penetration through mucus barrier. Stomach targeting is a good choice for the drugs molecules that absorbed in the stomach, low solubility in intestine milieu due to different pH, has narrow absorption window in the stomach and upper intestine, and that undergo degradation in intestine milieu [35]. Mucoadhesive polymeric oral drug delivery system offers various strategies to overcome these existing challenges.

Mucoadhesive polymeric oral drug delivery system for effective targeting to stomach, formulation should withstand the peristaltic activity of the stomach. Gastric retention of mucoadhesive polymeric oral delivery system depends on food, fed/fasted state, and pH [36]. Hence, engineering the mucoadhesive polymeric oral drug delivery systems are needed to protect the therapeutic molecules from the harsh gastric environment. Another challenge is mucoadhesive polymeric drug delivery system need to adhere on or penetrate through mucus barrier for retention in stomach. In general, the mucus thickness in stomach ranges from 50–450 micron [37]. GI mucus protect epithelium from pathogens along with nanoparticles. Hence, efficacy of gastric mucus passage is exceptionally important for eradication of *H. pylori* infection [38]. Mucoadhesive polymeric oral drug delivery system showed enhance penetration of mucus barrier compared to conventional oral drug delivery systems. However, floating and therapeutics incorporated into gastro-retentive dosage form enhance gastro retention. Hence, mucus penetrating mucoadhesive polymeric oral delivery vehicle need to be achieved for stomach targeted therapy for *H. pylori* [39].

3.2. Targeting small intestine

In absorption of therapeutics such as nutrients, drug, electrolytes, and vitamin, small intestine plays crucial role [40]. The aim to achieve targeting to small intestine is easy through enhancement of mucoadhesive polymeric oral drug delivery system uptake and local release and absorption. The promising physiological aspects need to be considered for designing small intestine targeting mucoadhesive polymeric oral drug delivery system [41]. Mucoadhesive polymeric oral drug delivery carriers' surface can be functionalized to improve cell specific interactions in small intestine to enhance retention time and uptake. Mucoadhesive polymeric oral drug delivery system should withstand harsh gastric milieu hence formulation should bypass the stomach. Towards this direction, polyanionic polymers having stability at acidic pH and labile to neutral pH need to be used as carrier in mucoadhesive polymeric oral drug delivery system for effective bypass of stomach [41,42]. Hence, mucoadhesive polymeric oral drug delivery system can be a potential carrier for small intestine targeted drug delivery.

The cells such as enterocytes, specialized absorptive columnar epithelial cells are the major cells present in the small intestine with various characteristic and receptor. The other cells are goblet cells, and microfold cells (M cells) [43]. Bacteria, viruses, and

immunogens transcytoses from mucosal surface of the Peyer's patches to the subepithelial dome through the M cells [44]. Hence, Peyer's patches and M cells gave key role in transportation and absorption of therapeutics. It is more important to design the mucoadhesive polymeric oral drug delivery system with efficacy to penetrate the mucus and reach the cell surface. Enzymes, like papain or thiols have used to functionalize on the surface of mucoadhesive polymeric oral delivery vehicle to improve mucus penetration [45,46]. Further to target the mucoadhesive polymeric oral drug delivery system to specific cells, receptor-targeting ligands need to be used to functionalize the surface. Over the last decades, neonatal Fc receptors has been explored to improve oral delivery [47]. However, M cells targeted mucoadhesive polymeric oral drug delivery system got huge attention due to lack of continuous mucus coating, reduced membrane hydrolase activity, scarce glycocalyx, and drug efflux transporters are enhanced absorption of drug [48]. Vaccination and immunotherapies have been delivered successfully through targeting M cells [49,50], in pre-clinical and clinical stages. Lectins are the widely studied ligands and found very effective in targeting M cells [51].

3.3. Intestinal lymphatic targeting

The lymphatic system is a complex network of lymphatic vessels, lymph nodes, spleen, thymus, Peyer's patches, and Tonsils [52]. Diseases like filariasis, tuberculosis, AIDS, metastasis cancers, and other chronic inflammatory diseases can be managed through mucoadhesive polymeric oral targeted delivery of therapeutics to lymphatic system. Intestinal lymphatic targeting also help circumvent first pass metabolism and reached to systemic circulation directly. This strategy is also useful to enhance oral bioavailability [53]. Intestinal lymphatics transportation pathway plays key role in oral absorption of dietary lipids. The lymphatic transportation pathway was used to study the oral absorption of drug such as halofantrine, penclomedine, ontazolast, and cyclosporine [53]. It is also proven that the chain length of the lipids affects oral absorption and fatty acids of 14 or higher carbon chain length. Prior studies showed that such peptide resulted in enhancement of transportation of fatty acid via intestinal lymphatic transport. Prodrugs mimicking triglycerides showed enhancement in lymphatic transportation compared to prodrug with mimicking to monoglycerides [54].

3.4. Colon targeting

Color targeted drug delivery can be achieved through designing the mucoadhesive polymeric oral drug delivery system with reduced absorption at GI tract prior to reaching colon. Colon targeted mucoadhesive delivery system has great potential to treat the diseases such as inflammatory bowel diseases, colon cancer, irritable bowel syndrome, diverticulitis, colon dysmotility, and parasitic disease [55]. It has reported that colon targeted mucoadhesive delivery effectively lower proteolytic activity, decreases CYP3A4 activity, diminished p-gp expression, and increased transit time in the colon compared to the small intestine [56,57]. The challenges need to address in colon targeting mucoadhesive oral delivery are protection of drug release in stomach and small intestine and feasibility of release of drug only after entering the colon.

One of the widely used strategies in colon targeting delivery have used of pH responsive polymers as carrier. Colon has pH range from 6.2 to 7.2. Among the polymer Eudragit, a methacrylic acid copolymer is extensively studies for colon targeting. Eudragit polymer dissolved at pH 6 to 7. Colon targeting Eudragit polymer are Eudragit S-100, Eudragit L-100, and Eudragit FS-30D [58,59]. However, the pH at colon changes based on diseases at colon such as ulcerative colitis pH 2.7 –5.5, Crohn's disease pH 5.3. Eudragit polymers Eudragit L100–55 can dissolved at pH below 5.5 and Eudragit E100 dissolved at pH below 5 [60]. However, pH responsive mucoadhesive polymeric oral delivery offer further benefits of longer retention time. Various mucoadhesive pH responsive polymers have been studied for colon-targeted delivery.

4. Absorption pathways

There are various parameters effects the drug absorption in gastrointestinal tract which are presented in Table 3.

4.1. Transcellular pathway

The absorption pathways are two types such as transcellular pathway and intracellular pathway. Various factors affect drug absorption in gastrointestinal tract and the absorption are categorized as transcellular and paracellular pathway [33]. Fig. 2 showed schematic illustrations of (A) the structure of the intestinal epithelium comprising enterocytes, goblet cells and M cells in Peyer's patches; (B) the presumed mechanisms of the transcellular and (C) paracellular transport of therapeutics [61]. Mucoadhesive polymeric oral drug delivery system enhanced absorptions via both pathways. In transcellular pathway, therapeutics taken up by enterocytes or M cells. Particle's size and mucoadhesive feature are the key parameters for transcellular pathway. Mucoadhesive polymeric oral drug delivery system with below 100 nm favorable for absorption by enterocytes [62]. Whereas particles 500 nm or more taken up by M cells [61]. Mucoadhesive polymeric oral drug delivery system uptake by epithelial cells can be increases by increasing mucoadhesive ability [61]. Chitosan, alginate, pectin, poly (acrylic acid), carboxymethyl cellulose are well-known mucoadhesive polymers due to electrostatic interaction with negatively charged sialic acid residues on the mucosal surface. Mucoadhesive polymers showed longer half time of its clearance from GI tract [63]. Number of studies investigated the mucoadhesive effectiveness of mucoadhesive polymeric oral drug delivery system [64,65].

4.2. Paracellular

Paracellular absorption is normally restricted due to paracellular channels and tight junctions, which are composed of transmembrane integral proteins (Claudins), junctional adhesion molecules, plaque proteins, and regulatory proteins. Claudins forms seal between cells, plaque protein offers structural support to tight junctions, and regulatory proteins regulate signals related to tight junction permeability and cell differentiation [66]. Theoretically, paracellular uptake is infeasible because the space between epithelial cells area ranges from 0.3 to 1 nm, and it is only 20 nm when tight junctions opened fully. Several studies achieved the tight junction opening in caco-2 cells monolayer using mucoadhesive polymers [67]. Various mucoadhesive polymeric oral drug delivery system have been used

to deliver the drug through opening tight junctions [68,69]. Schematic illustrations showing the mechanism of chitosan mediated reversible tight junction opening has demonstrated in Fig. 3 [67]. Mucoadhesive polymers opening tight junctions and paracellular permeability in rats has proven by microscopic and ultra-structural approaches [70]. Further transmission electron microscopic studies revealed that aggregation and retention of mucoadhesive polymeric nanoparticles occur at intestinal villi. Further, lanthanum staining also used to investigate and visualize the tight junctions opening activity of mucoadhesive polymers [67]. All these studied provided the evidence of mucoadhesive polymers activity of tight junctions opening. Due to small space between epithelial cells permeability of polymers nanoparticles anticipated release of drug from mucoadhesive polymeric oral drug delivery system. All these conclude that mucoadhesive polymeric oral drug delivery systems are effective and safe.

5. Mucoadhesive polymeric formulation for oral delivery

Most of the new therapeutic small molecule drugs are hydrophobic and hence limited their use due to low solubility in the gastrointestinal trace and poor permeability across intestinal biological membranes [71,72]. Hence various alternative strategies have been developed. However, the efficacy of oral drug delivery mainly depends on retention duration at site of target. Polymeric nanoparticles based oral delivery is one of the promising strategies to improve intestinal retention. In last 2 decades polymeric drug delivery systems such as polymeric nano-particles, polymeric micelles, hydrogel, and nanocomposites gains significant attention. Therapeutic agent can be delivered through various polymer based oral drug delivery vehicle which release the drug at desired site of action [73,74]. Polymeric nanoparticles can be administrated through different routes such as oral, intravenous, and transdermal. Among them, oral delivery is more favorable and feasible. Among the various polymeric oral drug delivery system, mucoadhesive polymers-based oral drug delivery has emerging potential and possibilities. The most promising mucoadhesive polymers used in oral drug delivery are chitosan, alginate, pectin, poly (acrylic acid), and carboxymethyl cellulose [75]. In following section, we have discussed the mucoadhesive polymeric oral drug delivery systems to target stomach, intestine, and colon.

The ideal characteristic of mucoadhesive polymer included- a polymer should not be toxic, non-absorbable from the GI tract, nonirritant to the mucous membrane, feasibility to form strong bond with mucin epithelial cell, should not be hindrance to drug release, good storage stability, longer shelf life, and should be cost-effective.

The most important factor effects the mucoadhesion of a polymer including molecular weight, chain length, spatial arrangement, flexibility, hydration of polymer, hydrogen bonding, charge, degree of ionization of polymers, and polymer concentration. The environmental factors are such as pH, applied strength, contact time, and swelling, as well physiological factors such as mucin turnover and disease state play critical role in mucoadhesiveness [76].

5.1. Chitosan

Chitin is one the polysaccharides produced by marine organism. Due to the properties such biocompatibility, bioactivity, biodegradability, and high mechanical strength chitin gained attention from researcher. Low solubility limited its use [77]. Researchers modified the chitin to produce chitosan. Chitosan consists of d-glucosamine and n-acetyl-d-glucosamine united with 1, 4-glycosidic linkage. Recently chitosan and its derivatives have been considering as carrier for mucoadhesive oral drug delivery to improve stability, controlled release, reduce side effect, and to enhance bioavailability [78]. Moreover, large number of studies proved the efficacy of chitosan for mucoadhesive oral drug delivery including gastric cancer.

5.1.1. Functionalization—Further to improve the physicochemical properties and to introduced functionality as per required many studies modified the chitosan. Modified chitosan showed enhance solubility and absorption at neutral pH [79]. More interestingly, immobilization of thiol groups of chitosan showed significant enhancement of mucoadhesive capability [80]. In this section, we have discussed the chitosan and modified chitosan polymer use in mucoadhesive oral drug delivery.

Due to the availability of reactive hydroxyl and amino functional group, chitosan can be easily modified with diverse array of moieties. The most common modification reported in literature are quaternization, thiolation, carboxylation, alkylation, acylation, PEGylation, and graft copolymerization to improve the beneficial physicochemical properties of chitosan such as water solubility, musoadhesion, enzymatic inhibitory, and tight junctions opening activity [81].

Quaternization mainly increases solubility of chitosan [82]. Various quaternized chitosan are synthesized such as trimethyl chitosan (TMC), dimethyl ethyl chitosan (DMEC), diethyl methyl chitosan (DEMC), and triethyl chitosan (TEC). TMC widely used in mucoadhesive polymeric oral drug delivery. The order of tight junctions opening activity is TMC > DMEC > DEMC > TEC > CS. Recently, quaternary ammonium palmitoyl glycol chitosan has been reported. It formed polymeric micelles were considered as solubilizer to enhance dissolution rate of hydro-phobic drugs [83].

Thiolated chitosan can be synthesized via coupling with sulfhydryl bearing agents such as cysteine, thioglycolic acid, and glutathione on backbone of chitosan. The most common thiolated derivatives are chitosan-thioglycolic acid (CS-TGA), chitosan-cysteine (CS-Cys), CS-glutathione, CS-4-thio butyl-amidine (CS-TBA), and chitosan-thio ethyl amidine (CS-TEA) [84]. Mucoadhesive activity increases for thiolated chitosan compared to chitosan. Due to cysteine rich glycoproteins in mucus layer, the interaction between cationic thiolated chitosan and anionic mucosal substances is strong. Mucoadhesive activity increases with increase of degree of thiolation [85]. Trimethyl chitosan – cysteine conjugate was synthesized to enhance mucoadhesion and permeation activity [86].

To increase solubility of chitosan in water, chitosan can be modified by carboxyl group. Carboxymethyl chitosan and n-succinyl chitosan have been synthesized. It has proven that carboxylate chitosan derivatives deceases transepithelial electric resistance and increases

paracellular permeability of heparin in epithelial cell monolayer [61]. Carboxylate chitosan grafted poly (methyl methacrylate (PMMA)) nanoparticles showed pH sensitivity and hence pH sensitive insulin delivery was achieved [87].

Chitosan can be used to deliver both hydrophobic and hydrophilic drug through preparing derivatives by reaction with n-acylation and fatty acids, which formed nanoparticles through self-assembly in aqueous media. The acidic group interact with sialic acid and hydrophobic methyl group interact with fucose residue [88]. Insulin delivery has achieved through lauryl succinyl chitosan. Where lauryl group offers mucoadhesion and carboxyl group open the tight junctions [89].

Poly (ethylene glycol) (PEG) is a highly hydrophilic and flexible polymer makes interesting polymer. PEG offers flexibility to modify the surface to increase hydrophilicity and circulating half-life [90]. Modified PEGylated chitosan used as coating on nano capsules, which showed enhanced stability in simulated gastric fluids and reduced cytotoxicity [91].

5.1.2. Chitosan as oral delivery vehicle—Due to range of physicochemical and mechanical properties, chitosan based various types of nanocarriers have been developed such as chitosan-drug conjugate, hydrogel, micelles, microsphere, microparticles, nanocomposites, nano-capsules, and nanoparticles. Hence, chitosan is widely explored mucoadhesive polymer in oral drug delivery [92]. In vivo efficiency of drug loaded chitosan NPs in enhancing the drug absorption via the intestinal epithelium thereby increasing the drug available for absorption (Fig. 4A).

Chitosan widely used mucoadhesive polymer in oral delivery [99]. Chitosan based oral drug delivery formulation can transport through different mechanism such as transcellular route and paracellular route [100]. To improve and tune the physicochemical properties of chitosan to achieve desired drug delivery system, chitosan can be modified as quaternized chitosan, thiolated chitosan, carboxylate chitosan, amphiphilic chitosan, chitosan derivatives with chelating agents, and PEGy-lated chitosan [101]. Delivery of insulin, exendin-4, salmon calcitonin, cyclosporine, proteins, nucleic acids, and polysaccharides delivery can be achieved through chitosan [61,102].

Transcellular uptake of chitosan based oral drug delivery formulation proceeds through transcytosis, in this process formulation taken up by enterocytes (<100 nm) or M cells (<500 nm) [101]. Particle's size and mucoadhesiveness enhance transcellular mechanism. In para-cellular, route nanoparticles can uptake through space between the epithelial cells [61,101]. Theoretically, paracellular transport is not possible. However, Chitosan has ability to open the tight junctions in intestinal cells; hence, chitosan used as paracellular permeation enhancers. Further paracellular transport of chitosan proven by microscopic and ultra-structural approaches, and visualization using electronic microscopic examination [100,103].

More interestingly, chitosan exhibits mucoadhesive which offers prolong residence time in the small intestine. Chitosan facilitate the paracellular transport of drug through opening tight junctions between epithelial cells. Therefore, many studies have focused on chitosan

based nanocarriers formulation for oral delivery of drugs for gastric cancer. The features such as tight junctions opening, mucoadhesive properties, and solubility at acidic pH and aggregation at neutral pH suggested that chitosan could be an effective mucoadhesive agent and enhance absorption only an intestine lumen only at pH below its pKa i.e., 6.5 [104].

5.1.2.1. Chitosan-drug conjugate.: Due to availability of various active functional group in chitosan, provide flexibility to modify their backbone. The most common chitosan derivatives are trimethyl chitosan, carboxymethyl chitosan, and thiolated chitosan [105]. Trimethyl chitosan and carboxymethyl chitosan are water soluble polymers and forms nanoparticles through ionic gelation. Trimethyl chitosan is a partially quaternized chitosan derivative having solubility at neutral pH. Trimethyl chitosan used to conjugate with drug or peptide for delivery. Chen et al. reported the trimethyl chitosan-CSKSSDYQC peptide conjugate for delivery of gemcitabine in porcine intestine [106]. It improved the oral bioavailability of gemcitabine and anti-tumor efficacy increases 3.3-fold [106]. Carboxymethyl chitosan also showed great potential in oral delivery such as carboxymethyl chitosan/chitosan as nanocarriers to delivery extracellular products and effective absorption in intestinal mucosa. Compared to Trimethyl chitosan and carboxymethyl chitosan, thiolated chitosan promising in oral delivery due to mucoadhesive property. There are various thiolated chitosan have been developed such as chitosan-cysteine (CS-Cye), chitosan-glutathione (CS-GSH), chitosanthioglycolic acid (CS-TGA), chitosan-thiobutylamidine (CS-TBS), and chitosan-N-acetyl cysteine (CS-NAC). Among all CS-NAC showed excellent characteristic [107]. Diabetics is fast growing disease and number suggested the death rate about to double between 2009 and 2034. One of the best treatment options is insulin. The most commonly insulin administrated through subcutaneous injections. However, the major disadvantages are cause of peripheral hyperinsulinemia, which lead to hypertension and atherosclerosis [108]. The best option is oral delivery of insulin, which also reduce side effects [105]. The main issue with oral delivery of insulin is liable to GI tract and poor permeability. Hence, suitable oral delivery system is required to deliver the insulin effectively. Among the various drug delivery system, encapsulation into polymer is promising system for insulin delivery. Among the various polymer, mucoadhesive chitosan based oral drug delivery can be an effective carrier. Chitosan is biocompatible polymer with ability to protect from enzymes in GI tract [105]. Sudhakar et al. synthesized the thiolated chitosan nanoparticles (200 nm) loaded with insulin [107]. Pentaerythritol tetrakis (3-mercaptopropionate) (PETMP) used to synthesis thiolated chitosan (TC). TCNP showed sustain release of insulin at pH 5.3. It showed no effect on cell viability. The in vivo studies conducted in diabetic rats, due to mucin interactions, insulin remain prolonged period and increases biodistribution and bioavailability. FITC labelled TCNPs showed absorption and uptake in caco-2 cells [107]. This study offers better oral delivery of insulin for diabetic treatment.

Chitosan can conjugate with other polymers easily and forms chitosan-polymer conjugates. Alginate, poly-lysine, and poly (γ-glutamic acid) are the major polymers form conjugate with chitosan. PY-CAPLA copolymer has synthesized which showed excellent uptake in Caco2 cells and formed nanoparticles loaded with PTX (paclitaxel) through self-assembly. The bond between cysteine and mucin results due to mucoadhesive property [109]. It

improved oral bioavailability of PTX and enhanced anti-tumor activity in Heps tumor bearing mice. Polymers along with conjugation, they also used as crosslinking to fabricate nanoparticles. Polymers such as γ-glutamic acid have used as cross-linker in formulation of chitosan-based nanoparticles. Chitosan also used as coating material to coat on the negative charge composites. Trimethyl chitosan coated PLGA (poly (lactic-co-glycolic acid)) nanoparticles used to deliver the insulin. Trimethyl chitosan-PLGA showed permeation across caco-2 cell monolayer through opening tight junctions [109].

Yearly, 990,000 incidents with 738,000 deaths are cause because of gastric cancer worldwide. 18.1 million new cases and 9.6 death with cancer were reported in 2018. Approximately 5% of patients have hereditary forms. About 30–40% of hereditary cases have identified mutations in the CDH1 gene coding E-cadherin [110]. Gastric cancer has 5-years of survival. Gastric cancer is the fourth common cancer and second according to death. Compared to male, more than double cases has reported in women. Eastern Asia and Eastern Europe are remained at top with high number of gastric cancer incidence [110]. According to WHO, gastric cancer are two types such as adenocarcinoma, carcinoma with lymphoid stroma and the hepatoid adenocarcinoma. Nearly 90% of gastric tumors are adenocarcinoma again divided as tubular, papillary, mucinous, poorly cohesive, and mixed. Pathogenesis is multi step multi factorial and complex in gastric cancer [111]. Gastric antrum cancer and gastric carcinoma are the most common types of gastric cancer. Gastric cancer has low rate of diagnosis is the reason for high rate of incidence and metastasis and mortality. Gastric cancer can determine as sporadic and familial disease. At early stage of gastric cancer is limited to mucosa and submucosa and at advanced stage it is beyond the gastric muscular layer, subserosa, and other organs [112]. Factors such as salt in diet, medication, smoking, alcohol consumption and *H. pylori* infections are major factors for chronic gastritis. The major risk factor in familial gastric cancer is such as *H. pylori*, diet habits, and gene polymorphism in pro- anti-inflammatory cytokine gene [113].

Radical surgery and chemotherapy at early-stage gastric cancer is offering nearly 90% survival. However, it is difficult to detect the gastric cancer at early stage due to lack of specific symptoms. Hence, early-stage detection rate is very low. In other hand, at advanced stage there is no chance for surgery. Due to detection of gastric cancer at advanced stage, tradition chemotherapy has limited efficacy [114]. Hence, patients leading to poor prognosis. Overall, the treatment available are poor and hence remain survival rate low. Hence, there is a high demand for research and development of treatment for gastric cancer.

Targeted delivery of therapeutics mainly two approaches such as systemic delivery of therapeutics using nanocarriers or localized delivery of therapeutics to the diseased tissue. Usually, nanocarriers are used to pack the therapeutics. Encapsulation of therapeutics candidate such as small molecule, RNAi polymer and peptide into the nanocarrier improves their solubility and bioavailability, which alter their bio distribution and can facilitate to reach site of interested [115]. This is the extensively studied approach for targeted delivery to gastric cancer.

Selenium (Se) is a potential chemotherapeutic agent against malignant tumor. The major source is selenium oligosaccharides. Artificial synthesis on demand due to lack of enough

natural production. Jiang et al. synthesized the chitosan oligosaccharide (COS) conjugated selenium (COS-Se) [94]. They have studied the COS-Se toxicity, activity to improve immune function and inhibition of growth of gastric cancer. The COS-Se showed immune enhancing effect by promoting phagocytic index, spleen index and thymus index without toxicity in Kunming mice. It also showed proliferation and metastasis inhibition. COS-Se reduced CD34, VEGF and MMP-9 levels in nice mice and showed good potential as a functional food ingredient [94]. The COS-Se integrating the advantages of both entities and showing significant enhancement of immune function and blocking gastric can cancer growth (Fig. 4B). This study concluded COS-Se as a new functional food ingredient in cancer prevention.

Compared to chitosan and chitosan derivative-based nanoparticles system, conjugation of chitosan with drug is more effective for targeted delivery. Polymer strongly hold the drug due to covalent conjugation and drug release after degradation of polymer due to local conditions. Polymer-drug conjugate system widely studied for gastric cancer treatment. As chitosan has interesting properties for oral delivery, to investigate the efficacy of chitosan carboxymethyl in drug-polymer conjugate system, previous studies also reported that, NCTD showed antitumor effect in gastric cancer. However, its use in limited due to poor absorption, short half-life, and nephrotoxicity. Chi et al. conjugated NCTD to carboxymethyl chitosan and antitumor efficacy evaluated in vitro and in vivo [116]. Results suggested that conjugate more effective in triggering apoptosis of SG-7901 cell relative to free NCTD. CMCS-NCTD conjugate remarkably reduced toxicity and improve antitumor efficacy in vivo with a 59.57% tumor suppression SGC-7901 gastric tumor in mice. It also upregulates the TNF-α and Bax, and downregulate CFGF, BLC-2, and MMP-9 [116]. These results suggested that CMCS-NCTD conjugate might be promising therapeutics for gastrointestinal tumor therapy. Recently, various studied used the targeting agent conjugated polymer for targeted therapy to gastric cancer. Lin et al. synthesized the fucose-conjugated chitosan, PEG-conjugated chitosan complexes with gelatin of encapsulated green tea polyphenol extract of EGCG (epigallocatechin-3-gallate) [95]. PEG is a hydrophilic nonionic polymer with antigenic properties and non-toxic. PEG extensively used in graft formulation for oral delivery. Fucose is a deoxyhexose sugar used as targeting agent. Site-specific and target activated oral delivery can be a promising approach to treat gastric carcinoma. This formulation showed protection at gastric acid and inhibited gastric cancer cell growth, induced cell apoptosis, reduced VEGF protein expression. It also showed anti-tumor activity in in-vivo in orthotopic gastric tumor mouse model (Fig. 4C) [95]. This study opens a new window to explore further EGCG loaded nanoparticles combination with various chemotherapeutics agents needs to be investigate.

IBD is a gastrointestinal inflammatory disorder characterized by their chronic and inflammations throughout the GI tract. IBD basically two types such as Crohn’s disease (CD) and Ulcerative colitis (UC). In CD, the inflammation is discontinuous and starts from lower part of intestine and colon. In UC, inflammation is continuous from rectum to colon. Both significantly affect the quality of life of patients [117]. It also increases risk of death. IBD affected 3.5 million population globally. The major factors associated with IBD are genetic factors, environmental factors, and microbial dysbiosis. Despite of extensive research the etiology of IBD not fully understood. Drugs such as corticosteroids, amino

salicylates, and antibiotics are the conventional medicine used for IBD [118]. Recently, monoclonal antibodies such as anti-tumor necrosis factors have identified for effective therapy. However, 30% of patients non-responsive to anti-TNF agents. Various drug delivery systems have been developed for IBD therapy. However, they have suffered with premature release and inability to survive with various GI barriers such as mucus layer, opening tight junctions, and ability of retention at desired site [119,117]. Hence, it is challenging to develop effective mucoadhesive oral drug delivery system for IBD therapy.

There are various types of conventional drug delivery systems have been developed for IBD treatment. Very recently, mucoadhesive polymers showed promising results with excellent physicochemical and biological properties. Among the various mucoadhesive polymers chitosan showed great potential towards IBD therapy. Chitosan oligosaccharide shows high solubility non-toxicity, and biocompatibility and hence studied extensively. Chitosan oligosaccharides also used for gastric cancer treatment. Yousef et al. investigated the chitosan oligosaccharide potential in inflammatory bowel disease therapy [120]. They have prepared chitosan oligosaccharides with 5–10K Da and more than 90% of degree of deacetylation. Oral administration of COS protected against mortality and intestinal inflammation in a mouse model of DSS (dextran sulfate sodium). The nuclear factor kappa B (NF-kB) activation and suppressed the level for tumor necrosis factor-alpha and interleukin-6 (IL-6) in colon tissue after treatment with COS to DSS and another mouse model of acute colitis induced by rectal installation of 4% acetic acid. COS also prevented the oxidative stress induced apoptosis of T84 cells. This study encourages for extensive investigation of COS activity and mechanism against IBD [120]. The prodrug approach has proven as a most successful method for colon targeted delivery of 5-ASA (5-amino salicylic acid). The prodrug of 5-ASA commercially available in the market with name sulfasalazine. However, it has several side effects such as hematuria and hepatitis. To overcome it various azo conjugated of 5-ASA investigated. However, these synthesis polymers have own disadvantages as they are no biodegradable and not biocompatible. However, mucoadhesive polymers have excellent physicochemical properties to use them as drug delivery carrier. Shen et al. explore the mucoadhesive polymer-drug conjugate system for IBD treatment [96]. They have synthesized the quercetin conjugated glycol chitosan product micelles. They used ROS responsive linker to conjugate drug to polymer. ROS (reactive oxygen species) is overexpressed at site of inflammation in colon so it can be used as stimuli for targeted delivery. At physiological pH, less than 20% and in presence of H_2O_2 total drug released. Bio-distribution analysis showed accumulation of micelles in colitis mice model. Micelles successfully suppressed YNF-α, IL-6, ad iNOS in DSS mice model. This study demonstrated the inflammatory targeted delivery of quercetin for improved therapeutic effect of IBD (Fig. 4D). This study encourages for smart drug delivery designing for IBD [96]. Nalinbenjapun et al. studied the 5-aminosalicylic acid conjugated with N-(4-aminobenzoyl)-chitosan for colon targeted delivery to treat IBD [121]. 4-amino benzoyl used as spacer. The drug from sulfasalazine has not release in simulated gastric fluid, simulated intestinal fluid and simulated colon fluid. However, release of 70% of drug in 24 h observed in all above mediums containing rat gastrointestinal contents. Whereas the chitosan-5-ASA conjugate release only 25% of drug in 24 h. This study proven that mucoadhesive polymer-drug conjugate system can be effective in colon targeted delivery

for IBD. However further formulation of nanoparticles of mucoadhesive polymer-drug conjugated further enhanced the efficacy towards IBD [121].

5.1.2.2. Chitosan based micelles for oral medicine.: Other polymeric nanocarriers for oral delivery are micelles. Micelles are spherical core-shell nanoparticles with hydrophobic core and hydrophilic shell. Shell protects the drug loaded in core from aqueous environment [105]. Hence, Amphiphilic polymers gained great attention in drug delivery of hydrophobic drugs due to their efficiency of self-assembly structure having hydrophobic core and hydrophilic shell in aqueous media. The core can accommodate hydrophobic drug. The shell provides colloidal stability [122]. Various amphiphilic copolymers-based micelles have investigated in oral drug delivery. Recently natural polysaccharides such as chitosan gained attention in their use as carrier for oral drug delivery. Kumar et al. reported on polymeric micelles composed of amphiphilic oleic acid modified carboxymethyl chitosan (OA-CMCS) used to deliver BCS (Biopharmaceutical Classification System) Class IV drug and evaluated intestinal permeability and pharmacokinetic, where docetaxel was used as model drug [97]. Spherical docetaxel loaded OA-CMCS micelles with size 213 nm having EE of 57% formulated. The micelles showed apparent permeability of more than 6-fold. In vivo pharmacokinetics results show C_{max} 1.9-fold and AUC 2.6-fold enhancement (Fig. 4E) [97]. This study demonstrated that chitosan based amphiphilic polymers can be a potential mucoadhesive oral drug delivery carrier. Wang et al. synthesized the carboxymethyl chitosan rhein polymeric micelles for oral delivery of paclitaxel and evaluated their intestinal permeation [123]. Paclitaxel loaded polymeric micelles shows size below 200 nm with drug loading capacity of 35%. The micelles enhance the absorption of paclitaxel without causing injury to intestine villi. Results reflected the micelles uptake into the enterocyte independent to P-gp. Biodistribution studies confirm the absorption of micelles at intestinal villi. It also further supported by bioimaging of tumor-bearing mice [123]. Due to ability of micelles for significant internal permeation enhancement, these micelles are promising oral delivery carrier for water insoluble drugs.

H pylori infection is a major disease at stomach. It occurs 25–50% and 70–90% of population in developed and developing countries respectively [124]. Hence, complete eradiation of *H. pylori* is a global challenge. Antibiotics in the stomach to cure *H. pylori* is not effective due to adverse gastric environment. Cong et al. developed polymeric micelles [98]. They have fabricated ureido-modified carboxymethyl chitosan graft stearic acid polymeric nano-micelles to delivery clarithromycin targeted to *H. pylori* [98]. The prepared nano-micelles showed 200 nm size, no cell toxicity against AGS cells, stable in simulated gastric fluid for 24 h in 1x PBS. Ureido facilitate the excellent targetability to *H. pylori*. Nano-micelles showed excellent drug loading efficiency and control release of clarithromycin. In-vitro studies confirmed superior anti *H. pylori* effect (Fig. 4F). Lin et al. has developed a stimuli pH responsive chitosan/heparin nanoparticle for stomach specific anti *H. pylori* therapy [125]. Through instant addition of heparin solution to chitosan generates the pH responsive nanoparticles with size of 300 nm, positive surface charge and stable over pH 1.2 to 2.5 offer protection from gastric fluids. They have demonstrated the nanoparticles adhere and infiltrate cell-cell junctions and local interaction with *H.*

pylori. In vivo studies conducted using mouse model and results proven the localization of nanoparticles at spaces of the gastric villi [125].

5.1.2.3. Chitosan based microsphere for oral medicine.: Microspheres are one of the extensively studied nanoparticles. Microsphere of various polymers such as chitosan, chitosan derivatives, alginate derivatives, PLGA, PLA (poly (lactic acid)), and PCL (poly (caprolactone)) have widely studied in drug deliver due to their excellent physicochemical properties such as biodegradable, non-toxic, and non-immunogenic properties. Kim et al. investigated the phytic acid cross-linked chitosan microspheres for oral insulin delivery [126]. The optimum formulation achieved 97% of EE (encapsulation efficacy) and 67% insulin loading. Microsphere showed 2 h retention potential in gastric and show sustained release behavior in intestinal fluid. The permeability of microsphere in Caco-2/HT-2 monolayer showed 1.6-fold higher with negligible toxicity. The pharmacological bioavailability showed 10.6% and significantly reduced the blood glucose level with long lasting hypoglycemic effect in diabetic rats after oral administration [126]. It showed that simple ionic crosslinking could be a promising strategy for efficient oral delivery of insulin.

Selenium is an indispensable trace element need of living organism such as animal and human. The deficiency of selenium lead to acute gastric mucosal injury. Various health benefits also associated with selenium. Recently, selenium nanoparticles with bright red color gained great attention of research community. It shows free radical scavenging, immunomodulation, growth promotion, anti-tumor, antimicrobial, and anti-inflammatory effects. Moreover, selenium nanoparticles not available commercially due to lack of stability. Bai et al. developed selenium nanoparticles (60 nm) embedded chitosan microspheres and their potential on alcohol induced gastric mucosal injury in rats [127]. The microsphere enhances selenium retention in Se deficient Wistar rats. It also attenuates the ethanol induced gastric mucosal damage on pre-treatment. It also observed that reduction in lipid peroxidation and decreases aggressive nitric oxides [127]. It can take into consideration se supplement for oral delivery for prominent gastro protective effect.

Among the various APIs, curcumin also showed potential efficacy towards IBD. Various reports demonstrated the therapeutic activity of curcumin. However, poor oral bioavailability is a major concern limited its clinical use [128]. Zhang et al. developed pH responsive composite hyaluronic acid/gelatin hydrogel drug delivery system containing CMC microspheres loaded with curcumin for IBD treatment [129]. The in-vitro studies showed 65% of drug release in 50 h. In vivo pharmacokinetics study in mice showed high level the curcumin maintained in colon tissue for more than 24 h. H&E staining, myeloperoxidase and immunofluorescent staining confirm the anti-inflammatory effect of formulation. Compared to control group, formulation showed IL-6 level inhibition and TNF-α secretion was observed. Best therapeutic effect of formulation confirmed by pharmacodynamics studies. This study demonstrated that mucoadhesive polymeric microsphere could be potential nanocarriers for targeted and controlled delivery of curcumin and other drugs for IBD. This study provided a new system for delivery of hydrogel loaded microsphere system for oral delivery for long term treatment [129].

5.1.2.4. Micro/nanoparticles.: Over the last decade, chitosan-based drug insulin delivery system has shown emerging potential in oral delivery insulin with excellent bioavailability [130,131]. It has reported that chitosan coated alginate nanoparticles and beads reduced insulin release in gastric buffer whereas accelerate in intestinal buffer [132]. Zhang et al. have formulated a microparticle of chitosan/casein with bilayer shell-core for oral delivery of nattokinase [133]. Nattokinase is a thrombolytic enzyme obtained from Japanese traditional food natto [133]. It is used to treat thrombosis related cardiovascular diseases. However, oral delivery is limited due to it loss activity in gastric fluids. So, Zhang et al. developed functional oral drug delivery system [133]. Chitosan-based microparticles used to load the nattokinase through genipin crosslinking then covered by casein based protective shell via transglutaminase cross-linking [133]. Xu et al. developed microparticles based on alginate/chitosan/casein three-dimensional system for oral insulin delivery [132]. They prepared alginate/chitosan nanoparticles then coated with casein to protect NiM (NPs in MPs) (Fig. 5A), which improve the stability of the payload in stomach. They achieved 51% EE and 13% insulin release in 2 hr at simulated gastric fluid. Around 57% of insulin release slowly in-simulated intestine fluid for 10 hr (Fig. 5B). These results suggest that coating of casein on alginate/chitosan nanoparticles enhanced the stability of insulin. These microparticles significantly reduced the blood glucose levels in diabetic mice [132]. This can be a potential oral drug delivery system for insulin.

Colon suffered with IBD. Ulcerative colitis and Crohn’s disease are the two major types of IBD. Till now etiology of IBD not elucidated. There is no such effective treatment available for IBD. Hence, it is in priority in to develop an effective therapeutic modality and strategy for better management of IBD in clinic [137]. Oshi et al. developed colon-targeted dexamethasone microcrystals with pH-sensitive chitosan/alginate/Eudragit multilayers for the treatment of IBD [136]. They fabricated nanoparticles of dexamethasone microcrystals coated with multilayers of chitosan oligosaccharide, alginate, and finally Eudragit S 100 (ES) (ES1AG4CH5-DXMCs) using a layer-by-layer coating technique. Nanoparticles showed size and surface charge 2.34 μm, and −48 mV, respectively. More interestingly, drug release was not observed in acidic pH condition of the stomach and small intestine, however adequate amount of drug release was observed in the colon pH. Nano-particles showed significant therapeutic activity in mouse model of colitis (Fig. 5C) [136]. Layer by layer protection to drug with desire and suitable mucoadhesive polymer and pH responsive polymer. This study demonstrated the layer-by-layer system has potential for colon targeted local delivery of the therapeutic modalities for efficient treatment of IBD. Very recently, Kurakula, et al published a review on progress, trends, and evaluation of colon targeted drug delivery using chitosan, progress made till 2020 [138]. Extensive reports and tremendous progress of chitosan in oral delivery confirm that chitosan is a potential mucoadhesive polymer for oral drug delivery and development.

Nanoparticle mediated drug delivery system has various benefits over small molecule therapeutics such as reduce off-target side effects and enhance drug potency. The chronic disease such as polycystic kidney disease (PKD) need continuous treatment over decades. Parenteral delivery is not found to be as effective as expected to treat PKD. Wang et al. have developed chitosan nanoparticles based oral delivery of metformin for the treatment

of PKD [135]. Mucoadhesive chitosan nanoparticles was utilized to successfully deliver the metformin which showed effectiveness to treat PKD. In vitro studies confirm the permeation across intestinal barriers. The metformin loaded chitosan nanoparticles were administered orally in mice to conduct in vivo studies. The in vivo bioimaging results showed the nanoparticles are heavily accumulated within the intestine. It shows 1.3-fold higher AUC with controlled release over 24 h [135]. Moreover, the lower cyst disease has observed comparatively (Fig. 5D). The recorded blood urea nitrogen and creatinine levels were same to untreated mice, revealed that the formulation was biocompatible and nontoxic. This study demonstrated that chitosan nanoparticles could be a potential oral drug delivery system for PKD. Du et al. has developed a polylysine and cysteine functionalized chitosan nanoparticles and used as efficient platform for oral delivery of paclitaxel [109]. The amphiphilic polymer PY-CA-PLA formed nanoparticles encapsulated with paclitaxel through self-assembly with size 165 nm. The drug release follows sustained release behavior. In vitro studies conducted with caco-2 cells showed the cellular uptake profile of the formulation. In vivo studies showed oral bioavailability enhancement to 5.6-fold compared to Taxol. Bio-distribution studies confirm the improved distribution and higher tumor concentration of the drug, thereby better antitumor efficacy in Heps tumor bearing mice (Fig. 4G) [109]. It concluded that PY-CS-PLA nanoparticle could be a great oral delivery vehicle to improve oral bioavailability and therapeutic efficacy of hydrophobic anti-tumor drug.

Chitosan is a cationic mucoadhesive nontoxic, anticoagulant, and safe polymer. Heparin is anionic mucopolysaccharide with 15k Da molecular wright. Heparin consists of glucosamine and uronic acid linked by 1–4 bond. Heparin bioactivities elevate nitric oxide, which stimulate basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF) and enhance gastric mucosal cell proliferation and regeneration. Yang et al formulated the nanoparticles of chitosan-heparin for drug delivery to gastric cancer [139]. Doxorubicin (DOX) used as model drug. They have studied the anticancer effects through MTT, LDH, ROS, and qPCR assays using peripheral blood mononuclear cells (PBMCs). Dox@CS-HP nanoparticles showed IC_{50} 26.14 μg/ml. Formulated nanoparticles enhanced LDH release, intracellular ROS, mRNA levels of Bax/Bacl-2, caspase-9 and caspase-3 without altering the caspase-8 [139]. This confirmed that nanoparticles activate the intrinsic apoptotic pathway. Recently, scientific community reported that cholesterol enriched rafts play critical role in progression of gastric cancer. Several studies reported the CdtB use for cancer therapy. Based on these reports, Lai et al. fabricated the chitosan/heparin nanoparticles encapsulated CdtB for gastric cancer therapy [140]. Immunoblot analysis revealed the nanoparticles followed the p53 activation pathway. It also enhances the cell cycle arrest at G2/M, followed by apoptosis. CtdB induced cell death is mediated by ATM dependent DNA damage checkpoint response [140]. Further, detail investigation needs to explore the therapeutic activity of CtdB before clinical use.

Targeted delivery is a promising way to treat the gastric cancer because it offers tremendous advantages. Mostly in targeted delivery systems, ligand and reception binding strategy has widely used. A cyclic 9-merpeptide, GX1 (CGNSNPKSC) is exhibited high affinity and specificity with gastric cancer vasculature. Previous studies confirm the GX1 as a promising vascular marker of gastric cancer. Zhang et al used GX1 to developed multifunctional

vascular targeting DTX loaded nanoparticles with N-deoxycholic acid glycol chitosan (DGC) as carrier and GX2-PEG-GPD (deoxycholic acid) conjugate as a targeting agent [141]. The synthesized particles showed 150 nm with spherical shape. The formulated GX1-DGC-DCT showed cytotoxicity to co-cultured gastric cancer cell and human umbilical vein endothelial cells than DTX 100 μM. Nano-particles showed improved cellular uptake. Nanoparticles showed 67.05% tumor inhibition rate at in-vivo in SGC791 and no weight loss in tumor bearing mice [141]. It may be potential strategy for gastric cancer therapy.

Compared to polymer-drug conjugate system, nanoparticles based oral drug delivery shows more therapeutic efficacy. Several studies have already reported the nanoparticles based oral drug delivery system has higher potential than polymer-drug conjugates. Chitosan and chitosan derivatives have been used as drug delivery carrier for IBD. Oshi et al. fabricated colon targeted dexamethasone microcrystals with pH sensitive chitosan/alginate/Eudragit S multilayers for the treatment of IBD [136]. The size of the particles is 2.3 μm with -48 mV surface charge. The particles showed sustain drug release in colon pH and protected in gastric and intestine due to coating. The therapeutic activity of the particles enhanced significantly in mouse model compared to uncoated microcrystals [136]. This study encourages the layer-by-layer coating as potential option for colon targeted delivery. However, due to multiple mucoadhesive polymer coating, the loading content of the drug becomes less. Hence, frequent dosing needed. It is also difficult to controlling the coating thickness, which directly affect the drug release kinetics. Reproducibility of coating also challenge. So smart coating technology need to be explored.

Chitosan also used for ligand/receptor mediated colon delivery system. The ligand/receptor mediated drug delivery system is more effective for localized treatment for colonic diseases. Targeted delivery can be achieved through selective interaction between ligands and surface specific receptor expressed on disease site. various ligands receptor system has been used for colon targeted delivery such as antibodies, peptides, folic acid, and hyaluronic acid [142]. The receptors overex-pressed at site of inflammatory bowel disease are such as mannose receptor, macrophage galactose lectin, transferrin receptor, folate receptor, CD98, CD44 PepT1, F4/80 [142]. Chitosan is one of the polymers widely used in colon targeted delivery. It was reported that chitosan-based nanoparticles could target the fucose receptor located on epithelial cells in vitro. Chitosan fucoidan nanoparticles fabricated through ionotropic crosslinking with loading of eggshell membrane protein. These nanoparticles showed pH specific release profile in vitro and significantly ameliorated the degree of lipopolysaccharide induced inflammations by suppressing the production of NO, TNF-alpha and IL-6 [143]. Chitosan based nanoparticles with functional properties showed excellent efficacy towards IBD. However, detailed preclinical studied need to be conducted before clinical studies.

Chitosan based ligand-receptor mediated targeted drug delivery for gastric cancer need to be explore. Clinical studies need to be conducted to for formulated having excellent in-vivo performance with feasibility of scalability and commercialization aspects.

5.1.2.5. Nanocomposite.: Lee et al. developed colon-targeted oral delivery of insulin using the ternary nanocomposite of organoclay/glycol chitosan/Eudragit S100 [144]. The

nanocomposite loaded insulin and aminoclay prepared through spontaneous co-assembly then coated with glycol-chitosan and Eudragit S100. It shows more than 90% of EE (encapsulation efficiency) and pH responsive drug release behavior. Nanocomposite showed improved drug permeability 7-fold in caco-2 cells compared to free insulin and improved drug absorption in colon in rats. The insulin loaded nanocomposite (organoclay/glycol chitosan/Eudragit S100) showed significant reduction of glucose level in blood in diabetic rats. This study demonstrated the nanocomposites based colonic oral delivery of insulin could be a potential carrier. Taken together nanocomposite might be useful to enhance the bioavailability and efficacy of oral insulin [144]. Shirzadian et al. fabricated deesterified tragacanth-chitosan nanocomposite as a potential carrier for controlled and targeted oral delivery of insulin [145]. They have conducted in vitro and ex vivo studies. The nanocomposites synthesized using coacervation technique and optimized using response surface methodology. The efficacy of nanocomposite studied using in vitro release and ex vivo. The nanocomposite particles showed 20 nm size and +17 mV zeta potential. At gastrointestinal condition insulin release pH dependent manner [145]. These results encouraging that, nanocomposites can be potential carrier for oral insulin delivery. However, the nanocomposites fabrication techniques are not well developed. The controlling physicochemical properties of nanocomposites if a major challenge. The nanocomposite internal organization of composition may be different for batch to batch. Hence, reproducibility is major challenge.

5.1.2.6. Micro/nanocapsules.: Micro/Nanocapsules are vesicular structure compose of polymeric shell and aqueous oil core. Drug can load into oil core. Chitosan based oral capsules are a potential system to enhance oral absorption of drugs. Nanocapsules showed great stability over other [105]. Drug release at intestinal is challenging to developed system to pass stomach and do not enter colon. One of the best strategies is targeted delivery. There are number entities available in intestine and can be used as target to deliver the ligands. Ghaffarian et al. developed chitosan-alginate microcapsules as nanocarriers to target ICAM-1 [146]. They have formulated nanoparticles coated with antibodies against intercellular adhesion molecule – 1 (anti-ICAM) and nonspecific immunoglobulin G (IgG) encapsulated in chitosan-alginate microcapsule. They have achieved more than 95% of drug encapsulation efficiency, drug release at storage, gastric pH, and intestinal are respectably <10%, <10%, and 75–85%. Microcapsules showed 20-fold enhancement in cell targeting and 65% of improved protection in GI, reduced 40% of gastric retention, and enhance biodistribution 4 times. The nano capsules even after transit through gastric and intestinal milieus, retain stability, targetability in-vitro, cell culture, and mice [146]. This study illustrated antibody coated polymeric nanocarriers. Similar approach may have potential to developed therapy to other diseases.

Aprepitant is a selective neurokinin 1 antagonist and used to treat acute and delayed chemotherapy induced nausea and vomiting. Poor water solubility limited its use. Towards this direction, Erdogar et al. design the navel nanocapsules of chitosan-PEG coated cyclodextrins to improve oral bioavailability of aprepitant [147]. The nanocapsules are synthesized using cyclodextrins derivative with 9-carbon alkyl chain. Then coated with CS-PEG to enhance the interaction with cell membrane. Details characterization, in vitro

and in vivo efficacy has evaluated. The fabricated nanocapsules showed low cytotoxicity, sustained in vitro release profile, improved intestinal permeability. Nanocapsules spewed 93% of EE of aprepitant. The nanocapsules shows sustained release profile over 24 h and nontoxic against L929 cells. Nanocapsules offer highest permeability through caco-2 cells. Oral bioavailability in rats shows great drug absorption over commercial aprepitant products in market [147]. Hence, this study revealed that these nanocapsules are potential candidate for treatment of chemotherapy induced nausea and vomiting. However, very limited number of polymers have ability to form capsules. The fabrication techniques of nanocapsules are very limited and need to be explore. Overall, the research and development of nanocapsules need to explore.

The novel system called “tablet-in-capsule” developed in 2004 by Li and Zhu [148]. It consists mini matrices inside a hard gelatin capsule. The simplicity of method and easiness of administration gained great attention in short time. Gomez-Burgaz et al. design chitosan and caroboxymethylcellulose (CMC) sodium inter polymer complex using tablet-in-capsule method (Fig. 5E–5F) [134]. They have studied the effect of molecular weight of chitosan and ratio of chitosan to CMC on physicochemical and release behavior of clarithromycin (CAM). Swelling depends on MW and ration of components. The formulation showed Fickian diffusion at pH 1.2 and non-Fickian diffusion at pH 4.2. CAM release is faster at pH 1.2 when chitosan MW is high whereas at pH 4.2 CAM release kinetics are zero order and no effect of chitosan MW. Controlled release achieved at CS/CMC 80/(75:25) (w/w) are suitable swelling and drug release profile for gastric cancer [134]. This study suggested that one should considered all these factors when designing stomach targeted delivery system.

5.1.2.7. Hydrogel.: Hydrogels are nanoscale size networks with combination of properties and features of hydrogels. Nanogels are compose of physical and chemical cross-linked polymers can be used to deliver the drug without leakage before reaching the target site [105]. Zhang et al., achieved oral drug delivery of curcumin through pH sensitive composite hyaluronic acid/gelatin HA/GE hydrogel containing carboxymethyl chitosan microsphere loaded with curcumin for inflammatory bowel disease treatment [129]. The system showed sustained drug release behavior in vitro such as 65% of drug in 50 h. In vivo studies confirm the maintenance of curcumin in the colon tissue more than 24 h. Hematoxylin and eosin, myeloperoxidase and immunofluorescence staining further confirm the therapeutic activity of curcumin. It also inhibits IL-6 and TNF-α level. Pharmacodynamics showed that the hydrogel best way to treat colitis in mice. It can be effective delivery system for curcumin [129]. Yang et al. developed hydrogel microparticles for controlled and sustained delivery of insulin [149]. Carboxymethyl β-cyclodextrin grated carboxymethyl chitosan using carbodiimide as a cross linker. The formulation shows great protection of insulin inside hydrogel in gastric environment and slowly releases at intestinal conditions. The hydrogel shows nontoxic and transported across Caco-2 cell monolayer via paracellular pathway. Formulated treated to diabetic mice and result showed significant and sustained reduction of blood glucose level. This study shows that CDCD-g-CMCs is a potential protein carrier for oral drug delivery [149]. Further, Belabassi et al. synthesized the PEGylated (mPEG2000-COOH) and fluorinated chitosan (TFB-COOH) [150]. These chitosan derivate forms nano gels presence of hyaluronic acid (HA) and tripolyphosphate (TPP) through ionic gelation

method. Nano-hydrogel (CS-mPEG2000-TPP/HA) and CS-TFB-TPP/HA showed no effect on functions of cells RAW 264.7 [150]. Hence, these nano-hydrogels can be used as a targeted drug delivery to gastric cancer. Various mucoadhesive polymer chitosan based oral drug delivery literature is summarized in Table 4.

5.2. β–glucan

β-glucan is a major structural component of cell walls of fungi and plants especially mushrooms, yeast, bacteria, oats, barley, seaweeds, and algae. β-glucan is monomer of polysaccharide D-glucose linked with β-glycosidic bond with different molecular weight, solubility, viscosity, ad three-dimensional shape [173]. β-glucan enhances activities of macrophages and antimicrobial activity of mononuclear cells and neutrophils [174]. β-glucan derivative β-hydroxyl- β-methyl-butyrate exhibits excellent therapeutic effect on canine colitis by reducing IL-6 and enhancing IL-10 levels. Yeast glucan exhibits positive effect on mice intestinal inflammation caused by DSS. Further properties of β-glucan area such as acts as anti-insulin resistance, anti-obesity, and antioxidant. It is also acting as anti-colitis [175]. Because of range of properties, β-glucan has gained a promising system for oral drug delivery.

5.2.1. β–glucan oral delivery—β-glucan is a biopolymer and widely used for oral drug delivery. It also has different therapeutic effect along with carrier. Various researchers investigated the therapeutic and immunological potential of β-glucan. Liu et al. conducted the study with aim to investigate the potential protective effect of oat β-glucan against DSS colitis in mice [176]. Treatment of β-glucan significantly reduced clinical symptoms with less weight loss, diarrhea and shortening of the colon. Further it reduced disease activity index and degree of histological damage in colon. It also decreases MPO, NO, MDA levels and inhibited TNF-alpha, IL-1β, IL-6, and iNOS. This study concludes that oat in diet can be provides immunity to against colitis. $CD4^+$ T cells or T helper cells are more important in immune system. They remove tumor cells. hence, to elevate $CD4^+$ T level is important to produce infiltrating $CD4^+$ T cells [176]. Zou et al. investigated the inhibition of tumor growth by β-glucan through promoting $CD4^+$ T cell immunomodulation and neutrophil-killing in mice [177]. They have extracted β-glucan from Lentinus edodes. Antitumor activity studies on mice model through intragastric, intraperitoneal and intratumoral injection (Fig. 6A). Interestingly, showed S-180 tumor suppressing ability. It also increased $CD4^+$ T numbers which leads to tumor growth inhibition [177]. This study concluded that β-glucan can be used as effective agent for cancer immunotherapy. Nurunnabi et al. investigated the theoretical and experimentally the interfacial interactions of β-glucan with fat molecules and aqueous media [178]. The major risk factors of triggering cardiovascular, obesity and type 2 diabetics are such as excessive body fat and high cholesterol [179]. They study the dietary effect of barley-extracted on docosahexaenoic acid uptake and impact of the aqueous medium. Theoretically and experimentally their interaction are studies. Density functional theory, Monte-Carlo, molecular dynamics simulations have used for theoretical studies. DFT analysis revealed the β-glucan hydrogen bonding and nonbonding interactions with DHA. Further characterization confirms the electro-static interaction between BG and DHA (docosahexaenoic acid) experimentally. All together the mechanistic pathway is responsively for delayed fat digestion and halting the fat molecule absorption in GI

tract [178]. These studies open the new window of β-glucan based oral mucoadhesive drug delivery system.

5.2.1.1. β–glucan-peptide conjugate.: β-glucan based oral drug delivery system have been studies extensively. β-glucan was used widely in oral vaccine development. Because vaccine oral delivery is a major challenge due to vaccines instability and lack of absorbability. Hence, antigen get degraded. β -glucan has active functional group which allow to conjugate the drug, peptides, and fluorescence probe for biomedical applications. Recently Nurunnabi et al. investigated the PR8 antigen oral delivery using β-glucan-GRGDS conjugate to enhance M-cell targeting ability to induce immunity [183]. For adequate microfold-cell (M-cells) targeting and uptake, they have conjugated β-glucan with glycinearginine-glycine-aspartic acid-serine (GRGDS), which protect antigen in stomach and target to M-cells. Through electrostatic interaction, β-glucan-GRGDS encapsulate antigen and forms nanoparticles size range 200–250 nm. More interestingly nanoparticles showed high cell viability and stability. In vitro M-cell model investigation confirm the M-cell targetability of nanoparticles. Superior results observed in in vivo studies with increasing antibody concentration significantly in serum, intestine, and mucus even on 21 days after oral administration [183].

5.2.1.2. β–glucan micro/nanoparticles.: β-glucan is a good carrier for inflammatory bowel diseases targeted delivery. Sun et al developed targeted delivery of methotrexate using glucan particles for IBD treatment [182]. The clinically used anti-inflammatory drug methotrexate loaded into yeast glucan particles through re-precipitation and gelation reaction. Fig. 6B presenting the yeast glucan particles loaded with methotrexate targeting inflammatory sites and suppressing intestinal inflammation after intragastric administration. These particles showed internalization into Raw 264.7 macrophages through dectin-1 and CR3 receptors. The signal pathway of β-glucan binding to dectin-1 shown in Fig. 6C. It also affectively down regulated the pro-inflammatory cytokines. More intestinally glucan particles accumulated disease site in colitis mice. Particles also suppressed the LPS induced NO production. It targets intestine macrophages and suppress their proliferation and intestinal infiltration and reduces MPO, MDA, NO, TNF-alpha, IL-6, IL-1β, CCL2 [182]. Lee et al. synthesis and functionalize the β-glucan micro/nanoparticles for effective doxorubicin delivery [184]. β-glucan is a polysaccharide biopolymer and one of the entities of cell walls of microorganisms, basidiomycetes, and plants. It can induce innate immunity and control acquired immunity. β-glucan is a biocompatibility, biodegradability high stability, and low toxicity; therefor used in drug delivery. Lee at al. designed porous, hollow β-glucan microparticles with doxorubicin. The results showed that sustained release of Dox and showed excellent antitumor activity against breast cancer cells. immunological activity was observed in culture of immune cells and cancer cells together [184]. It may be activated patients' immune system which needs to be investigated. Enteric diseases still have an impact on healthcare system. Oral vaccination is a promising strategy to avoid the infections. So far developed vaccines limited their efficacy due to various barriers. Hence, targeted oral vaccines development is needed to overcome the limitations. Baert et al. developed β-glucan microparticles targeted to epithelial APN as oral antigen delivery [185]. They have developed aminopeptidase N (APN)-targeted β-glucan microparticles

for antigen delivery. Using bio linker protein G microparticles conjugated with APN and intestinal epithelial receptor. The microparticles showed enhanced uptake by enterocytes dan dendritic cells results the great proinflammatory cytokine response. Compare to control microparticles showed higher serum antigen-specific antibody responses [185]. This study demonstrated the use of β-glucan micro or nanoparticles for antigen targeted delivery. Nanotechnology aimed to enhance immune response against modern antigens. Polysaccharides are particularly interesting candidate for oral delivery. They facilitate recognition by antigen-presenting cells. Xie et al. studied the glucan microparticles targeting M cells through oral delivery [186]. Glucan microparticles labeled with near-infrared fluorescent probe. The in vivo imaging confirms the prolong residence of glucan microparticles in GI tract over 12 Histological studies further revealed the biodistribution and no fluorescent observed in any other organs and tissues. After 12 h, liver, spleen, and lung and after 24 h al, these three showed 2.3% of accumulation. Glucan microparticles successfully transported across caco-2/Raji and Caco-2/Raji/J774A.1 co-culture monolayer. These results confirmed that glucan microparticles absorbed by M cells pathway at Peyer/s patches [186].

Li et al. developed multifunctional PLGA nanoparticles embedded carboxymethyl-β-glucan porous microcapsules for gefitinib oral delivery [187]. The gefitinib loaded FCPP (GFB/FCPP) nanoparticles showed 255 nm size and amorphous state. After encapsulation the size increases to 2.2 um. In vitro release study showed pH responsive prolonged release. Confocal imaging showed excellent cellular uptake. It showed IC50 in A549 cells as 3.82-fold lower than free drug [187]. Altogether conclude that multifunctional nanoparticles are excellent candidate for sustained drug delivery. hydrophilic taurocholic acid (TCA) as an absorption enhancing agent to increase the bioavailability of heparin and heparin derivatives through direct interaction with the bile acid transporter of the small intestine. Taurocholic acid-based formulation such as taurocholic acid linked heparin-docetaxel conjugates for anti-angiogenesis effect and taurocholic acid linked-docetaxel conjugated for cancer therapy through oral administration was investigated [188,189]. Based on these studies, Nurunnabi et al. studied the bile acid linked β-glucan nanoparticles for liver specific oral delivery of biologics. They have introduced hybrid carrier compose of taurocholic acid and β-glucan, which is more effective to protection of biologics in gastric fluid and enhance absorption and transportation through small intestine. We have used eGFP-encoded plasmid as a model biologic. After 4 h incubation, TAG showed two folds higher eGFP expression in the cell. In vivo studies revealed the TAG containing particles showed higher eGFP expression (Fig. 6D) [180]. TAG carrier effective in protection and transportation to liver. This strategy can used for effective oral delivery of biologics to liver for various types of disease treatment. Hwang et al. synthesized the β-glucan nanoparticles for single strand DNA delivery. They used DMSO and water to prepare the nanoparticles with size is 250 nm. ssDNA interested into glucan triple helix structure [190]. The interesting results suggest that β-glucan can be used as carrier for immune response enhancement.

5.3. Alginate

Alginate is natural and mucoadhesive polymer obtained from brown seaweed. Salt of alginate with sodium and calcium used in oral drug delivery [191]. Mucoadhesive activity

of alginate is comparatively less. Mucoadhesive activity of alginate depends on molecular weight (MW) such as low MW alginate chains remain rigid than high MW alginate. Hence, low MW alginate results less mucoadhesive than high MW alginate [8]. Hence, in drug delivery system based on alginate cross-linked to enhance mucoadhesive activity. Alginate with combination of other mucoadhesive carriers is extensively studied in oral drug delivery [192].

Alginate is an anionic mucoadhesive polymer. It creates hydrogen bond with mucin type glycoprotein by carboxyl and hydroxyl interactions. It is a linear, water soluble, polysaccharide with 1–4 linkage of alpha-L-guluronic acid and β-D-mannuronic acid. It undergoes gelation with multivalent cations such as Ca^{2+}, results gel [191]. Another mucoadhesive polymer is PEG. PEG is widely used in biomedical application. It is non-toxic, non-immunogenic, water soluble, rapid invivo clearance depends on molecular weight, and non-antigenic United States Food and Drug Administration (US-FDA) approved polymer. PEG has mucoadhesive properties due to feasibility to form hydrogen bond with sugar residues on glycosylated protein [193]. Davidovich-Pinhas et al. synthesized novel mucoadhesive alginate-polyethylene glycol acrylate (alginate-PEGAs) [194]. Alginate-PEGAc showed non-toxic, hence, it can used as potential polymer in many biotechnology applications. This study opens new window to enhance the mucoadhesive properties of polymer for improved mucoadhesive oral drug delivery for gastrointestinal disease treatment [195]. Further, they have synthesized alginate thiol. Alginate and alginate thiol both shown similar swelling nature. This conclude that adding thiol group to the alginate did not affect the swelling property [194]. Bernkop-Schnurch et al. attempted to improve the mucoadhesive properties of alginate through conjugation with cysteine [196]. The thiolated alginate showed 50% of enhancement of viscosity in aqueous mucus. Tablet made of thiolated alginate showed 150 min stability whereas it is just 49 min for alginate alone. All these properties encourage to thiolated alginate use in mucoadhesive oral drug delivery carrier for gastric cancer therapy with improved stability and prolonged residence time [196]. These features offer useful various dose form such as matrix, tablet, and microparticles of alginate derivative for delivery of therapeutics.

5.3.1. Alginate oral delivery

5.3.1.1. Micro/nanoparticles.: Alginate is an anionic polysaccharide extracted from marine brown algae. It forms nanoparticles by ionotropic gelation with divalent cations or cationic polymers. However, they are not stable at room temperature, so the drug loaded into polymeric nanoparticles get leak. Hence, alginate nanoparticles used to coat with suitable materials such as chitosan. Such type of alginate nanoparticles widely used in oral drug delivery. It has reported that curcumin diglutaric acid orally delivered through chitosan/alginate nanoparticles for cancer treatment. Curcumin diglutaric acid is a prodrug of curcumin, which shows good water solubility and antinociceptive activity. To improve properties further Sorasithanukarn et al encapsulated into chitosan/alginate nanoparticles [197,198]. Chitosan/alginate shows good biocompatibility, biodegradability, non-toxicity, musoadhesivity and good film formation properties. Oil-in-water emulsification and gelification method used to prepare chitosan/alginate nanoparticles. The chitosan/alginate mass ratio 0.04:1 is used. The chitosan/alginate nanoparticles showed good stability in

SGF and release the CG slowly in SGF without enzymes and in body fluid. The drug release follows the Fickian diffusion and erosion of polymer mechanism. The nanoparticles showed higher cellular uptake and better anticancer activity against Caco-2, HepG2, and MDA-MD-231 cells [197,198]. It concludes that chitosan/alginate nanoparticles system is promising approach for oral administration of CG for cancer therapy. Long et al. investigated the vitamin B12 modified amphiphilic sodium alginate derivatives to enhance oral delivery of peptide drugs [199]. Peptide drugs have been used to treat various diseases. However, they suffer with poor bioavailability. Insulin loaded Vitamin B12 modified amphiphilic sodium alginate derivate (CSAS-B12) nanoparticles (50 nm) has formulated. The CSAD-B12 showed higher permeation ability through intestinal enterocytes in caco-2 cell model. In vivo studies conducted on Type 1 diabetic mice and results shows higher accumulation of nanoparticles at intestinal site, absorption, and higher activity (Fig. 7A) [199]. It indicates that it can be a promising candidate for oral peptide delivery and further studies needed before entering into clinical applications.

Salmonella enterica serovar gallinarum cause fowl typhoid. Currently injections available but has limitations such as efficiency significantly reduced in gastric acid. Hence oral vaccines delivery to treat fowl typhoid not explored yet. Towards this direction, Onuigbo et al. developed oral delivery of fowl typhoid vaccine using chitosan/alginate microparticles [202]. They have evaluated the immune response of birds treated with fowl typhoid vaccines coated with chitosan/alginate microparticles. They have used 6 days old chicks. Vaccination done at 10 weeks and 14 weeks of age followed by challenge at 16 weeks of age. The vaccine loaded microparticles range between 0.5 to 10 μm and 60% of EE. The results shows that ELISA E-values 0.10, 0.07, and 0.02 for OCV 567, SC 634 and NEG 451, respectively after vaccination, which are 0.25, 0.19, and 0.0008, respectively after boost vaccination [202]. The results conclude that there is no significant difference the vaccine administration route. However, coating the chitosan and alginate protect the vaccines destruction in GI tract. This study demonstrated that vaccines could be delivery through oral route using mucoadhesive polymers.

In last decades, various drug delivery system such as floating, mucoadhesive, high density, and swelling have gained great attention. However, any one of the systems not able to overcome all the challenges associated with oral delivery. Hence, researchers working interdisciplinary to design the drug delivery system using combination of different systems. Floating and mucoadhesion combined approach receiving overwhelming attention [203]. In this direction, Bera et al. fabricated the core shell alginate-ghatti gum modified montmorillonite core-shell nanoparticles for stomach-specific flurbiprofen delivery for intragastric fluorbiprofen delivery through combination of floating and mucoadhesion mechanism [204]. Formulated core-shell nanoparticle at optimum condition has 91% drug encapsulation efficiency. The drug release from the nanoparticles through anomalous diffusion mechanism [204]. Alginate-AG gel membrane coated alginate modified MMT core shell nanoparticles are appropriate for intragastric delivery of flurbiprofen for long term with improved therapeutic activity. Ling et al. fabricated alginate/chitosan microparticles for gastric passage and intestinal release of therapeutic protein nanoparticles [205]. Protein nanoparticles increases the intracellular delivery of enzymes. The gastro protective microparticles of alginate and chitosan used to deliver the protein, which offer retention of

activity in SGF. Whereas in SIF it released the protein. Oral administration of microparticles reduced inflammation in DSS colitis model [205]. This suggested that alginate/chitosan micro/nanoparticles are potential oral delivery vehicle for protein delivery.

5.3.1.2. Micro/nanocapsules.: Li et al developed alginate hydrogel/gum arabic/gelatin based composite capsules and their application for oral delivery of antioxidants [206]. They have formulated composite capsule loaded with antioxidant *Perinereis Aibuhitensis* (PaE) loaded gum arabic/gelatin microcapsules in calcium alginate hydrogel (PaE:CA/GA/GECCs). In vitro studies confirm that it is potential to protect PaE in gastric acid. It shoes O_2^- scavenging capacity 1.8-fold higher in SIF. The in vivo studies revealed that after oral administration for 30 days, the oxidative stress reduced significantly and lower malondialdehyde content in liver cells [206]. This study revealed that composite capsules could be interesting carrier for intestinal targeted delivery to enhanced absorption potential. Shamekhi et al. developed chitosan coated calcium alginate nanocapsules for oral delivery of liraglutide for diabetic patients [207]. The oral sustained delivery of lirglutide achieved through nanocapsules. Nanocapsules compose of 0.5% chitosan, 0.5% alginate, calcium chloride 0.5% in the volume ratio 3: 1:1. The nanocapsules showed 92% EE and 54% lirglutide. Nanocapsules stable over 60 days at 4 °C. In SGF 595 of lirglutide release in 6 h [207]. This study demonstrated that natural biodegradable polymer based nanocapsules are very interesting for oral drug delivery.

Huang et al. used chitosan-alginate capsules for oral probiotic vaccine expressing koi Herpesvirus ORF81 protein delivery [208]. They have demonstrated the mucoadhesive polymeric capsules as a promising strategy for mass oral vaccination of carps against KHV infection. The oral probiotic vaccine pYG-KHV-ORF81/LR CIQ249 encapsulated into chitosan-alginate capsules as oral drug delivery system for treatment of koi carp against koi herpesvirus infection. It protected vaccine from digestive system. The oral vaccination significant level of antigen specific IgM induced and showed KHV-neutralizing activity. It also offers handling stress free, cost effective, and suitable for mass oral vaccination [208]. This study confirms the mucoadhesive polymeric oral drug delivery system can be a promising candidate for vaccine delivery.

5.3.1.3. Microspheres.: Astaxanthin is a carotenoid pigment having antioxidant activity. It is found in algae, shrimp, and yeast. The major benefits of it for human health is anti-lipid peroxidation, anti-inflammation, anti-cancer and anti-diabetes, and immunomodulation. But use of it is limited due to poor water solubility and highly unsaturated structure [209]. Zhang et al. fabricated astaxanthin-enriched colon targeted alginate microsphere for effective drug delivery to dextran sulfate sodium-induced ulcerative colitis in mice [200]. Through high-pressure spraying and ionic gelation method, they fabricated Astaxanthin rich alginate microsphere, and most of the particles are in the rage of 0.5–3.2 μm in a diameter. Microsphere tolerated in mouth, stomach, and small intestine, and release Astaxanthin in colon due to fermentation of gut microbiota. DSS colitis model mice treated with microsphere through oral gavage add highly showed reduction of DSS colitis, weight loss, oxidative damage, inflammation, colon mucosal integrity, and disease activity index. H&E staining analysis further confirm the reducing the histological score in treatment group (Fig.

7B) [200]. More interestingly, microsphere regulated the gut microbiota composition. This approach is promising for colon targeted delivery for therapy to colon diseases. It is safe, simple, and inexpensive. However, further detailed in vivo studies need to conduct. Icariin is an active flavonoid glucoside isolated from Herba epimedii. Icariin's pharmacological activities such as anti-aging, anti-tumor and anti-inflammatory has confirmed. However, solubility is the major challenge to limit its use [210]. Wang et al. icariin loaded alginate-chitosan microsphere formulated for treatment of ulcerative colitis [211]. The therapeutic activity of formulation has studied in trinitrobenzene sulfonic acid/ethanol induced colonic mucosal injured rat model. Microsphere able to protect the icariin and release only 10% in simulated gastric fluid and 65% of icariin releases in 12 h, at colon. Formulated significantly reduced the colonic injury, but also showed reduce inflammatory responses through decreasing the production and gene expression of inflammatory mediators and cytokines in colon mucosa [211]. These studies showed that there are plenty of opportunities to treat for oral delivery to treat different disease at in-vivo and in vivo studies. However, clinical studies are very limited and most of them may have various limitation. Clinical studies need to increase research organization to make the productive research toward public healthcare.

5.3.1.4. Beads.: The ulcer and chronic gastritis are the results of poor diet, spicy food, stress, smoking, and other lifestyles. Hence, development of controlled drug delivery nanoparticles with gastroretentive ability promising approach to enhance bioavailability and activity for treatment of *H pylori*. Raafat et al. formulated gastroretentive amoxicillin trihydrate floating alginate-based beads for treatment of *H. pylori* using radiation [212]. Alginate has modified with N, N-dimethyl amino ethyl methacrylate achieved through radiation. Alg-g-DMAEMA copolymer-based amoxicillin-trihydrate floating hollow beads formulated using calcium chloride and calcium carbonate have used as cross linker and gas forming components. Nanoparticles showed excellent retention time in gastric fluid 24 h, 97% of drug encapsulation, and controlled release of drug for 15 h. More interestingly, in vitro studies confirm the 95% of eradication of *H. pylori* [212].

Probiotic lactic acid bacteria have many health benefits on the human health because they improve intestinal flora, strengthening immunity, inhibiting tumor growth, and promoting nutrient absorption. However, lactic acid bacteria will die before they reach to small intestine when it contacts with the gastric acid in stomach [213]. Hence, for intestine targeted delivery, formulation need to protect from acidic environment. Mei et al. developed novel intestine targeted calcium alginate beads carrier for pH sensitive protection and release of lactic acid bacteria [201]. The fabricated Ca-alginate/protamine (CAP) shell and *lactobacillus-casei*-encapsulated ca-alginate (CA) core. The CAP provide protection to lactobacillus casei but also offer intestinal targetability. When beads reach to small intestine, carrier dissolved in neutral environment and cooperation between protamine and trypsin (Fig. 7C) [201]. The beads at pH 2.5 simulated gastric acid after 2 h immersion bead prepared with 25% (w/v) Na-alginate has 46% of lactobacillus casei. It is 60 times low than ordinary CA bead. In 50 minutes, 100% release of drug achieved in pH 7 simulated intestinal fluid, and it is 380 min for normal ordinary CA bead [201]. This carrier provides novel efficiencies of protection and controlled release and targetability.

The colon targeted drug delivery is important to treat colon diseases such as ulcerative colitis, Crohn,s disease, amebiasis, colonic cancer, etc. Number colon targeted drug delivery systems have been developed such as drug-polymer conjugates, pH responsive polymers such as Eudragit polymers, mucoadhesive polymers such as chitosan, alginate, biodegradable polymers [214]. Recently novel systems such as pressure-controlled drug delivery, CODESTM (combined approach of pH dependent and microbial triggered drug delivery), osmotic pressure-controlled drug delivery, and multi particulate system [215]. Agarwal et al. explored pH responsive swelling, musoadhesivity, colon microflora-catered biodegradable drug delivery system for colon targeted delivery [216]. They fabricated calcium alginate carboxymethyl cellulose (CA-CMC) beads through ionic gelation for colon targeted drug delivery. The formulated beads show slow degradation in colonic fluid and nearly 90% of drug (5-fluorouracil) release presence of colonic enzymes. Further studies such as cytotoxicity, nuclear condensation-fragmentation and apoptosis analysis studies against colon adenocarcinoma cells proven the therapeutic potential of formulated beads [216].

5.3.1.5. Hydrogel.: Hydrogels are three-dimensional network of polymer having great potential to use as drug delivery carrier, scaffold in tissue engineer, biocomponents, and food systems. Biocompatibility, biodegradability, and ability to absorb biological fluid, and more amount of water offer their use in controlled delivery system. Recently natural and synthetic polymers gained interest in hydrogel. The most widely used polymers are PEG, PVA, PHEMA (poly (2-hydroxyethyl methacrylate)) and natural polymer such as chitosan, alginate, agarose, hyaluronan, collagen, fibrin, pectin, xanthan gum, guar gum, and gelatin [217,218]. In recent years, hydrogel showed wide variety of application. Pharmaceutical and medical industries also showing an interest to use the biopolymers. Cikrikci et al. developed pH sensitive alginate/gum tragacanth-based hydrogel for oral insulin delivery [219]. Fig. 8A presenting the release and absorption of insulin from intestine following oral administration of hydrogel-based systems. Insulin loaded alginate-gum tragacanth hydrogel prepared through ionotropic gelation method and chitosan polyelectrolyte complexation. Hydrogel showed nearly 100% of insulin retention in simulated gastric environment and released insulin sustain manner in simulated intestinal buffer. This showed the pH sensitivity of hydrogel [219]. The detail characterization and investigation suggest the ALG-GT gel formation at optimum concentrations can be a potential carrier for insulin oral administration. This study concluded that hydrogel of biocompatible and biodegradable, nontoxic natural polymers can be a good choice of oral inulin delivery. Yin et al. investigated the potential of agar and alginate composite hydrogel in oral drug delivery [221]. They attempted to enhance the mechanical strength of calcium alginate hydrogel for sustained drug delivery. They prepared pH responsive composite gel beads of agar and alginate in the presence of agar. The detail characterization of hydrogel revealed the enhancement of mechanical strength compared to alginate beads without agar. The content influences the swelling and release behavior. At higher agar content lower the rate of swelling and released the drug in 720 min. In vitro studies further, confirm the potential of hydrogel for controlled drug delivery [221]. Ilgin et al. synthesized the pH responsive alginate-based hydrogel for oral drug delivery [220]. They have developed pH responsive alginate hydrogel for oral colon targeted delivery. Water absorption efficiency of hydrogel investigated under

the influence of various monomer composition and tuning the conditions such as salt, pH, and temperature. In vitro and in vivo studies of diclofenac sodium has studied at gastric pH 1.2 and intestinal pH 7.0. Antibacterial potential studied using gram-positive and gram-negative bacteria. The formulated hydrogel showed 22.8% drug loading and drug release profile showed 4.5% of diclofenac sodium release at pH 1.2 in 3 h and 95% at pH 7 at 20 hr. Antibacterial studies revealed that hydrogel is not harmful (Fig. 8B) [220]. Various mucoadhesive alginate polymer based oral drug delivery literature is summarized in Table 5.

5.4. Pectin

Pectin is a natural and mucoadhesive polymer with biodegradability, biocompatibility, non-toxic and heterogeneous polysaccharide. Pectin can be extracted from citrus peel and apple pomace [238]. Henri Braconnot first isolated pectin in 1825 [239]. It is a part of human diet but do not contribute nutrition significantly. It is a linear chain polymer with 1–4 linkage of d-galacturonic acid residues, which have carboxyl group [240]. Pectin follows two mechanisms of mucoadhesion, first is hydrogen bonding (carboxylic group of pectin) with mucin and electrostatic interaction between pectin and mucin molecule [238]. Interestingly, Jorgensen et al. investigated effect of MW of pectin on mucin layer penetration efficiency and reported that low MW pectin has more penetration on mucin layer easily [241], Pectin with low degree of esterification shows higher mucoadhesion activity than high degree of esterification. To improve the mucoadhesion activity of pectin, researchers studied the combination of pectin with other polymers such as pectin-gellan gum beads, modified pectin-acrylate combined carrier, pectin – jackfruit seed starch beads [8]. Recently, atomic force microscope (AFM) used to study and visualize the absorption of pectin on mucosal cell surface [238]. Thirawong et al. studied the pectin-mucin interaction using viscosity in various media [242]. After extensive investigation, scientist found pectin as a promising mucoadhesive polymer for oral drug delivery.

5.4.1. Pectin mediated oral delivery—Pectin has various functional group such as hydroxyl, carboxyl, carbomethoxy, and acylamino which area capable to synthesize broad spectrum of derivatives. Fig. 9 showed the schematic of potential reactions and products of pectin [243]. Due to above properties pectin-based hydride materials for drug delivery applications. Solid lipid nanoparticles stabilized by emulsifier with particles size below 1000 nm made great success in last 30 years. Various drug delivery system and products have been developed based on SLNs. SLNs widely used in oral delivery [244,245]. Due to thickening, gelling and degradation nature, pectin can be a potential polymer for coating to enhance stabilization of SLNs. Pectin coated SLNs showed enhanced stability and encapsulation efficiency. SLNs showed lower melting point due to Kelvin effect [246]. Drug release has controlled in pectin coated SLNs where as normal SLNs showed burst release. Pectin also used in targeted delivery to colon due to pH and enzymatic activity. Pro-drug approach can be used for colon targeted delivery. EDC/DMAP used as cross linker to prepared pectindihydroartemisinic (DHA) conjugates (PDC) which undergo self-assembly with hydroxy camptothecin (HCPT). The formed pectin-DHA/HCPT nanoparticles (70 nm) achieved 20% of DHA loading and 14% of HCPT encapsulation. Nanoparticles showed 4.8-fold and 6.8-fold higher retention in blood respectively compared to DHA and HCPT.

Survival rate of 4T1 tumor bearing mice increasing compared to free DHA and HCPT (Fig. 10A) [247].

5.4.1.1. Pectin-based nanoparticles.: Over the past decade, great progress has devoted on oral drug delivery system. However, only few formulations show therapeutic promise in clinical trials. Zang et al. developed oral insulin delivery system through dual crosslinking of folic acid modified pectin nanoparticles [250]. Pectin has excellent gelling property, good mucoadhesive nature, and high stability in gastrointestinal tract; it offers great potential for oral drug delivery with having capacity to hold drug. However, pectin alone cannot be able to target the enterocytes. Toward this direction, Zhang et al. developed folic acid modified pectin nanoparticles (INS/DFAN) for insulin oral delivery using cross linker calcium ions and adipic di hydrazide [250]. The in vitro studies revealed that the release of insulin depends on COOH/ADH molar ratio. INS/DFAN with FA graft ration of 18.2 showed small size of particles, high encapsulation efficiency, and high stability and cellular uptake. The formulated nanoparticle administered orally to type I diabetic rats, which showed considerable amount of blood glucose level reduction, and improved oral bioavailability (Fig. 10B) [250]. Altogether, this study conclude that dual crosslinking and FA modification is an effective strategy to develop pectin-based nanocarriers for insulin oral delivery. Prezotti et al. developed gellan gum/pectin nanoparticles for oral colon targeted delivery of resveratrol [251]. They used nebulization/ionotropic gelation method for synthesis of nanoparticles having size 330 nm, spherical share shape and more than 80% of drug loading. Drug release and permeability studies using caco-2 cell model and mucus secreting triple co-culture model. The mucoadhesive polymeric nanoparticles showed 3% of resveratrol release in 2 h in gastric acid media and 85% in 30 h in pH 6.8. The permeability achieved 5.5% [251]. This study indicated that mucoadhesive pectin-based nano-particles are safe and promising carrier for controlled and targeted delivery of resveratrol to the colon.

5.4.1.2. Pectin-based microparticles.: Deshmukh et al. formulated microparticles of amidated pectin for controlled delivery of sulfasalazine for inflammatory bowel disease [252]. They have used ionic gelation method to fabricate amidated pectin microparticles. The microparticles loaded in Eudragit S 100 coated hard gelatin capsules for pH and time dependent drug delivery to colon for IBD treatment. The optimum formulation showed 463 nm size, -32 zeta potential, 91% yield and 95% EE. The swelling index are 0.88 and 0.98 at pH 6.8 and 7.4, respectively. Drug releases 91% in simulated colonic fluid and 98% in rat cecal content for 24 h. The capsule dissolved at colonic pH 7.4 and release the drug from microparticles when administered to rabbit orally. The microparticles showed great stability and exhibited 3.3 Years of shelf life [252]. This study concluded that amidated pectin microparticles filled with Eudragit S 100 coated hard gelatin capsules can be potential delivery system for IBD management.

5.4.1.3. Pectin-based microspheres.: Parietal cells secrete the hydrochloric acid hence gastric pH always 1.7 – 4.7 but vary based on fast and fed state. It increases gradually in small intestine to pH 5.9 – 6.3 and in the proximal segment it is 7.4 – 7.8. The colon pH is 5 to 8 [253]. Several drug delivery systems used pH for colon delivery. Hence pectin coated nanoparticles system used as colon targeted delivery. The enteric coating protects in stomach

and release in colon. Several enteric coating-based products available such as Mesren® MR, Salofalk®, Asacol® MR, Ipocol®, budenofalk®, Entocort® commercialized [254]. Vaidya et al. formulated metronidazole loaded pectin microsphere for colon targeted delivery [255]. Microspheres fabricated through emulsion-dehydration method and coated with Eudragit S-100. In-vitro studied showed no release of drug at gastric pH and release continuously at colon pH. The release increases presence of rat caecal contents. Biodistribution in-vivo studies confirm the accumulation of microsphere in colon [255]. This study provided a Eudragit coated pectin microsphere can be a potential colon targeted drug delivery nanocarrier. Pectin extensively studied for colon targeted and excellent in-vitro and in-vivo therapeutic activity was reported widely in literature [256]. The major limitation is that not suitable for stomach, small intestine, and intestine lymphatic targeting. This is challenging and we strongly believe that scientific community can achieve it soon.

5.4.1.4. Pectin-based beads.: Lack of toxicity and low cost of production get great attention towards formulation of controlled release dosage. It used in matrix tablets, gel beads and gel-coated pellets. Drug bioavailability and absorption can be increases significantly using pectin based floating drug delivery approach. Pectin is interesting for colon targeted drug delivery due to it degraded by colonic pectinolytic enzymes [240]. Iron deficiency is the most common nutritional deficit worldwide. Iron is essential metal for all organisms. The major key role of iron in human is binding oxygen to hemoglobin and catalysis in enzymes. Iron required 5–30 mg per day depending on age. Various fortified food available in market containing iron. They are in different color. However, iron may react with food components and color. There are other disadvantages of iron products [257]. Ionic gelation is the alternative method to prevent such undesirable effect of fortified foods. Pectin is a low degree of esterification and useful for ionic gelation. Pectin has resistant of hydrolyzation in the upper part of GI tract. Hence pectin widely used for colon targeted delivery [258]. Ghibaudo et al. fabricated iron-pectin beads for iron delivery. The beads were spherical shape with diameter 1–2 mm, density 1.29 g/ml and 93% of porosity proven the high permeability [259]. Beads get swell in simulated intestine medium than simulate gastric medium. After 4 h of treatment transport of iron higher from the bead than $FeSO_4$. This study described the interesting iron transport system [259]. It may be an excellent method to enrich food products with iron without affecting sensory performance. Based on these studies, there is feasibility to fabricate the complex of iron with organic compounds and natural fibers as a functional ingredient in food products. It has great potential for pharmaceutical and food industrial applications.

5.4.1.5. Pectin-based nanocomposite.: Wang et al. developed novel and simple oral colon specific drug delivery system based on pectin/modified nano-carbon sphere nanocomposite gel film [260]. 3-aminopropyltriethoxysilane modified nano-carbon sphere added into pectin Ca^{2+}film to improve pectin based oral colon targeted delivery 4-fluorouracil. They achieved 30 to 52% of EE. All the composite fluid showed better release rate such as 32, 22, 635 in SGF, SIF, SCF, respectively. The in vitro cytotoxicity studies confirm the biocompatibility of nanocomposite [260]. Hence, further studies need to be conduct before conducting clinical trials.

5.4.1.6. Pectin-based nanocomplex.: Biopolymer polyelectrolyte complexes have attracted increasing attention in recent years. PECs formed through electrostatic interactions between two or more opposite charged polyelectrolytes. The dimension and shape depend on bio-polymers and fabrication conditions. Recently it has reported that protein and polysaccharides-based PECs showed interesting results in food and pharmaceutical applications [261]. Towards this direction, Luo et al prepared nanocomplex of casein/pectin for oral delivery application [261]. They prepared nanocomplex of sodium caseinate and pectin in ration 1:1 with smaller and uniform size. Heating increases the yield and encapsulation efficiency of rutin. Nanocomplex showed potential to release the rutin in simulated intestinal conditions [261]. This system can also use for nutrients and medicines oral delivery. Hua et al. also made casein-pectin nanocomplex for oral delivery of curcumin [262]. They have prepared curcumin loaded casein micelles and surface coated with pectin through electrostatic interaction. It showed excellent performance at pH 4 then pH 2 and pH 3. The size of nanocomplex is 266 nm and 93% loading capacity with spherical shape. The anti-oxidant activity of nanocomplex showed tremendously keep bioactivity of curcumin. Delay release has observed due to surface coating confirmed by in vitro studies in SGF and controlled release in SIF [262]. This study demonstrated the oral delivery of bioactive ingredients. Potential application needs to be explored and conduct the comprehensive studies.

5.4.1.7. Pectin-based hydrogel.: Gautam and Santhiya et al. developed pectin/OEG food grade hydrogel blend for the targeted oral co-delivery of nutrients [248]. Ca^{2+} with vitamin D/Fe^{2+} with vitamin C is entrapped in edible pectin/PEG polymer blend matrix to formulate PPCaD and PPFeC hydrogel. The metal ions showed the electrostatic interaction and hydrogen bonding with pectin. In vitro studies confirm that lowest release of metal ions and vitamins in SGF at pH 1.2 for 3 h concluded that efficacy of pectin protection. However, in SIF at pH 6.8 showed highest swelling of hydrogel and highest release of nutrients at intestinal site. Fig. 10C–10D showed swelling ratio of the hydrogels and degradation behavior in SIF at pH 6.8 for various hydrogels. [248]. Zhou et al. prepared alginate hydrogel beads as a carrier of low-density lipoprotein/pectin nanogels for potential oral delivery applications [263]. Alginate beads widely studies due to their potential stability in gastric conditions. Zhou et al. utilized alginate hydrogel fabricated with Ca^{2+} or Fe^{2+} to serve as carrier for egg yolk low-density lipoprotein/pectin nanogels [263]. Beads showed great protection in gastric conditions and release at intestinal. Beads made of low viscous alginate and Ca^{2+} showed limited swelling and sustained release of curcumin compared to bead made of high viscous alginate and Fe^{2+}. They also studied the dissociation of nanogels from beads using TEM (transmission electron microscope) [263]. This investigation demonstrated that potential pf alginate beads to protect and delivery the nanogels at desire site by passing gastric conditions.

5.5. Poly (acrylic acid)

PAA (poly (acrylic acid)) is a derivative of acrylic acid. PAA is a homopolymer and forms variety of co-polymer and cross-linked polymers. It is anionic polymer and may loss proton from side chain of PAA results negative charge. Deprotonated PAA showed ability to absorb water and swell many times than its original volume. PAA can be synthesized

by free radical polymerization using potassium persulfate and AIBN [264]. It also used as dispersants. PAA is consider as mucoadhesive polymers because at protonated form at acidic pH is responsive for mucoadhesion. It forms H-bond between its COOH and sialic COOH of mucin glycoprotein. This bond formation enhanced viscosity [265]. Due to high viscosity the PAA based hydrogels can used in various biomedical applications such as to treat ocular irritations. PAA has various application including hygiene products, ultrafiltration, hemodialysis membrane and controlled drug delivery devices [266]. PAA based mucoadhesive oral drug delivery system have been extensively investigated. Various mucoadhesive pectin polymer based oral drug delivery literature is summarized in Table 6.

5.5.1. Poly (acrylic acid) oral delivery

5.5.1.1. PAA-based hydrogels.: PAA widely used in drug delivery through formulation of hydrogel and releasing the drug through swelling nature. In stomach targeted delivery, hydrogel loaded with drug can be use as oral delivery, which swell in stomach fluid and release the drug. Mucoadhesive properties of PAA allow binding the mucin. So enhanced therapeutic efficacy [281]. Kumar et al. achieved clarithromycin delivery targeted to stomach by formulating interpenetrating polymeric network hydrogel [282]. They have prepared inter-penetrating polymeric network by crosslinking of chitosan, PAA and PVP with glutaraldehyde and N, N'- methylenebisacrylaide. The fabricated interpenetrating polymeric network shows enhanced mucoadhesive nature and higher swelling behavior. Release the drug at low pH. Hence clarithromycin showed the sustain release at stomach and maintain the antibiotic concentration [282]. However, the efficacy of the formulated polymeric network in vivo has not evaluated by these researchers. In-vitro and in-vivo studies are crucial to get therapeutic potential of formulation. Li et al recently made advancement in PAA based graft for oral drug delivery [283]. They have synthesized the xanthan gum-graft-PAA. GO-DCFP composite hydrogel. Using improved Hammers method prepared GO and used to study the absorption of mechanism of model drug Diclofenac potassium. The absorption kinetics showed pseudo second order and Freundlich model mechanism. The absorption mechanism mainly involved the pi-pi staking and hydro-phobic interaction along with electrostatic and hydrogen bonding. By in sit polymerization xanthan gum-graft-poly (acrylic acid)/GO composite hydrogel has synthesized. The hydrogel showed increase in welling with increasing pH. The in vitro release studies confirmed that controlled release behavior as it releases 96 h in artificial intestinal fluid than artificial gastric fluid. The in vivo studies exhibited the half-life of composite hydrogel as 10.7 h revealed the prolong drug release properties. The composites showed $AUC_{0\text{-}t}$ of DCFP 116, which is more than twice of AUC of DCFP alone [283]. The bioavailability of drug greatly enhanced. This study demonstrated the potential of composite hydrogel for sustained drug delivery. Aktas et al. developed pH resistive poly (acrylic acid-co-acrylamide) anionic hydrogel for jejunum targeted drug delivery [284]. Ionic hydrogels are favorable conduce for oral drug delivery. They have investigated the welling properties for P(Aac-co-Aam) hydrogel in the presence of 30% vol% Aac at different pH values by steady state fluorescence technique. Pyranine 4 (4sPy) a pH independent fluorescence probe has entrapped in hydrogel network during the gelation before selling. Fluorescence intensities monitored during selling process. At very high pH most of the probe release. It reached maximum swelling ration at pH 9 [284]. All results together concluded that anionic hydrogel could be a potential system

for jejunum targeted drug delivery. Kunjiappan et al. enhanced the anticancer activity of 5-FU and rutin by oral delivery using pH sensitive Zein-co-acrylic acid hybrid hydrogel [285]. It is a natural and synthetic polymer combination grafted hydrogel. Both polymers and hydrogel are intrinsic biocompatibility, biodegradability, offer protection to labile rug from metabolism and controlled release. The Zein-co acrylic acid hydrogel loaded with rutin and 5-FU for effective anticancer activity. The optimum formulation showed high encapsulation efficiency and drug loading such as 12 and 10 and 89 and 81 respectively for 5-FU and rutin. Hydrogel with 52.5 ug/ml 5-FU and rutin showed 50% cell death at 34 h in cytotoxicity against MDA-MB-231 and MCF-7 [285]. Drug released at pH 7.4. Hence, this pH responsive hydrogen; can be a favorite carrier for anticancer drug oral delivery. Liu et al developed hybrid microgel of carboxymethyl starch/poly (2-isobutyl-acrylic acid) [286]. It is a pH and amylase responsive effective enteric carrier for oral insulin delivery. The hybrid microgel made through aqueous dispersion copolymerization of acrylate-grafted-carboxymethyl starch (CMS-g-AA) and 2-isobutyl acrylic acid (iBAA). The hydrogel has 13–45% of PiBAA and showed pH and amylase sensitivity. Insulin loaded microgel showed release of loaded insulin with responsive to pH change and amylase (Fig. 11C). Microgel also showed good biocompatibility and cellular update by Caco-2 cells. Further microgel shows in vitro intestinal absorption. Oral delivery of microgel to STZ induced diabetic rats led to continuous decrease of blood glucose level within 2 to 4 h and maintain hypoglycemic effect over 6 h in vivo [286]. More interestingly, pharmacological availability of insulin increases 23–38 times. It concluded that novel starch based microgel potential carrier for oral insulin delivery. Magnetic nanoparticles gained great attention and made excellent progress in last decade. US-FDA also considered magnetic nanoparticle as biocompatible and allow using in biomedical application. Mohammadi et al. further developed pH responsive hydrogel beads through formulation of interpenetrating magnetic nanocomposite of carboxymethylcellulose/PAA/Starch and Fe_3O_4 magnetic nanoparticles [287]. The efficacy of nanocomposite studied through loading the anticancer drugs such as doxorubicin hydrochloride and 5-fluorouracil and evaluated the performance. The loaded 5-FU successfully release in stomach due to sensitivity of pH. It also showed enhanced stability of drug I colorectal area. Cytotoxicity studies revealed the excellent cytotoxicity against SW480 cell lines [287]. It can be efficient carrier for oral drug delivery [287]. This study inspired for PAA nanocomposites a potentials carrier for colon targeted drug delivery. The thiolated PAA based inserts not soluble. So, it can be used for controlled drug delivery. Because of hydrophilic nature and reticulated structure which makes it interesting carrier for control drug release. PAA polymer extensively used in bioadhesive pharmaceutical hydrogels such as Polycarbophil, and Carbopol [288]. Used for artificial tears and dry eye syndrome therapy [289]. Ahmad et al. developed mucoadhesive bacterial cellulose-g-PAA hydrogel for oral protein delivery. The hydrogel synthesized without cross linker using electron beam irradiation, which avoid the toxicity of cross-linking agents. Bovine serum albumin used as a model protein. BSA release only 10% in SGF. Swelling and deswelling behavior and BSA release profiles shown in Fig. 11A and 11B respectively. Ex-vivo studies revealed the BSA penetration across intestinal mucosa. Further properties such as cytocompatibility, no sign of toxicity indicates the safety of hydrogel, and it can be great choice for in vivo applications. PAA based targeted delivery to small intestine and intestine lymphatic need further investigation.

5.5.1.2. PAA-based grafts.: Dey et al. achieved pH sensitive delivery using PAA grafted with barley. They have used 5-ASA as a model drug in this study for colon targeted [292]. As barley is fourth highest cultivated food product globally. Barley contains 95% of polysaccharide mainly starch. Grafting is the promising method for modification of polysaccharides. Dey et al. formulated PAA grafted barley through microwave assisted method. Loaded with 5-ASA an anti-inflammatory drug to treat inflammatory bowel disease. Drug release follow the Fickian diffusion mechanism at both pH 1.2 and 7.2. drug absorption rate is high in lower GIT [292]. This study encourages towards the grafting of PAA with different entities for oral delivery. By using targeting agent grafted nanoparticles can be targeted to stomach, small intestine, intestine lymphatic, and colon. Oral delivery of hydrophilic macromolecular protein delivery is challenging. Kavitha et al. synthesized PAA-grafted graphene oxide for oral intracellular protein delivery system [293]. They have used in situ atom transfer radical polymerization to synthesized graft. The graft protected the model protein BSA labeled with FITC. It releases effectively in intestine and internalized in KB cells by endocytosis and release into cytoplasm. The GO-PAA is a new class of transmembrane transporter for potential protein oral delivery [293]. Pal et al. synthesized the pH sensitive cross-linked guar gum-g-poly (acrylic acid-co-acrylonitrile) for thymoquinone against inflammation [294]. They have used microwave assisted technique for fabrication of graft. They achieved optimum formulation by tuning the various parameter and their effect on graft properties. The loaded thymoquinone maximum release at pH 7.4 and in 6 h. the graft showed goo antioxidant activity, hemocompatibility and biocompatibility against the VERO cell lines [294]. It is a cost-effective green strategy for graft formulation for sustained release of oral drug delivery. Tian et al. developed the pH responsive PAA-gated mesoporous silica nanoparticles for oral colon targeted doxorubicin delivery [295]. The used PAA brushes to anchor on pore outlets of MSNs, which can act as gatekeeper. PAA capped MSN SBA-15 (PAA/SBA-15) showed good biocompatibility, pH sensitivity and very high drug loading efficiency such as 785.7 mg/g. PAA protect doxorubicin loaded into SBA-15 in gastric condition and in colonic environment PAA opens the pores and facilitate the release of drug [295]. The formulated nanoparticles showed enhanced aqueous solubility as well. pH responsive drug delivery system can be potential for colon cancer and other colonic diseases therapies.

5.5.1.3. PAA-based microsphere.: Controlling the retention of nanoparticles between stomach and colon is critical challenge. Dexamethasone widely used in treatment of inflammatory diseases. Das et al. demonstrated the controlled delivery of β-cyclodextrins to intestine using microsphere of poly (vinyl alcohol)-poly (acrylic acid) [296]. Fig. 11E presenting the SEM images of the formulated microsphere. Dexamethasone active in the treatment of every type of B-cell malignancy and side effects associated with it. Therefore, control drug delivery is an alternative to limit or minimize the adverse effects. They compare the inclusion complexes prepared through co-precipitation and freeze drying and compare with microsphere. Results suggested no release of drug from microsphere in gastric fluid but release in intestine. Microsphere showed no cytotoxicity. This suggested that microsphere biocompatible. These microspheres can be used as pH responsive drug delivery system for targeted intestine delivery. Moreover, it minimizes the adverse effects of dexamethasone [296]. Such system can also be applied for any other drug to reduce the side effects

and improved the therapeutic efficacy. Das and Subuddhi prepared microsphere of PVA-PAA containing drug-cyclodextrin complexes for controlled delivery of dexamethasone to intestine. Dexamethasone is a highly efficient treatment for every type of B-cell malignancy. However, it has various side effects. Hence, it demands controlled delivery. They have prepared hydrogel with addition of preformed solid inclusion complex of dexamethasone and β-cyclodextrin. The inclusion complex prepared through co-precipitation and freeze-drying method. Microsphere containing free drug, physical mixture and inclusion complex has formulated. Microsphere significantly protected the drug in gastric fluid and released the drug in intestinal fluid. The microsphere showed good biocompatible observed in cytotoxicity studies. Thus, microspheres are effective system for intestinal targeted drug delivery [291]. This study proposed novel system to minimize the adverse side effect of dexamethasone through controlled delivery using microsphere.

5.5.1.4. PAA-based micelles.: Zhao et al. fabricated pluronic-poly (acrylic acid)-cysteine/pluronic L121 mixed micelles improve the oral bioavailability of paclitaxel. The mixed micelles achieved 2.8% of drug loading capacity and pH sensitive release. Presence of verapamil and pluronic both improved intestinal permeability in rat. The pharmacokinetics studies revealed the AUC of mixed micelles loaded with paclitaxel is four times higher than the paclitaxel alone [297]. It proven that mixed micelles of PAA and pluronic to be potential oral drug delivery carrier for paclitaxel.

5.5.1.5. PAA based nanoparticles.: Pourjavadi et al. prepared mesoporous silica nanoparticles with bilayer coating of poly (acrylic acid-co-itaconic acid) and human serum albumin (HAS). They used to delivery gemcitabine to cancer cells. PAAIA used as pH sensitive inner shell and HAS as outer shell. Due to the electrostatic interaction between ammonium group of MCM-41 and carboxylate group of copolymers formed core-shell structure is formed. The copolymer-coated nanoparticles further coated with albumin layer. More interestingly, maximum release observed at pH 5.5, due to the collapse of bilayer [298]. This demonstrated that the potential of nanocarriers with good biocompatibility, controlled release, and pH responsive for tumor therapy. Various mucoadhesive PAA polymer based oral drug delivery literature is summarized in Table 7.

5.6. Carboxymethyl cellulose

CMC is a cellulose derivate. It is water soluble bio and mucoadhesive polymer. It is hydrophilicity, bioadhesive, pH-sensitivity, non-toxic, and gelation ability. CMC commonly used in drug delivery including oral delivery. It is also used in different fields such as lithium sulfur battery, water pollutants removal, conductive films, host in polymer electrolytes, catalyst, food packing, protein immobilization, and drug delivery. CMC shows interesting properties which encourages it use in oral delivery agent [312]. In 1990s, CMC has entered pharmaceutical industries. The CMC based therapeutics is inspiring in industry as well as academic research. CMC hydrogels are more interesting due to mucoadhesive responsive release features [312]. Drug delivery of CMC hydrogel can improve through functionalization, modification, and crosslink with natural and synthesis materials. The mucoadhesive polymeric oral drug delivery using CMC have discussed in following section.

5.6.1. Carboxymethyl cellulose for oral delivery—Oral drug delivery used to deliver drugs at duration, sustained and controlled frequency along with achieving the plasma concentration of drug at therapeutic levels. It can reduce the dosage rate. CMC based oral drug delivery system able to protect the drug from crystallization and degradation. CMC release the drug through diffusion, erosion/degradation so enhanced drug release time [312]. Gemici et al. studied the effect of hyaluronate-carboxymethyl-cellulose (HCMC) on the formation of postoperative adhesion in stomach visceral peritoneum damage [313]. The fabricated HCMC placed satured anterior wall of stomach of 15 rabbits. After 30 days relaparotomy was performed on the rabbits and adhesions were evaluated by an independent surgeon according to seriousness and prevalence scores. In controlled and treatment group postoperative adhesion (POA) observed in 12 and 5 respectively. The POA completely prevented 2 and 7 rabbits respectively in controlled and treatment group [313]. This study concluded that hyaluronatecarboxymethyl-cellulose could be beneficial on damaged peritoneum surfaces following surgery to reduced POA development. Among the various drug delivery system developed for targeted delivery to stomach has potential applications. Recently developed floating drug delivery system can be a potential candidate due to various advantages and it is gained great attention from the scientific community.

5.6.1.1. Hydrogel.: Khan et al developed stimuli responsive hydrogel for controlled delivery of 5-fluorouracil. Gelatin/carboxymethyl cellulose hydrogel used as carrier [314]. It is fabricated using free radical polymerization method and cross-linked with glutaraldehyde. Effect of various parameters, composition on physicochemical properties of hydrogel has investigated. Hydrogel showed maximum swelling and release at pH 1.2. in vivo pharmacokinetics showed control nature of hydrogel. MTT study confirm the biocompatibility and non-toxic nature of hydrogel. Hydrogel showed great potential against HeLa cells. Hydrogel shows safe even at 4000 mg/kg dose [314]. Altogether showed promising results of hydrogel in oral drug delivery application. Nia et al. prepared bio-nanocomposite hydrogel compose of CMC/layered double hydroxides [315]. The bio nanocomposites used for controlled amoxicillin delivery to colon to treat bacterial infections. It showed pH sensitivity. The prepared bio nanocomposite-based hydrogel beads showed excellent performance in oral delivery of amoxicillin. The toxicity studies exhibited it is safe against HUVEC cells. This hydrogel beads can be potential for oral delivery of amoxicillin [315]. However, further detail studies need to do before moving to clinical trials. From the discovery of carbon dots, in short span of time they gained great interested due to range of properties including fluorescence [316]. Rakhshaei et al prepared nanocomposite hydrogel for pH sensitive oral anticancer drug delivery with bioimaging properties [317]. They prepared graphene quantum dot cross linked CMC nanocomposite hydrogel using casting method. It showed excellent biodegradability and biocompatibility (Fig. 12B). The prepared CMC/GQDs showed pH sensitive swelling and degradation. GQDs showed fluorescence and provide the bioimaging opportunity. The doxorubicin has used as model drug. The drug loaded hydrogel showed good biocompatibility and pH sensitive drug release property [317]. It can be a promising pH triggered site-specific drug delivery system. However, further studies need to investigate. Javanbakth et al. prepare Cu cross-linked carboxymethyl cellulose/naproxen/graphene quantum dot nanocomposite's hydrogel beads for naproxen oral delivery [318]. The used copper acetate for crosslinking

agent. The prepared Cu-CMC/NPX/GQD showed controlled drug delivery characteristics. It successfully delivered the naproxen to gastrointestinal tract conditions. It effectively protected drug in gastric pH. MTT test showed the low toxicity against caco-2 cells. These beads are good choice for delivery to gastrointestinal tract [318]. Furthermore, it can used for oral delivery. Chavda et al. developed stomach specific drug delivery system using super porous hydrogel composite for sustained delivery of ranitidine hydrochloride [319]. The detail comprehensive characterization of composite using various analytical techniques confirmed that formation of interconnected pores, capillary channels, cross linked sodium carboxymethylcellulose molecules. The composites exhibited the floating and delivery of ranitidine hydrochloride for 17 h. The drug release kinetics follows the Korsmeyer-Peppas, Weibull, and Hopfenberg models. The release is anomalous non-Fickian transport [319]. This study showed that floating drug delivery can be a potential alternative for stomach targeted delivery.

5.6.1.2. Beads.: Colon targeted drug delivery system can be a potential candidate to treat colon diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer. Recently various system delivery to target colon such as polymer-drug conjugate, pH responsive polymer coated nanostructures, bioadhesive polymers, biodegradable polymers, stimuli responsive releasing systems. Agarwal et al. attempted calcium alginate-carboxymethyl cellulose beads for colon targeted drug delivery [216]. It is a pH responsive swelling, mucoadhesive and colonic microflora catered biodegradable nanocarriers system. The beads prepared through gelation process. The formulated beads show higher mucoadhesiveness and swelling and slow degradation in simulated colonic fluid. The degradation increases presence of colonic microflora. Anticancer drug 5-fluorouracil showed more than 90% of release presence of colonic enzymes. The beads efficacy evaluated against colon adenocarcinoma cells, and it showed excellent therapeutic potential [216]. This study demonstrated that CA-CMC based beads can be potential option for colon targeted delivery of therapeutics. Kim et al. fabricated alginate-carboxymethyl cellulose beads through ionic cross-linking for protein delivery [322]. Fe3+ cross linked Alginate-CMC beads prepared. With increasing the ratio of CMC, the pore size of beads increased. The beads showed tunable swelling and albumin release behaviors at different pH and different beads volume. Albumin showed controlled release kinetics in vitro studies under simulated gastric intestinal conditions over 24 h. the crosslinking protect the albumin [322]. The alginate-CMC beads showed interesting results in in vitro. However, further detail studies need to be conducted.

5.6.1.3. Microparticles.: Pharmaceuticals with low molecular weight and chemically unstable needed moderate and prolonged payload release in response to factor. Esculin, a model phytopharmaceutical. Tsirigotis-Maniecka et al. developed pH-responsive polyelectrolyte coating for carboxymethyl cellulose based microparticles in the controlled release of esculin [323]. The microparticles shows 575 of % EE with spherical shape. In vitro studies confirm that microparticles did not induce any cytotoxic effects. They have demonstrated the poly-electrolyte shell onto CMC-based microsphere may offer controlled delivery of drug with response to pH and ionic gastrointestinal conditions [323]. This study demonstrate that suitable materials need to be chose to prepare microparticles to achieve controlled delivery. Cerchiara et al formulated microparticles based on chitosan/

caroboxymethylcellulose polyelectrolyte complexes for colon delivery of vancomycin [324]. Using spray-drying techniques microparticles were prepared at different weight ratio of chitosan/CMC. The CH/CMC 1:3 ratio showed optimum properties based of high EE. Microparticles showed great potential to inhibit the drug degradation and showed good antibacterial activity against *S. aureus*. Further coating with lauric acid facilitates the drug release in colon. Microparticles showed limited release at pH 2 and improved and prolonged release at pH 7 [324]. It concluded that microparticles can be potential option for colon specific delivery of peptide drugs.

5.6.1.4. Nanoparticles.: CMC extensively studied for colon targeted delivery. Nejabat et al. fabricated acetylated carboxymethylcellulose coated how mesoporous silica hydride nanoparticles for nucleolin targeted delivery to colon adenocarcinoma [290]. DOX loaded HMSNs coated with Ac-CMC which covalently conjugated with AS1411 aptamer. These nanoparticles showed controlled, sustained drug release and enhanced blood circulation. In-vitro cytotoxicity and cellular uptake studied confirm that AS1411 targetability to nucleolin overexpressing MCF-7 and C26 cells. The formulation showed excellent therapeutic activity in vivo tumor inhibition (Fig. 11D) [290]. Even the study showed promising results, the cytotoxicity of silica nanoparticles and their clearance is a big challenge need to be address before going to clinic. SN38 poorly water soluble chemotherapeutic and other side effects limited its clinical use. CD133 is an aptamer against cancer stem cell marker. Alibolandi et al. self-assembled PEGylated CMC-SN38 nanoparticles (169 nm) for CD133 delivery to treat colorectal cancer. Nanoparticles showed enhanced cellular uptake by CD133 expressed HT29 cells. Nanoparticles showed lower IC50 in HT29 cells over-expressing CD133 [325].

5.6.1.5. Nanocomposite.: Even after great interest in the use of essential oils in food feed additives for better health there are number of factors such as oxygen, light, moisture, and acids have negative effect on stability and hence reduced biological activity. Hence, protection of essential oil is required. One of the best strategies is encapsulation [320]. Zhao et al. used self-nanoemulsifying drug delivery system for oral delivery of zedoary essential oil. They have achieved 30% of loading at optimum formulation. the loaded essential oil remained stable at 25 C more than 1 year. Oral administration to rat the AUC increases 1.7-fold and Cmax increases 2.5-fold compared to normal zedoary. Fig. 12C presents the plasma concentration after oral delivery. Ngamekaue et al. studied the effect of beeswax-carboxymethyl cellulose composite coating at various concentrations of beeswax on shelf-life and controlled release [326]. Through coacervation method they have fabrication of HBEO-loaded gelatin microcapsules. They have studied the loading content, surface oil content, crystallinity, antioxidant and antimicrobial activity, and storage stability over 3 months. Very high surface oil found even after 3-month storage of HBEO-G, antibacterial activity remains same. These microcapsules successfully delivered the essential oil to distal small intestine. CMC coating minimize the exposure to gastric fluids. More than 70% of HBEO released at distal small intestine where its antibacterial activity required [326]. This study demonstrated the microencapsulation is an ideal option for promoting essential oils with antioxidant and antibacterial activity for use in food, feed, and pharmaceutical products. This study showed promising in-vitro results. However, more details in-vitro studies need to be conducted extensively and in-vivo performance need to be evaluate.

In recent years, MOF (metal organic frameworks) gained attention to use as drug delivery carrier due to their range of properties [327]. Javanbakht et al. CMC capsulated Cu based MOF-drug monohydride as a pH sensitive nanocomposite for ibuprofen oral delivery (Fig. 12D) [321]. Oral drug delivery method commonly used due to avoid patient's pain and discomfort. Cu based MOF loaded with IBP protected with biopolymer CMC Nanocomposite developed for oral delivery. Drug release studies showed the great protection ability of nanocomposite in stomach and extended stability and controlled release at gastrointestinal tract. The MTT studies confirm the biocompatibility of nanocomposite [321]. It concluded that nanocomposite hydrogel beads can be an innovative approach for oral drug delivery. Javanbakht et al fabricated bio-nanocomposite of CMC-coated 5-FU@MOF-5 for anticancer oral delivery [328]. 5-FU loaded into Zn based MOF and CMC used as coating to protect the drug in digestive system. This system shows promising controlled drug delivery behavior. In-vitro studies showed the notable toxicity in HeLa cells [328]. This study needs further studies in-vivo and long-term therapeutic potential and adverse effects. MOF accumulation and clearance for the body need to be studied. Various mucoadhesive CMC polymer based oral drug delivery literature is summarized in Table 8.

5.6.1.6. Miscellaneous.: Maciel et al. fabricated CMC based films enriched with natural plant extract for oral ion delivery [314]. Using tape casting method various films fabricated. The results revealed that films are fast disintegrating below 50 s. the iron release can be done within 50 minutes through Fickian diffusion mechanism [314]. It is an innovative system for iron delivery and can be used as carrier for treatment of Iron deficient disorders. Barkhordari et al. hydride system of CMC capsulated layered double hydroxide/drug for cephalexin oral delivery [342]. pH sensitive CMC bead used as protective capsule for LDH-drug (Fig. 12A). Drug cephalexin intercalated between LDH layer through co-precipitation method. The formed nanohybrid used to prepared nanocomposite hydrogel beads by association with CMC. The beads showed controlled release of drug in GI tract and protected in stomach pH [342]. This system still ne to be explored for further understanding.

Overall, chitosan is a potential mucoadhesive polymer for oral delivery with feasibility to target stomach, small intestine, intestine lymphatic, and colon. Other mucoadhesive polymers widely investigated colon targeted delivery. They have limited potential or need novel formulation to target the stomach, small intestine, and intestine lymphatic. Hence, other mucoadhesive polymers need to be explored. Pre-clinical and clinical studies need to be conducted for chitosan based oral drug delivery formulation to make it realistic. Recently ionic liquids showed promising results in oral delivery [343]. We believe ionic liquid can be an alternative system for mucoadhesive polymers in oral drug delivery applications.

6. Conclusions and Outlook

This review highlights the various potential mu coadhesive polymers-based formulation that has potential to oral delivery of macromolecules effectively and efficiently. We have put together this article after reviewing over three hundred representative research publication from the last decades. It is evident that mucoadhesive polymeric oral drug delivery systems are interesting due to desirable and physiochemical properties. Among the several types of mucoadhesive polymers, chitosan is a promising candidate for controlled, sustained, and

targeted drug delivery to investigate mucoadhesive oral delivery of nanotherapeutics. Pectin is another suitable mucoadhesive polymer of choice for oral drug delivery, in terms of ease of formulation, availability of various functional groups offers range of derivatives for mucoadhesive oral delivery, and scalability. It has potential to control physico-chemical properties through desire choice of functionalization. Targeting agent can be conjugated with pectin to use as nanocarrier for targeted mucoadhesive oral drug delivery.

This review concludes that mucoadhesive polymeric oral drug delivery system is a good choice. However, sustainable mucoadhesive biopolymers need to explore. Furthermore, PAA and CMC have also recently gained great interest due to their promising properties. Mucoadhesive polymeric oral drug delivery systems are not extensively studied and well established due to limited number despite of huge potential and prospects. Moreover, toxicity of mucoadhesive polymeric nanoparticles is a major concern that need to be extensively evaluated before use of them in vivo and in pre-clinical studies.

Due to physicochemical properties, which offer the potential to survive with gastric fluids, and mucoadhesive properties, which allow the adhesion to mucus and facilitate the effective absorption of drug in the GI tract. We believe that mucoadhesive polymer based oral drug delivery systems are potential candidate for developing next generation personal medication. This review attempt to present potential of mucoadhesive polymers based oral drug delivery system to develop next generation multifunctional combination therapies, especially targeted delivery to stomach, small intestine, intestine lymphatic, and colon with control drug release. Designing of a through, extensive and realistic ex vivo experimental model is required to be able to investigate the potential of individual formulations and their physicochemical interaction with different parts of GI tract.

The impact of mucoadhesive polymer based oral drug delivery system has high significance for oral delivery science. The adverse side effects of chemotherapy can be controlled or overcome through modification with mucoadhesive polymeric oral drug delivery system. More than 5000 reports published on mucoadhesive polymer based oral drug delivery system in past decade. Despite of great development on oral formulation the existing gap and unmet needs still hindering the innovation translating from academic research to clinical application.

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Data availability

No data was used for the research described in the article.

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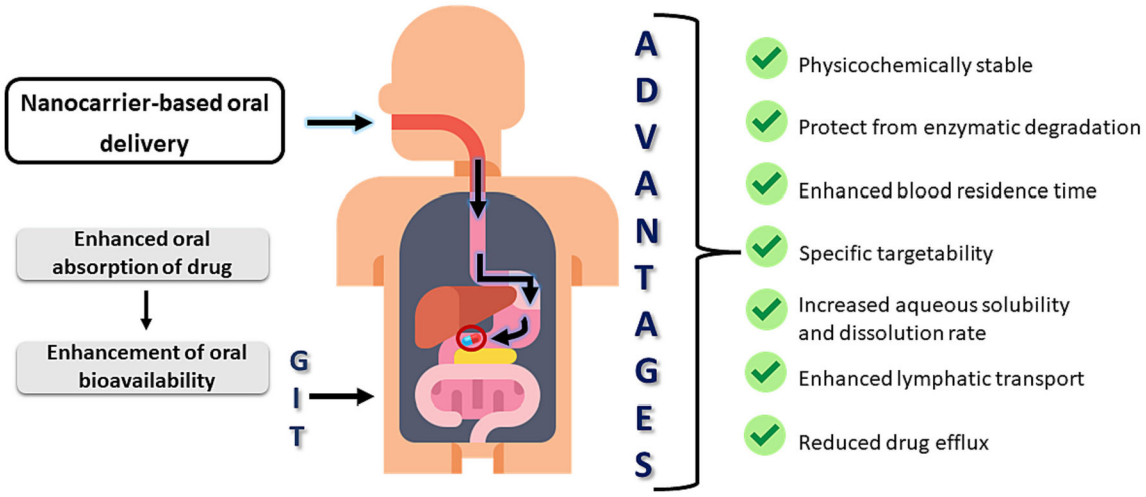

Fig. 1.

The scheme represents potential benefits of mucoadhesive-based formulation for oral drug delivery.

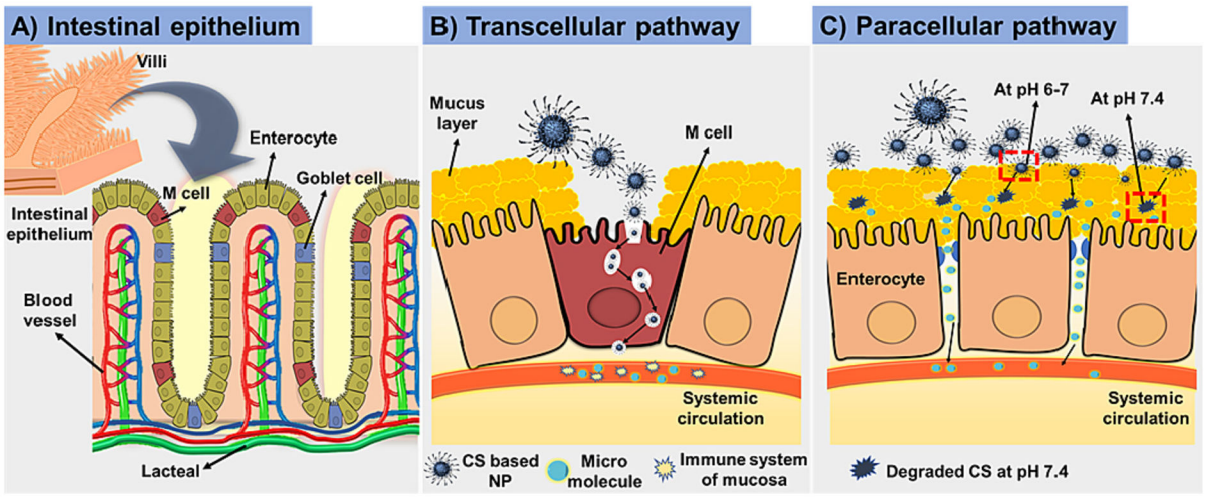

Fig. 2.

Schematic illustrations of (A) the structure of the intestinal epithelium (B) the transcellular and (C) paracellular transport of nanoparticles.

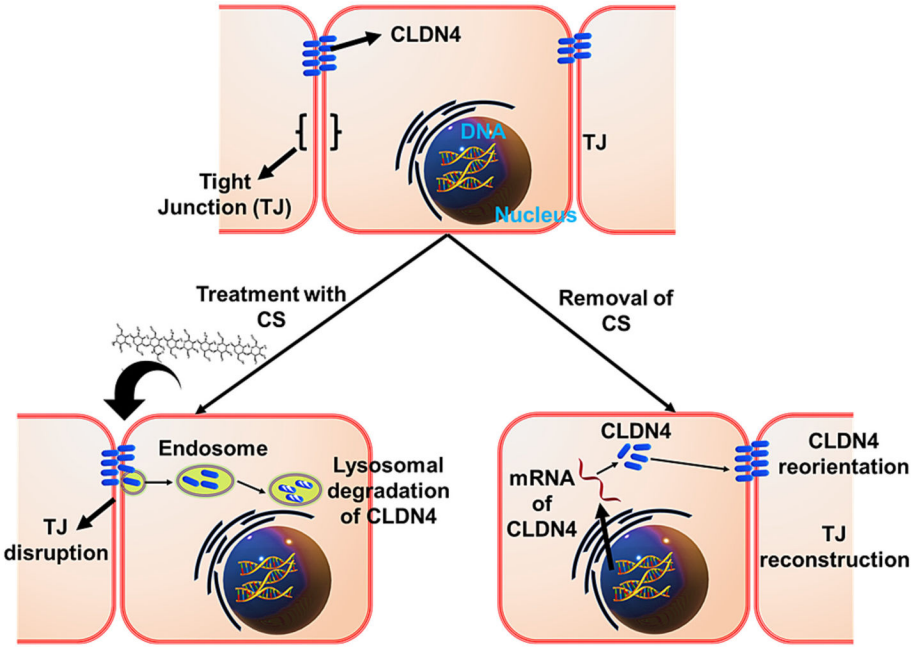

Fig. 3.

Schematic mechanism of chitosan mediated reversible tight junction (TJ) opening.

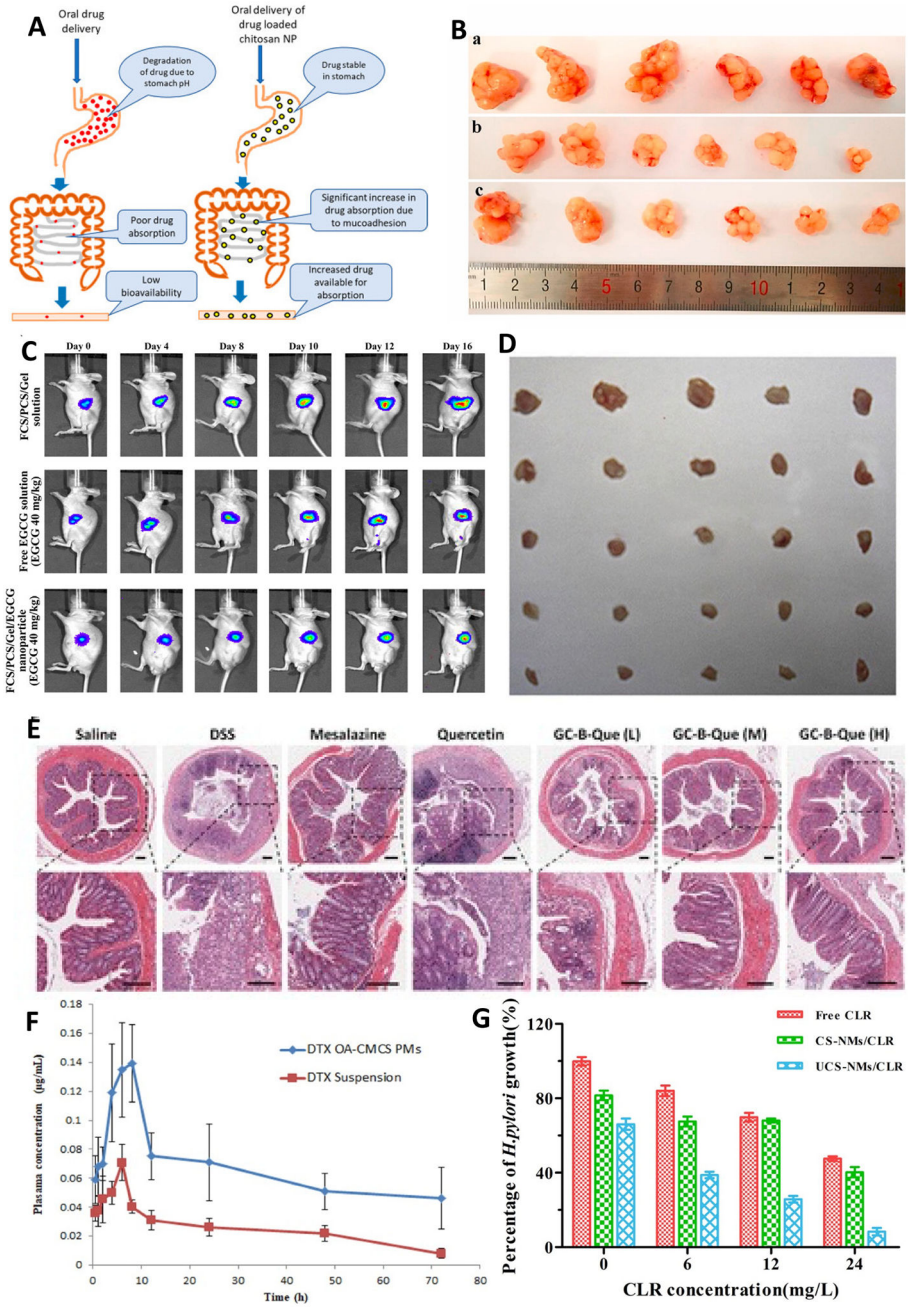

Fig. 4.

(A) in vivo efficiency of chitosan nanoparticles increasing absorption of drug through intestinal epithelium; (B) Photos of original tumor size. (a) control, (b) COS–Se (100 mg/kg), and (c) COS-Se (50 mg/kg); (C) The antitumor activities using a noninvasive in vivo imaging of Orthotopic Luc MKN45 xenograft models treated with different sample daily; (D) In vivo antitumor efficacy study (E) in vivo anti-inflammatory activity of smart responsive quercetin-conjugated glycol chitosan prodrug micelles, Histological study of inflammatory tissues after treatment by hematoxylin and eosin staining; (F) Plasma concentration vs time profile of DTX (Docetaxel) after oral administration of 10 mg/kg

dose of DTX suspension and DTX loaded OA-CMCS micelles; (G) In vitro anti-bacterial activity of free clarithromycin (CLR), clarithromycin-loaded CMCS-g-SA nano-micelles (CS-NMs/CLR) and clarithromycin-loaded U-CMCS-g-SA nano-micelles (UCS-NMs/CLR) against *H. pylori*;. Images of tumor tissues. Reproduced with permission from ref. [93–98]. Copyright 2019 Elsevier, 2017 MDPI open access, 2020 Elsevier, 2015 American Chemical Society, 2021 American Chemical Society, 2020 Elsevier, 2019 Elsevier.

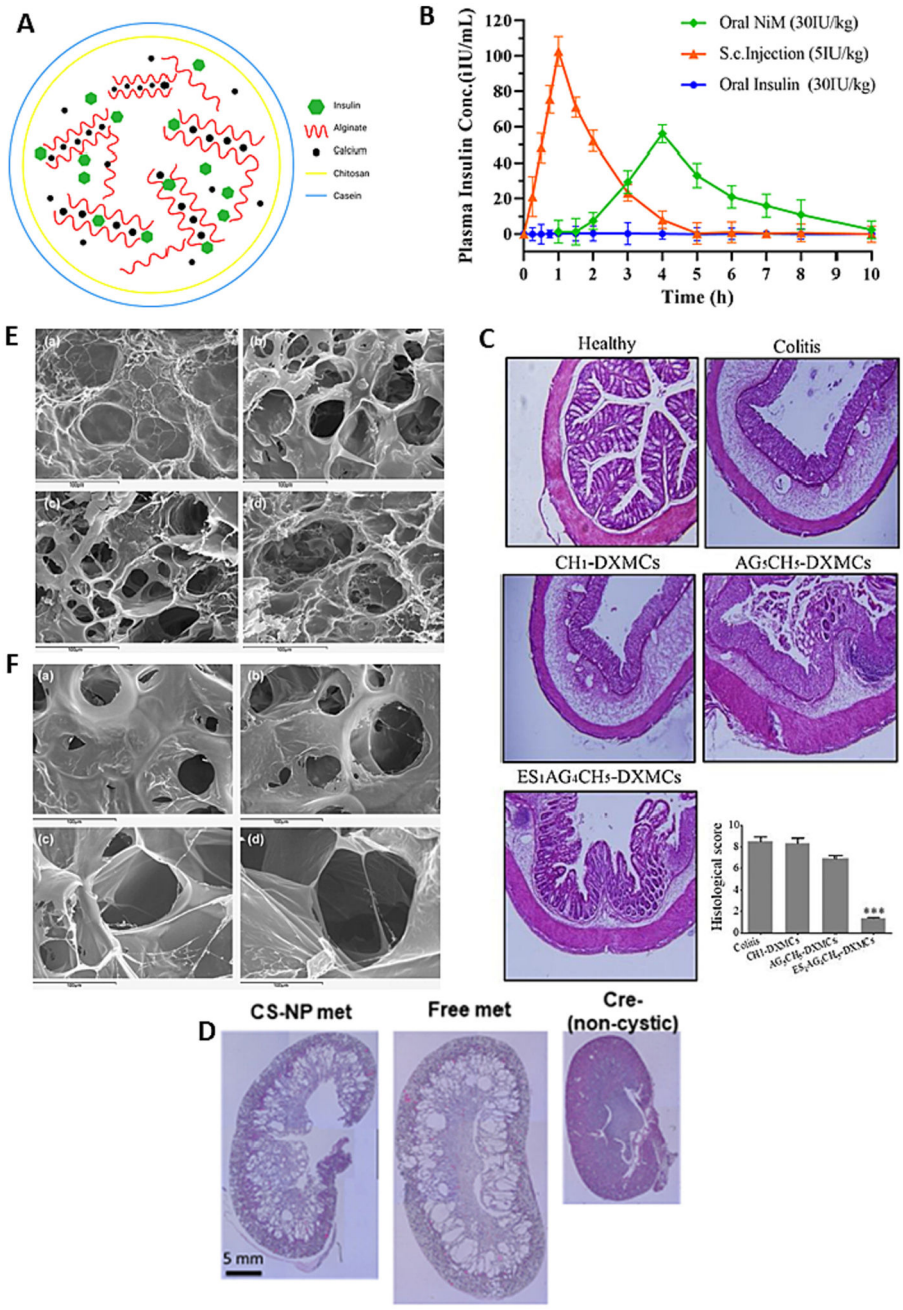

Fig. 5.

(A) Schematic representation of NiM particles; (B) Plasma insulin concentration-time curves after subcutaneous injection of insulin solution (5 IU/kg), oral administration of NiM (30 IU/kg), and oral administration of insulin solution (30 IU/kg) in diabetic mice; (C) Histological assessment of colitis in colon tissues from the different study groups shown remarkable in histological feature in mice treated with ES1AG4CH5-DXMCs; (D) H&E staining of whole kidneys shows less severe cystic phenotype in the CS-NP met group; (E) Scanning electron micrographs of CAM:[CS:CMC] 40:[25:75] (w/w) complexes. The first two micrographs depict top view of mini matrices at 30 min and pH 1.2 with low M.wt.

CS (a) and high M.wt. CS (b). The other two micrographs outline surfaces at 1 h and pH 1.2: low M.wt. CS (c) and high M.wt. CS (d); (F) Scanning electron micrographs of CAM: [CS: CMC] 40:[25:75] (w/w) complexes. The first two micrographs depict top view of mini matrices at 1 h and pH 4.2 with low M.wt. CS (a) and high M.wt. CS (b). The other two micrographs outline surfaces at 4 h and pH 4.2: low M.wt. CS (c) and high M. wt. CS (d). reproduced with permission from ref. [132,134–136]. Copyright 2008, 2020, 2018 Elsevier, and 2021 Wiley.

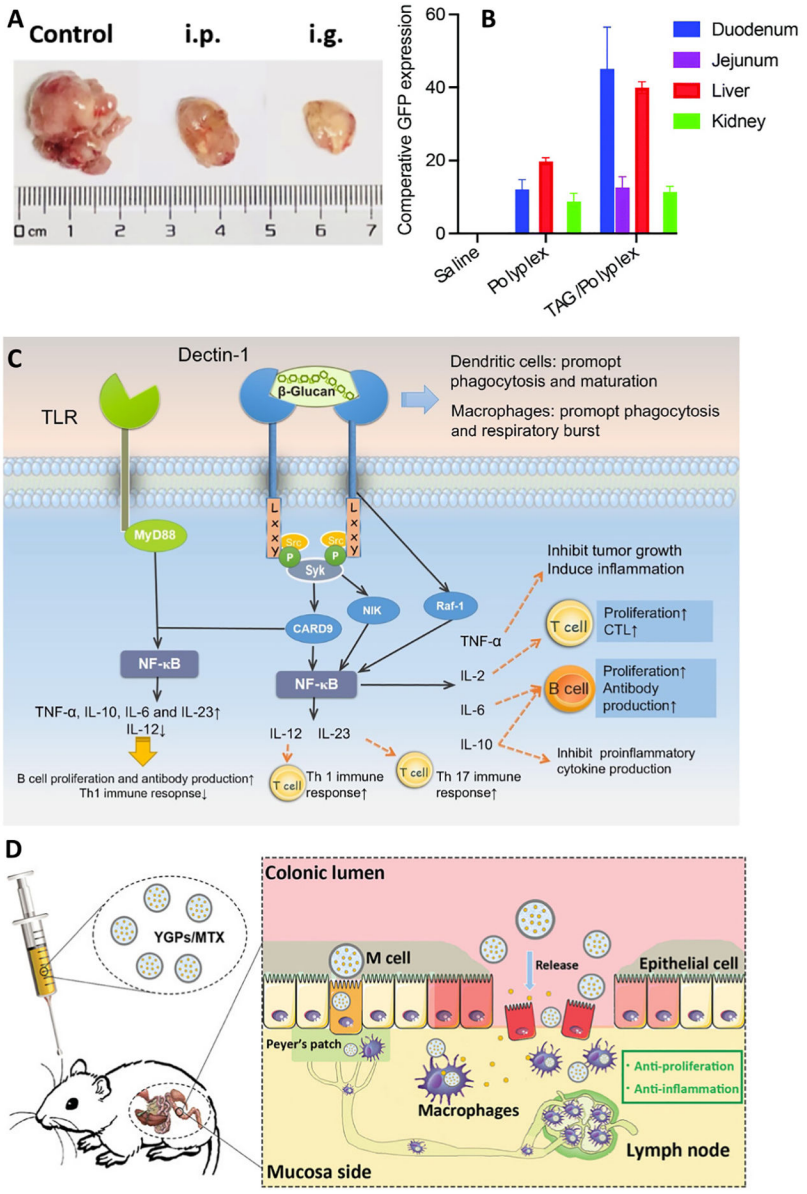

Fig. 6.

(A) representative photographs of S-180 tumors of mice were subcutaneously inoculated with S-80 cells. 2 mg/kg AG was intraperitoneally or orally administrated to mice daily after tumor inoculation for 1 week: (B) Quantitative expression of eGFP in different tissues/organs of orally administered polyplex and TAG/polyplex. TAG containing particles show duodenumspecific transportation and liver accumulation. Liver accumulation of eGFP for TAG-mediated particles was 3× higher than polyplex; (C) The signal pathway of β-glucan binding to dectin-1. Once they are bond, dectin-1 will activate Syk via double "LxxY" structures, and then trigger NF-jB mainly throughCARD9 or NIK to produce IL-10, IL-2, IL-23, IL-6 and TNF, resulting in T and B cells proliferation, DCs maturation and respiratory burst. Dectin-1 can also trigger NF-jB by Raf-pathway directly. When dectin-1 and MyD88 of TLRs are both activated, there will appear a coupling-signal that prompts the

production of TNF-a, IL-10, IL-6 and IL-23, and down regulates the expression of IL-12; (D) The preparation process of YGPs/MTX and the illustration of YGPs/MTX targeting inflammatory sites and suppressing intestinal inflammation after intragastric administration. Reproduced with permission from ref. [177,180–182]. Copyright 2019 Elsevier, 2022 The Royal Society of Chemistry, 2018 Elsevier, and 2020 Wiley-Vch.

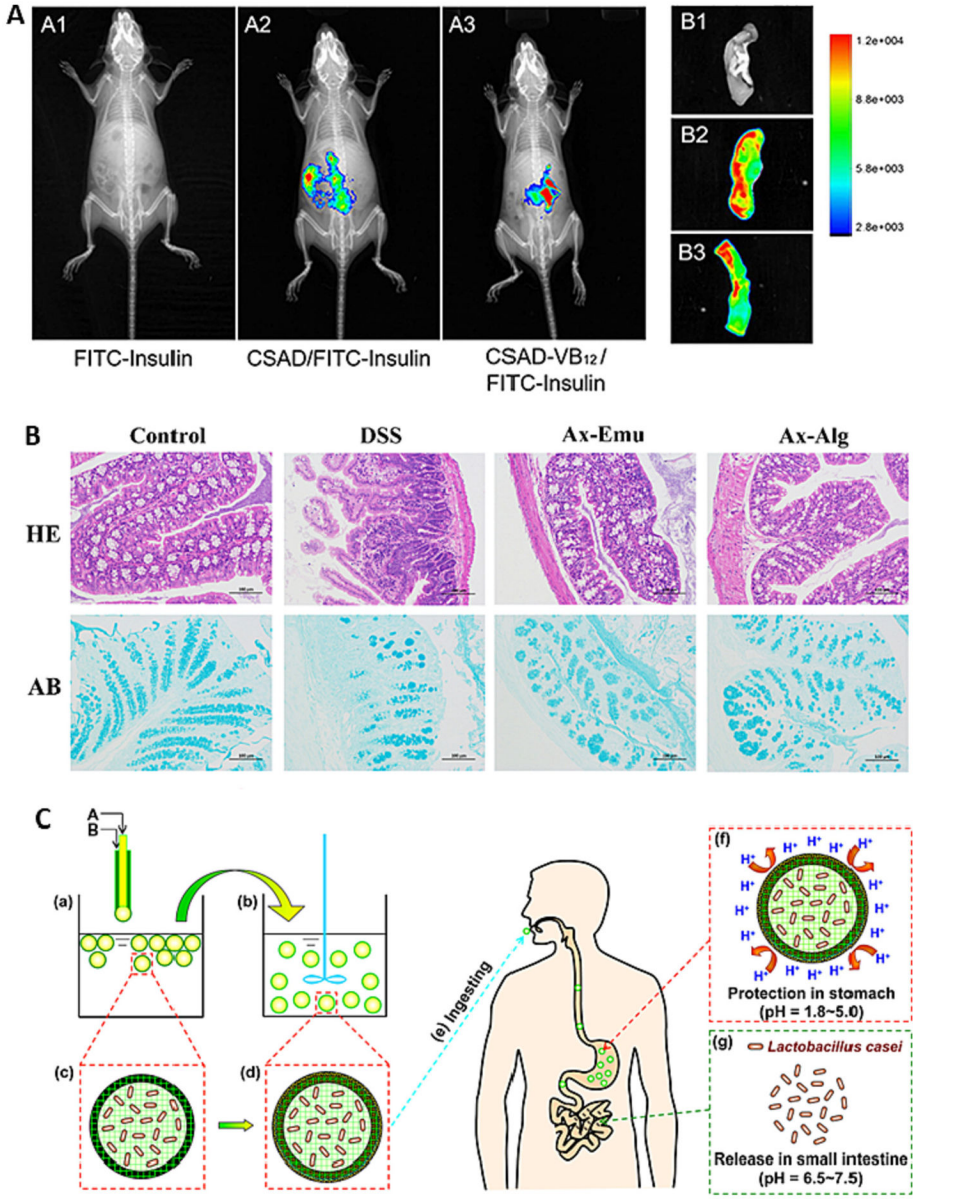

Fig. 7.

(A) The retention effect and absorption of FITC-insulin, CSAD/FITC-insulin, CSAD-VB12/FITC-insulin in intestine. (A) In vivo animal image system showed the fluorescent signal of FITC-insulin (A1), CSAD/FITC-insulin (A2), CSAD- VB12/FITC-insulin (A3) at the 1 h after oral administration in T1D mice. (B) Representative fluorescence imaging of small intestine from mice treated with FITC-insulin (B1), CSAD/FITC-insulin (B2), CSAD-VB12/FITC-insulin (B3); (B) Histological score of colon tissues by hematoxylin and eosin (HE) and alcian blue (AB) staining after treatment of Ax-Alg to DSS colitis mice. (C) Schematic illustration of the preparation process and the design concept of the proposed intestinal-targeted CAP carrier for pH-responsive protection and release of lactic acid bacteria. (a, c) CA beads prepared by a coextrusion method. “A” is Na-alginate solution containing Lactobacillus casei, and “B” is pure Na-alginate solution. (b, d) CAP beads

prepared by adsorption of protamine molecules. (e) Ingesting CAP beads in mouth. (f) CAP beads offer improved protection for Lactobacillus in stomach. (g) CAP beads release Lactobacillus casei rapidly in the small intestine. Reproduced with permission from ref. [199–201]. Copyright 2022 Elsevier, 2019 Dove press, open access, and 2014 American Chemical Society.

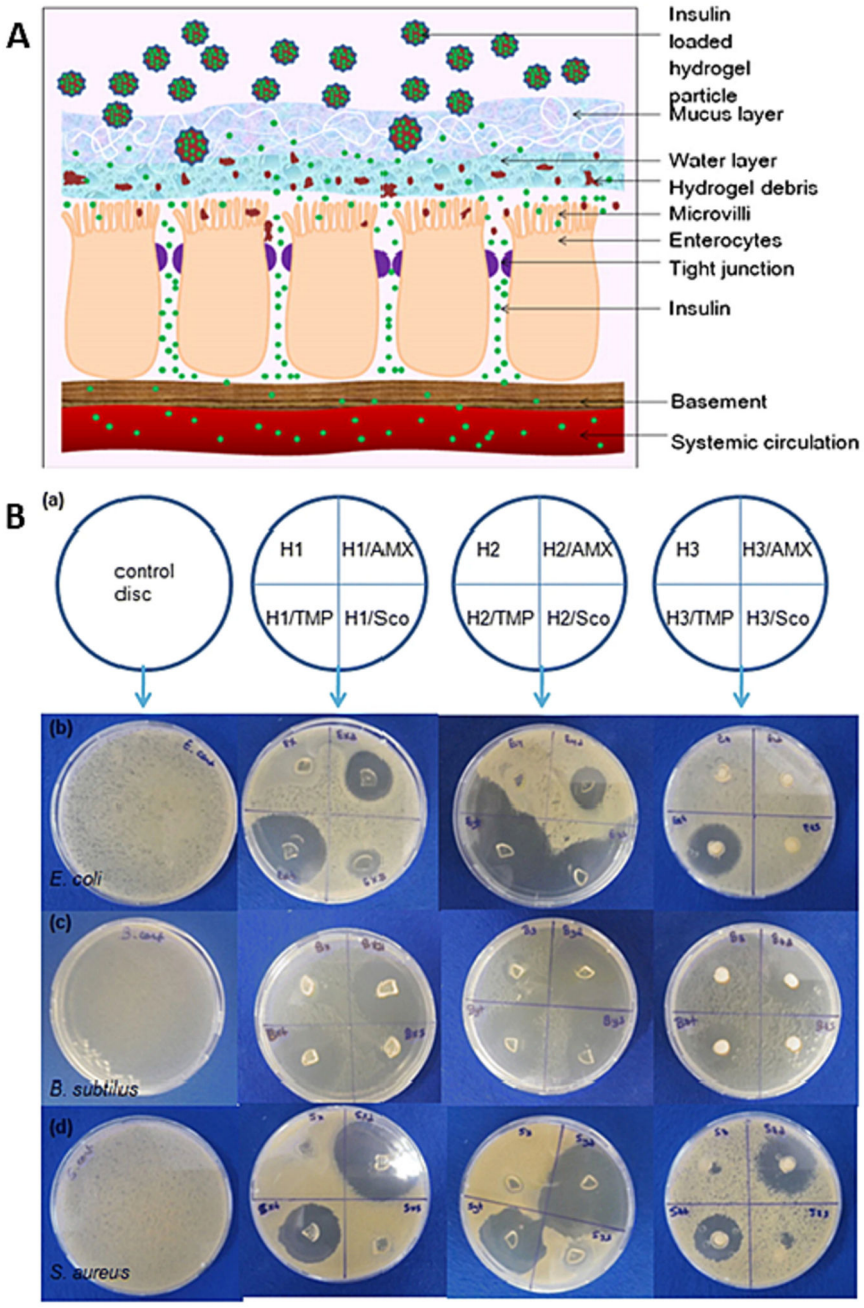

Fig. 8.

(A) Schematic diagram showing the release and absorption of insulin from intestine following oral administration of hydrogel-based systems; (B) Digital photographs of antimicrobial activity tests of drug-loaded and unloaded semiIPN hydrogels (a) Schematic representation of the test application for control disc, H1, H2 and H3 hydrogels (top to bottom), or the bacteria applied (b) *E. coli*. (c) *B. subtilus* (d) *S. aureus*. Reproduced with permission from ref. [218,220,220]. Copyright 2012 Elsevier, 2020 the Polymer Society, Taipei.

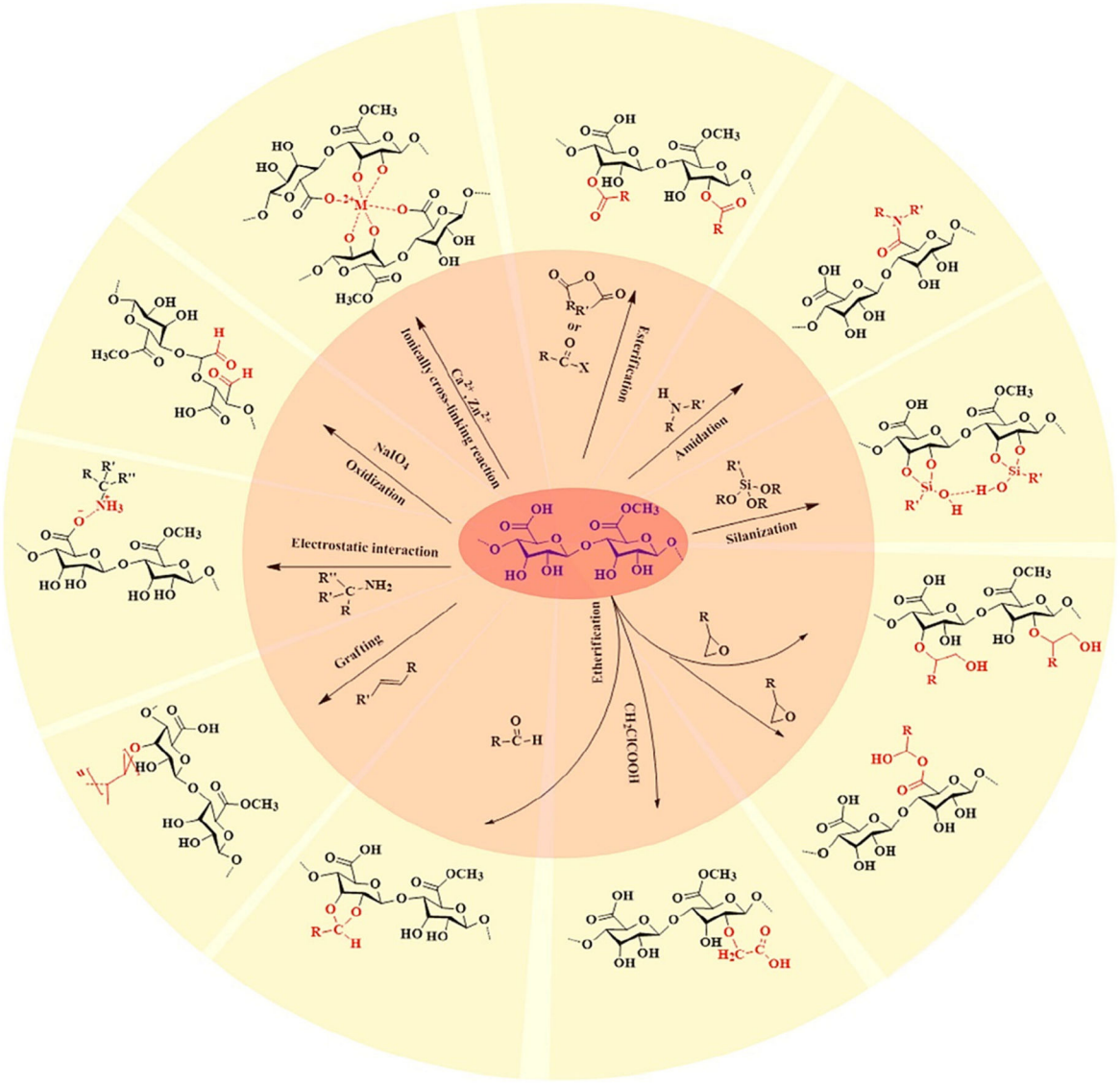

Fig. 9.

Potential reactions of pectin for synthesis of various derivatives. Reproduced with permission from the ref [243]. Copyright 2021 Elsevier.

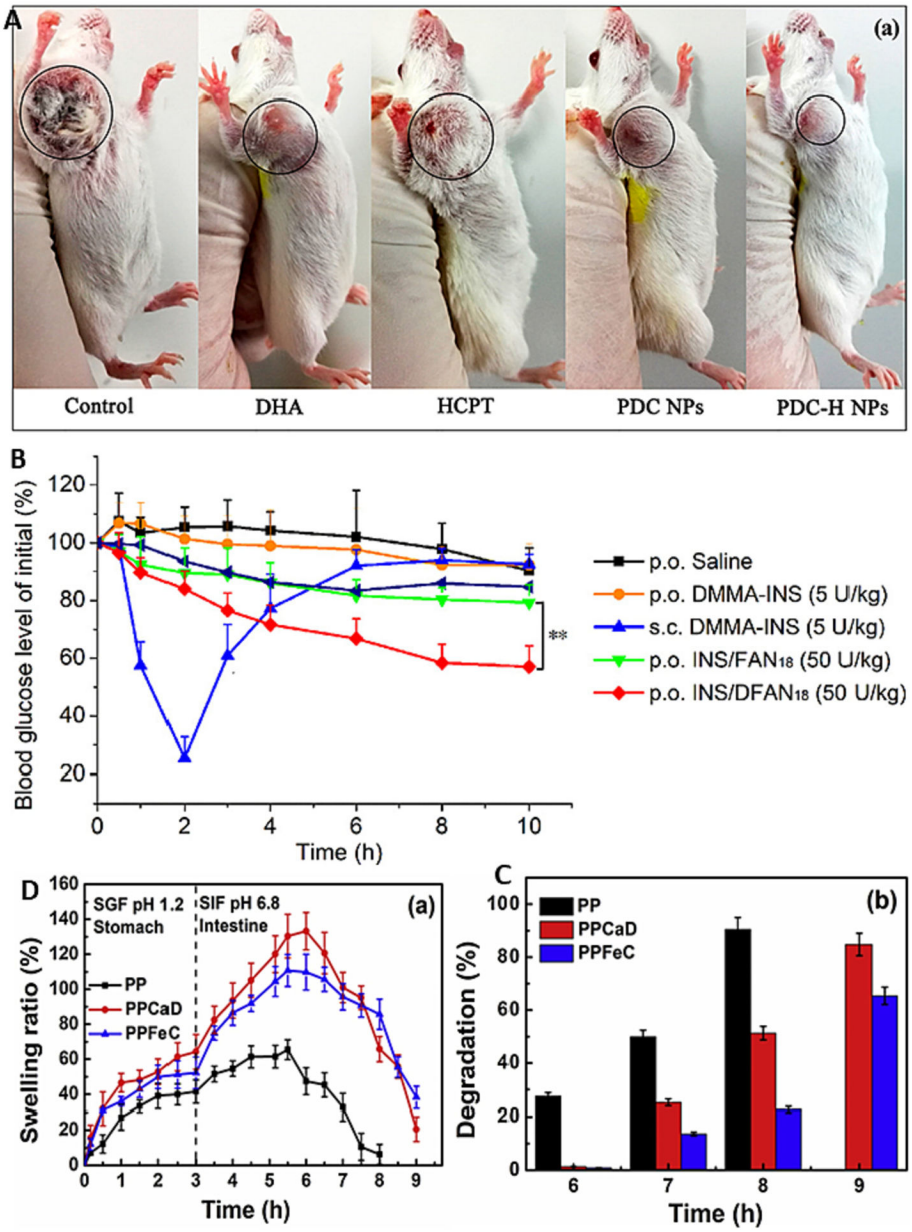

Fig. 10.

(A) Tumor photographs of each treatment group on day 24 of In vivo antitumor activity of free DHA, free HCPT, and nanoparticles in the subcutaneous mouse model of 4T1 cells. Tumor photographs of each treatment group on day 24; (B) Blood glucose level *vs.* time profiles of STZ-induced diabetic rats administrated with insulin solution, INS/FAN18 and INS/DFAN18 through different routes; (C) (a) Swelling ratio of the hydrogels PP, PPCaD and PPFeC in SGF at pH 1.2 and in SIF at pH 6.8 (b) degradation behavior in SIF at pH 6.8 for various hydrogels. Reproduced with permission from ref. [247–249]. Copyright 2022, 2019 Elsevier, and 2017 American Chemical Society.

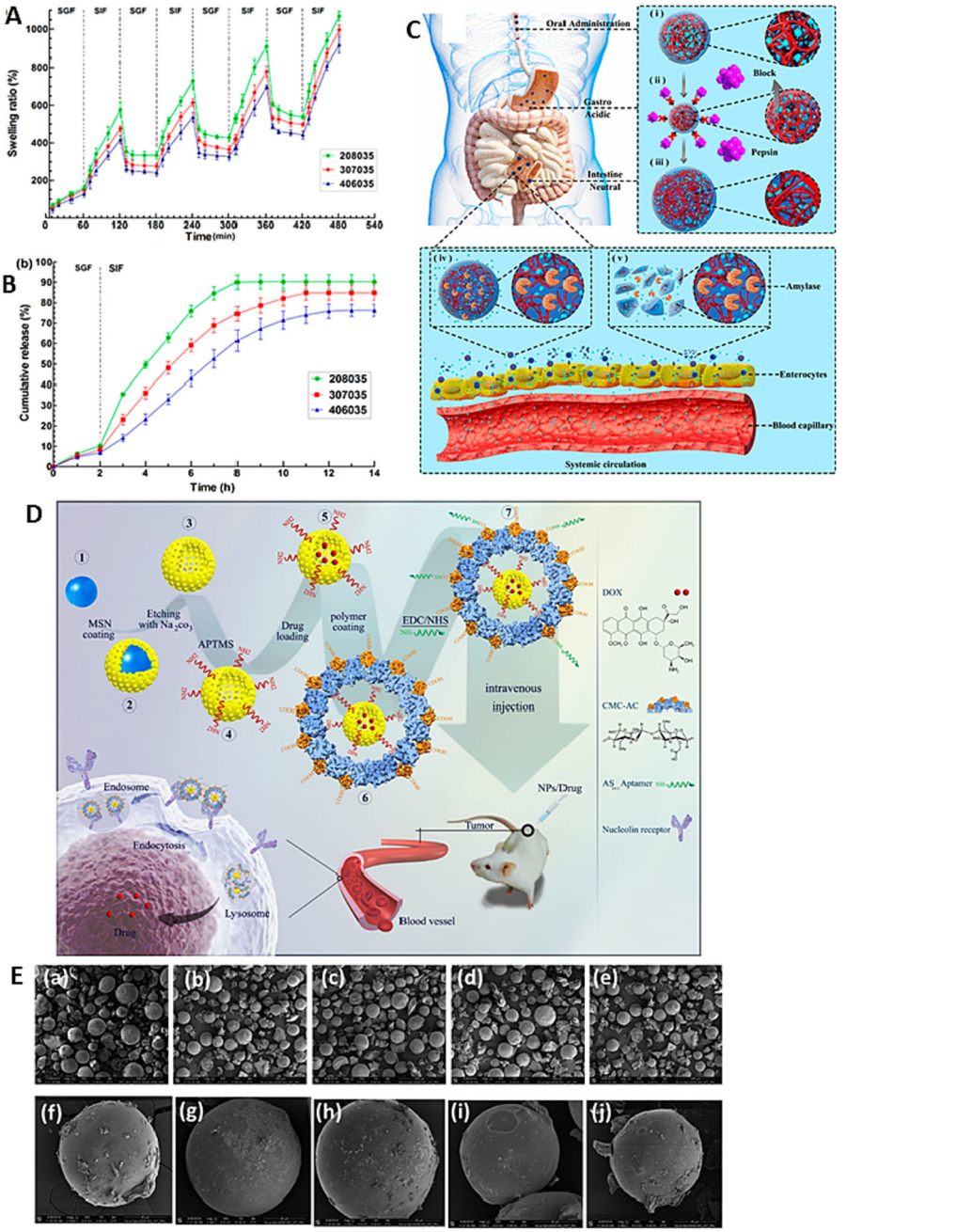

Fig. 11.

(A) Dynamic swelling/deswelling of hydrogels in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF); (B) in vitro BSA release profile of the hydrogels in SGF and SIF; (C) Proposed Schematic Illustration for the Behaviors of the Insulin-Loaded Microgels during the Delivery Process in the GI Tract; (D) Schematic presentation of the preparation of HMSNs, their coating with acetylated CMC and functionalization with AS1411 aptamer for targeting nucleolin over-expressing cancer cells; (E) SEM Micrographs of (a) MS1, (b) MS2, (c) MS3, (d) MS4, (e) MS5 microspheres at 150 magnification and single (f) MS1, (g) MS2, (h) MS3, (i) MS4, (j) MS5 microspheres at 2000 magnification. Reproduced with

permission from ref. [265,286,290,291]. Copyright 2014 American Chemical Society, 2018 Elsevier, 2014 The Royal Society of chemistry, 2018 American Chemical Society.

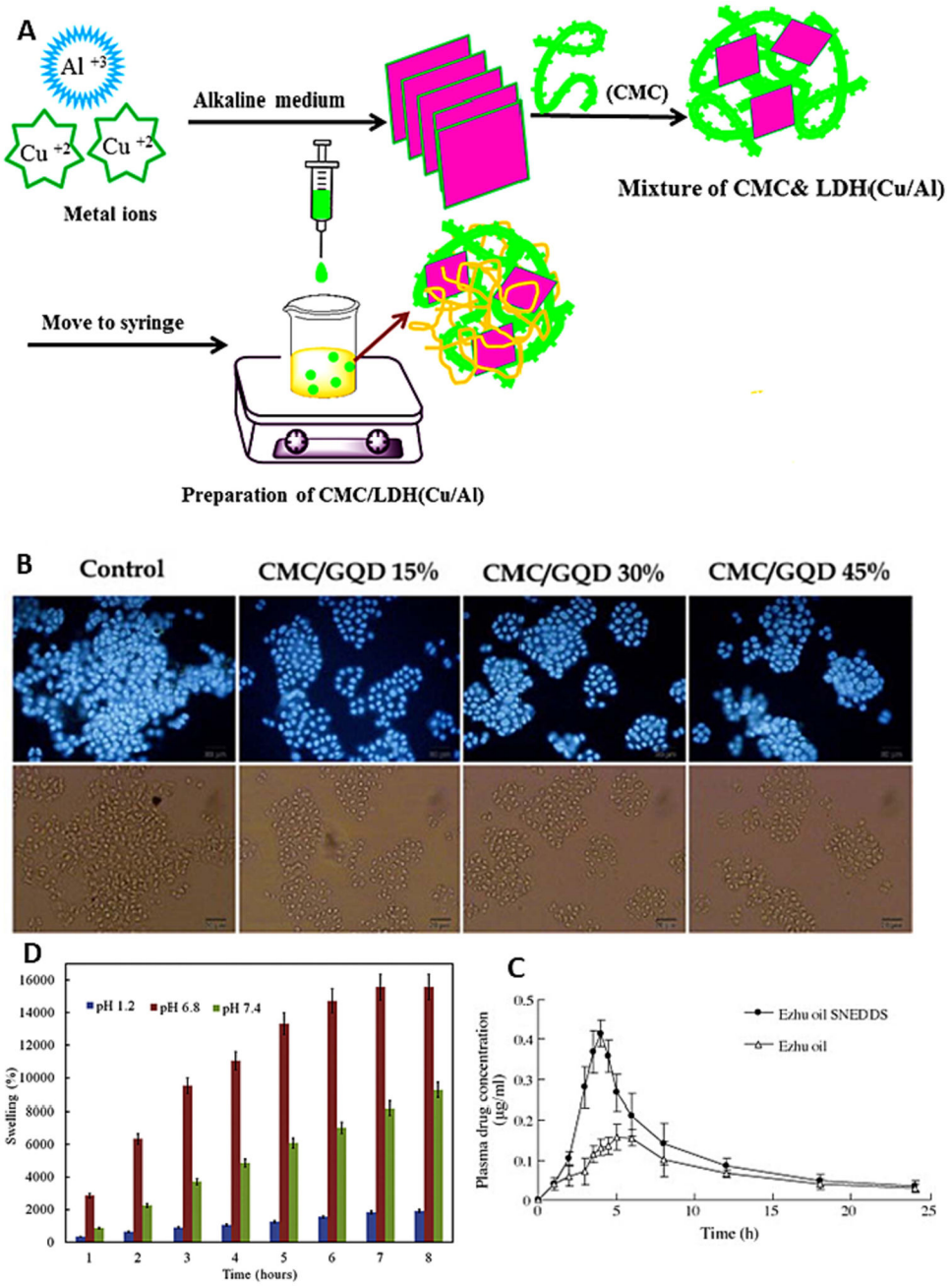

Fig. 12.

(A) Schematic procedure for preparation of CMC/LDH(Cu/Al) bio-nanocomposite hydrogel bead; (B) DAPI stained nuclei of colon cancer cells (HT29 cells) with CMC/GQDs at various GQDs percentage (15%, 30%, and 45%); (C) Plasma concentration of GM after oral administration of unformulated ZTO (500 mg/kg) or ZTO-SNEDDS (1625 mg/kg) to SD rats; (D) Swelling behavior of CMC/Cu-MOF@IBU at pH values of 1.2, 6.8 and 7.4. Reproduced with permission from ref. [315,317,320,321]. Copyright 2019, 2019, 2009, 2018 Elsevier.

Table 1

Review articles published 2015 to till date with title contains mucoadhesive, oral and polymer.

Year	Title of the review articles	The theme of the review articles	Ref
2015	mucoadhesive oral films: the potential for unmet needs	This article focused on mucoadhesive oral films. They have reviewed the status of products in clinical trials and studied the preferable therapeutic indications and market trends of mucoadhesive oral films research.	[6]
2016	Recent advancement in mucoadhesive floating drug delivery systems: a mini review	This study specially focused on the floating mucoadhesive drug delivery systems, which increases local absorption. Also discussed the different types of formulations potential towards floating drug delivery.	[7]
2017	Mucoadhesive polymers and their mode of action: a recent update	This study reported the various mechanisms of mucoadhesion. They studied and highlighted the polymers, which are using in research and their mucoadhesive mechanism was discussed.	[8]
2017	A critical review about methodologies for the analysis of mucoadhesive properties of drug delivery systems	In this study they have reported the in vivo in vitro and ex vivo methods for evaluation of mucoadhesive properties of formulation used for drug delivery. They also discussed the use of artificial and natural mucosa to study the absorption into mucus.	[9]
2020	Advances and applications of chitosan-based nanomaterials for oral delivery carriers: a review	this study comprehensively documented the chitosan-based formulation for oral delivery. They also discussed the various biotherapeutics including hydrophobic and hydrophilic drugs delivery using chitosan.	[10]
2020	Mucoadhesive electro-spun fiber-based technologies for oral medicine	This study especially focused in electro-spun mucoadhesive devices for the treatment of anti-inflammatory, local anesthesia and analgesics, and antimicrobial.	[11]
2020	Mucoadhesive formulations: innovation, merits, drawbacks, and future outlook	This article focuses on polymers involved in mucoadhesive drug delivery. the characteristics of polymers such as charge, surface groups, wettability, molecular weight and chain flexibility on mucoadhesive property and treatment potential.	[12]
2021	Mucoadhesion and mechanical assessment of oral films	This study studied the mucoadhesion and mechanical properties of film. They also discussed the various method to measure and evaluate the mucoadhesive and mechanical properties of oral films.	[13]
2021	Enhancement of oral bioavailability of natural compounds and probiotics by mucoadhesive tailored biopolymer-based nanoparticles: a review	This article is focused on mucoadhesive potential of food grade biopolymers nanoparticles and their potential to increase oral bioavailability of natural compounds. And their potential towards prebiotics, probiotics, and antimicrobials along the GI tact.	[14]
2022	Mucoadhesive nanocarriers as a promising strategy to enhance intracellular delivery against oral cavity carcinoma	This review discussed the potential of mucoadhesive nanocarriers towards the targeting, solubility and bioavailability enhancement and novel tumor targeted drug delivery for oral cancer treatment.	[15]
2022	Mucoadhesive formulations for oral delivery	We have discussed the mucoadhesive polymers, properties and range of formulation for targeted delivery to stomach, small intestine, intestinal lymphatic, and colon.	Present study

Table 2

Physiological features of the human gastrointestinal tract.

GI tract region	Length	Surface area	pH	Epithelial type	Retention time	Major enzymatic activities
Oral cavity	-	0.01	6.5	Stratified Squamous	-	Polysaccharides
Esophagus	0.2–0.25	0.02	-	Stratified Squamous	4–8 s	-
Stomach	0.25	3.5	1–3	Secretary Columnar	1–3 h	Proteases, lipases
Duodenum	0.35	1.9	4–5.5	Simple columnar	30–40 min	Polysaccharides, oligosaccharides, proteases, peptidases, lipases
Jejunum	2.8	184	5.5–7	Simple columnar	1.5–2 h	Oligosaccharides, peptidases, lipases
Ileum	4.2	276	7–7.5	Simple columnar	5–7 h	-
Colon	1.5	1.3	7.5–8	Columnar dominated	16–35 h	Broad spectrum of bacterial enzymes
Rectum	0.12	-	7	Columnar dominated	-	-

Table 3

Factors that affect drug absorption from the gastrointestinal tract.

Physiological factors	Physiochemical factors	Formulation factors	Miscellaneous
1 Physiology of GIT **i.** pH of various segments **ii.** esophageal transit time **iii.** esophageal motility **iv.** Presence/absence of food **2** Mode of transport across the GI tract **i.** passive diffusion **ii.** active transport **3** Metabolism	**i.** Drug stability in the GI fluid **ii.** Ionization constant **iii.** Lipophilicity of the drug **iv.** Drug solubility **v.** Crystal properties **vi.** Dissolution rate **vii.** Salt form **viii.** Protein binding **ix.** Complex formation **x.** adsorption	**i.** Solutions **ii.** Suspensions **iii.** Capsules **iv.** Tablets **v.** Coated tablets	**i.** Age **ii.** Gender **iii.** Smoking and alcohol abuse **iv.** Other drug use

Table 4

Chitosan based mucoadhesive oral drug delivery system.

Mucoadhesive nanocarrier system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		C
CS Nano particles	Alginate	Crocine *(Crocus sativus L.)*	Antitumor effects	%EE-91.5 %DL- 27.4 RP-In vitro release: 90% in both simulated gastric (pH 2) and intestinal pH (pH 6.8)	•	finely tuned NP formation (100 nm)	•	toxicity and in vivo efficacy need to be evaluate	P o c c n
					•	Increased encapsulation and loading efficiency			
					•	higher stability in simulated gastric fluid (SGF) (pH-2)			
CS Nano particles	Poloxamer 407 Tween 80	Insulin	Diabetics	%EE-57.23 %DL- 20.53 RP-more than 80% of insulin release in intestinal mucosa of goat at end of 6h. Ex vivo permeation-sustained permeation of insulin through Caco-2 cells up to 6 hours In vivo-showed significant hypoglycemic effect in diabetic rats	•	High ex vivo permeation through Caco-2 monolayer and sheep intestine	•	biodistribtion of nanoparticles and their toxicity on major organs need to investigate	E o li o d
					•	in vivo studies also showed good insulin efficacy with the proposed NP system			
CS Nano particles	Silica NP	Bovine serum albumin (BSA)	Enhancement of the immune response	%EE-25.34 %DL- 20.21 RP- at pH 6.8 only 5% at end of 24 hr whereas at pH 7.5 at end of 12 days around 50% of BSA release. Slow-release behavior observed. In vivo-produced systemic mucosal immune response in mice	•	High encapsulation and drug loading efficiency	•	No toxicity study was carried out	P o d
					•	Showed good immune response upon oral delivery			
CS Nano particles	De-esterified Tragacanth	Insulin	Diabetics	%DL- 5.39, RP- 20% of insulin released after 2 hours in gastric pH-2; 30% after 6 hours in simulated intestinal fluid of pH-6.8; 97% after 9 hours in simulated colon fluid of pH-7.4	•	Good loading efficacy and stability	•	In vivo studies not conducted	P o d
					•	NPs with size less than 200 nm	•	Bioavailability and biodistribution studies were not done	
CS-PEG Nano particles	Cyclodextrin derivative with 9 carbons alkyl chain	Aprepitant	Acute and delayed chemotherapy-	%EE (nanoparticles)- 55 % %EE	•	High loading efficiency (93%)	•	Particle size slightly higher (400–550 nm)	P o a

Mucoadhesive nanocarrier system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		C
			induced nausea and	(Nanocapsules)- 93. RP-Sustained drug release was shown up to 24h	•	Bioavailability was comparable to existing commercial drug formulations	•	In vivo toxicity study was not carried out	
3 different MW CS Nano particles	Hydrogenated soybean phosphatidylcholine (HSPC)/1,2-dipalmitoyl-snglycero-3-phosphoglycerol (DPPG) liposome	Insulin	Diabetics	DL- 10.7% by weight. RP- 6% in 1h for simulated gastric fluid, 2% in two weeks in simulated intestinal fluid, and 5% in two weeks in PBS. CT- Non-toxic to L929 cells. IP- 2–3-fold increase	•	Development of layer-by-layer (LBL) insulin coated on anionic nanoliposome carrier with CS	•	very slow drug release profile so difficult to achieve therapeutic concentration at side of disease	T c n c tr ir C tl
					•	Offered high insulin loading efficiency			
					•	Controlled release in simulated gastric and intestinal fluid			
CS-stearic acid nanoparticles	L-carnitine	(PTX	Anticancer effects	%DL- 15.91±0.20 RP- only 6.6% of drug release at end of 120 h. slow-release behavior. PK- Increase 2.03-fold peak concentration (Cmax) and relative bioavailability 165.8% compared to Taxol, indicating the enhanced absorption.	•	Increased oral bioavailability of PTX	•	In vivo studies need to conduct to compare the therapeutic potential and survival rate	P m si e o d o c tr (
					•	Small particle size (~157 nm)	•	No in vitro toxicity analysis was carried out with different cell lines	
					•	Enhanced intestinal absorption			
CS nanoparticles	Solid lipid nanoparticle (SLN)	Thymoquinone (TQ)	Anti-inflammatory effect	%EE- 82.66 %DL- 9.84 RP- TQ shows controlled release profile and release nearly 80% at end of 24 h. Oral bioavailability of TQ increases many folds.	•	CS based solid lipid nanoparticles (SLN) for improved oral delivery of TQ	•	Toxicity analysis was not done for the in vivo study	N m C p to b o
					•	Controlled release within 24 hours	•	Particle size was very large with high polydispersity so stability need to be evaluated	
TMC nanoparticles	Captex 355 Kolliphor RH40 Propylene Glycol	Amphotericin B (AmpB)	Visceral Leishmaniasis	DL- 0.71 mg/g CT- Cell viability was higher than 80% for all formulations. Formulation capable to open tight junctions and enhanced the permeability	•	Development of a self-nanoemulsifying drug delivery system (SNEDDS) based on TMC	•	Cell viability was observed for only 4h.	S o p tr v b ti b
					•	Spontaneous particle formation,	•	In vivo study was carried out	

Mucoadhesive nanocarrier system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		C
						high drug loading efficiency			
CS nanoparticles	Tripolyphosphate (Cs-TPP)	DNA vaccine	Disease caused by Aeromonas hydrophila in fish	%EE- 82.3%. Vaccines showed higher survival rate (76.2%) against *A. hydrophila*.	• Better DNA vaccine loading efficiency and sustained release profile • Higher survival rate of fish which were CS-TPP encapsulated vaccine		• PCR analysis showed presence of plasmid in tissue samples of different organs		C e p o v
CS nanoparticles	Poly-L-glutamic acid	Metformin	Polycystic kidney disease (PKD)	%EE- 37.3 %DL: 32.2. RP- at pH 1.2 and 2.5 the release efficiency was no more than 25%, while at pH 6.5, 7.4 it was around 50% at end of 3 h. Opening of tight junctions was observed. Formulation significantly accumulated in intestine and shows 1.3 times higher serum area under curve. PKD murine model (Pkd1fl/fl;Pax8-rtTA; Tet-O cre), a lower cyst burden was observed compared to free metformin, and was well tolerated upon repeated dosages.	• Controlled release of the drug in the intestine • serum transportation within 24 hours		• High concentration of metformin for oral delivery and its toxicity needs to be analyzed		T r n o f t
CS nanoparticles	Snail mucin Poloxamer Poly vinyl alcohol	Insulin	Diabetics	%EE- 92.5 %DL- 23.5 RP- 20% in 1 h, and >80% release in 10 h at PBS pH 7.4. Formulation showed significant anti-hyperglycemic effects in alloxan induced diabetic rats. Enhanced the insulin absorption and reduced the glucose levels and plasma insulin level reached max in 1 h. it shows no negative effect on liver cells	• Encapsulation efficiency of the NP is more than 80% • Showed better release profile within 8 hours' time		• Distribution and toxicity test for organs other than liver were not done. The mucoadhesivity and interaction with mucin need to be study		T b s t d i

Mucoadhesive nanocarrier system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		C
CS nanoparticles	PLA	Ursolic acid (UA)	Antitumor activity	EE- 97.47 RP- 53% UA was released within 144h through the diffusion mechanism. UA plasma concentration of 46 ng/mL was observed in the first 30 min after gavage. single oral dose in rats, increased the UA absorption, reduced its clearance and elimination, resulting in increased bioavailability. Half life increases 4.14. times. UA plasma	•	Emulsion-solvent evaporation technique was utilized to prepare the NP • High Encapsulation efficiency (90%) • Particle size 300 nm	•	In vivo UA CS/PLA showed lower cytotoxicity on the tumor cells • Cytotoxicity of UA on different organs was not studied	C si p re re o in b
CS nanoparticles	Alginate	Curcumin diethyl disuccinate (CDD)	Anticancer activity against MDA-MB-231 human breast cancer	%EE- 50 %DL- 5.72 RP- 86 %, 83 %, 81 %, and 64 % of CDD released from the CDD-CANPs in the SGF, STEF, SIF, and SBF, respectively, at 72 h.	•	Oil-in-water (o/w) emulsification followed by ionotropic gelation was followed to prepare CS-Ag NP	•	In vivo study was not done • Cytotoxicity comparison with normal cells was not done	C e C b b c a c
CS nanoparticles	Hyaluronic acid (HA) Sodium tripolyphosphate (TPP)	Insulin	Diabetics	%DL- 5.5 – 28.8 RP-After 8 h, the released amount of insulin plateaued to 75%. Strong and continuous hyperthermia effect (with a pharmacological availability (PA) of 13.8%).	•	Particle size is less than 200 nm • Reduce mucine absorption of insulin and increase the cellular uptake	•	extensive in vivo studied not conducted	H C p o in
Protonated CS nanoparticles	Sodium tripolyphosphate (TPP)	Immunogenic outer membrane proteins (OMPs) Flagellin (F) protein (FP)	Salmonellosis	%EE- 70 nanoparticles were localized in ileal Peyer's patches. The candidate	•	Ionic gelation Method was followed to prepare the FP-OMP-CS NP • Good immune response vaccine increased the expression of toll-like receptor (TLR)-2, TLR-4, IFN-γ, TGF-β and IL-4 mRNA expression in chicken cecal tonsils.	•	No cytotoxicity study was done for the in vivo disease model	C sa n ta in c in re

Mucoadhesive nanocarrier system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		C
CS nanoparticles	PLGA nanoparticles	Thymoquinone (TQ)	Breast cancer	%EE- 92.17 RP- formulation shows sustained release profile from 4 to 24 hr and 27% of TQ was released after 24h. Formulation showed statistically enhanced antioxidant potential and cytotoxicity against MDA-MB-231 and MCF-7. TQ-CS-PLGA-NPs exhibited about 1.92- and 3.15-fold higher P_{app} compared to TQ-PLGA-NPs and TQ suspension	• The nanocomposite was prepared by following emulsion evaporation method • The preparation method showed high LE and good stability		• In vivo study was carried out • Toxicity on healthy cell lines were not tested		C f s p t i
CS nanoparticles	Coconut oil Tween-80 Lecithin	AmpB	Nephrotoxicity	RP- Slow and sustained release was observed. Improved bioavailability of AmpB compared to control. The ChiAmpB NLC presents a lower risk for nephrotoxicity and higher accumulation in the liver and spleen.	• Prolonged retention of the encapsulated drug • Low nephrotic accumulation		• The reason for the improved bioavailability was not investigated. What are the side effects when accumulated in liver and spleen not explained		T e A n p a c a I' a o
Thiolated CS nanoparticles	Thioglycolic acid Mercaptonicotinic acid	Octreotide (OT)	Hormone therapy	%DL- 89 RP- sustained release of OT observed over 24 h. 50% release in 6h. Enhanced 4.1-fold permeation in 3 h and 7.2-fold oral bioavailability compared to OT	• The drug encapsulated NP was prepared by ionic gelation technique • Better mucoadhesive property of the NP		• In vivo toxicity study was not done		T p f o n s
CS nanoparticles	Citric acid PEG Propylene glycol (PG) Glycerol	Macromolecule	N/A		• Better tensile strength and mucoadhesive properties		• No in vitro or in vivo studies were carried out		C c c p n d
CS Micro particles	Alginate Casein	Insulin	Diabetics	%EE- 51.1%. RP- at Ph 6.8 insulin release 48.3% in 2 hr and at end of 8h releases 70.9%. oral Ac-NPs and NiM were	• Good entrapment efficiency (51.1%) • Sustained release of insulin in SGF		• Particle size was around 1.1 µm. so larger size particles may has low		T v w s e l s

Mucoadhesive nanocarrier system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		C
				gradually decreased blood glucose to 58.4% and 42.1% respectively in 4 and 6 h. NiM shows higher bioavailability and a better hypoglycemic effect on diabetic mice.				efficacy not explained	
CS Micro particles	Hypromellose (HPMC) Eudragit RS	Indomethacin Fluorouracil Curcumin	CRC	%EE- 58 (curcumin) and 70 (indomethacin). RP- Cur release is negligible; Indo in SGF < 5% release in 2 h, then in SIF (pH 6.8) for 6 h and SCF (pH 7.4) for 6 h resulted in release of 20% and 25%. Curcumin cytotoxicity was enhanced.	•	Controlled release of drug molecules from the microparticles in SGF, SIF and SCF • NP loaded curcumin decreased cancer cell proliferation by 83%	•	No in vivo cytotoxicity study was done	C b m c ta o to
CS Micro particles	Ascorbic acid (AA)	Selenium (Se)	Alcohol induced gastric mucosal damage	LE- N/A. RP- SeNPs releases in gastric condition pH 1.2. SeNPsCM with doses (0.6–2.4 mg kg-1 bw) were safe to Wistar rats. protect rats from the ethanol-induced gastric mucosal injury.	•	Size of the CS-Se NPs was found to be of 6 μm • Chemical synthesis CS decorated Se NPs (60 nm) followed by ultra-filtration and spray-drying	•	Biodistribution of SeNPs in the mouse model was not done. Side effects of SeNPs not investigated	T c c p fo o st tr in d
CS Micro particles	Casein Genipin Transglutaminase (TG)	Nattokinase	Thrombosis-related cardiovascular diseases	%EE- 2.9 mg per 100 mg. RP- 79% of the total loaded nattokinase was released in 12 h. Nattokinase microparticle significantly enhanced the oral effectiveness of nattokinase in prevention and cure of thrombosis in vivo.	•	Bilayer shell-core structure was prepared	•	For the in vivo mouse model, no intestinal toxicity study was carried out	T m w p n g a c re d
Carboxy methyl CS Nanocomposite	Oleic acid (OA)	DTX	Anti-cancer effect	%EE- 57.26 RP- 73 of DTX was released in 72 h at pH 6.8. Apparent permeability of DTX improved 6.57-fold. In vivo pharmacokinetic	•	Amidation reaction was carried to form OA grafted carboxymethylated CS polymer • Easy formation of micelles	•	No biodistribution or toxicity study was done	T p c st lo h w d

Mucoadhesive nanocarrier system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	C
				study demonstrates an increase in Cmax (1.97-fold) and AUC (2.62-fold) for DTX loaded OA-CMCS. Half-life of DTX increases 1.94 fold.	• Low (1μg/L) critical micelle concentration		
Acyl CS nanocomposite	Cinnamon oil Tween® 80 PEG 200 as oil	Cefixime (CFX)	Antibacterial activity	RP- 70 % was released at pH 6.8 within 24 h. PK- AUC and Cmax were 2-fold increased for CFX-SNEDDs, whereas 2.6 folds and 3.3 folds increase were observed for CHT-CFX-SNEDDs compared with free drug suspension.	• Muco-adhesive self-nano emulsifying drug delivery system (SNEDDs) • Particle size 156 nm	• No biodistribution or toxicity study was done	A S si p p c a b p
Glycol-CS nanocomposite	3-Aminopropyl-functionalized magnesium phyllosilicate (aminoclay) Eudragit ®S100	Insulin	Diabetics	%EE- 90%. RP- at Ph 7.4 in 15 minutes 40% of drug released. Oral EGAC-Ins significantly reduced blood glucose levels in diabetic rats.	• Spontaneous coassembly method was followed to prepare the nanocomposite • Effective drug permeability in Caco-2 cells • Enhanced drug absorption into colon of rats	• Biodistribution in the in vivo disease model was not shown	T si tı in a E N
Alginate coated CS nanocomposite	Monomethoxy polyethylene glycolpoly (Lactic-co-glycolic acid) (mPEG-b-PLGA) CS coated NP	Insulin	Diabetes	%EE- 81.5 (alginate coated) and 55.2 (chitosan coated). PR- pH 1.2 release 13.91% in 4 h reches 20.68% in 6h and 47.66% in 60h.atpH 6.8 in 4h 38%, 51% in 10 h and 80.54% in 60h. Reduction in blood glucose levels (decreases 60% compared with the initial level at 12 h) in diabetic rats. Resulted in a maximum plasma concentration (41.5 ± 4.4 [μIU mL1) at 10 h.	• Insulin loaded (mPEG-b-PLGA) particle was formed w/o nanoemulsion • Insulin-(mPEG-b-PLGA) encapsulated CS NP was formed via w/o/w double emulsion • Insulin-(mPEG-b-PLGA)-CS NP was further encapsulated with ALG NP via w/o/w emulsion	• In vivo cytotoxicity study was not done	T c (r P si d b o a

Table 5

Alginate based mucoadhesive oral drug delivery system.

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
Alginate nano particles	Casein NP	Curcumin	Anti-tumor effect	%EE- 70 RP- curcumin releases 77.5% at 24 h in SIF. PK- in vivo pharmacokinetic parameters (Cmax, T_{max} and AUC_{0-24}) for Alg-ch@CurCasNPs were significantly better than those for free curcumin. Oral administration of Alg-ch@CurCasNPs (6 doses/2 weeks-600 mg/kg) in mice showed higher therapeutic efficacy against Ehrlich carcinoma.	High encapsulation efficiency • sustained release in SGF • Better pharmacokinetic effects than free drug	The synergistic effect of the NP composition was not analyzed	Suitability for oral delivery of curcumin by using biodegradable polymers	[222]
Alginate nano particles	$CaCl_2$	l-Cysteine (Cys)	Antioxidant effect	%EE- 79.49 RP- The Cys release was 94.33% in PBS pH 7.4, whereas it was 11.78% in HCl pH 1.2 within 720 min.	• Slow mixing and stirring to form the Ca-ALG bead • Better encapsulation efficiency	• No toxicity study was done • In vivo analysis was not done	The Ca-ALG carrier has better swelling efficiency which made it profound for oral Cys delivery	[223]
Alginate nano particles	CS	Lactobacillus expressing pYG-KHV-ORF81/LR CIQ249	Koi herpesvirus (KHV)	Chitosan-alginate capsules protected the probiotic vaccine pYG-KHV-ORF81/LR CIQ249 from harsh digestive environments. Vaccine has a good	• Probiotic vaccine preparation encapsulated by CS-ALG • Significant antigen-specific immunogenicity	• Long term effect of the vaccine was not tested	The oral probiotic vaccination encapsulated with ALG-CS has been proposed for treating KHV	[208]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
				immunogenicity and displayed effective KHV-neutralizing activity.	arose after oral vaccination			
Alginate nano particles	PCL Pluronic127 (F127) CS	Insulin	Diabetes	%EE- 60 RP- SGF (Ph 1.2) 46% and 62% of insulin released from PCL/CS/ALG and PCL/CS respectively. When the particles were transferred to SIF, the release rate increased briskly to about 48 % within the first 2 h and 60 % after 6h.	• Double water-oil-water emulsion • pH sensitive ALG-CS based carrier	• No in vivo study was done	The ALG-CS utilizes the pH responsive properties of the polymer to release insulin	[224]
Alginate nano particles	CS Deoxycholic acid (DCA)	Insulin	Diabetes	%EE- 61.14 % DL- 3.36 RP- 28% insulin was released in 0.1 M HCl after 2 h. SIF insulin released 70.8% after 12 h (pH 6.8 PBS) and 92.9% after 36 h (pH7.4 PBS). Oral bioavailability of 15%. The CDA NPs (40 U/kg) improved the hypoglycemic effect of insulin by approximately 7.2 fold when compared to oral insulin solution at the same dose	• Better insulin encapsulation efficiency (61 %) • In-vitro cell permeability • High hypoglycemic effect	No in vivo toxicity effect was tested	pH responsive CS-DCA-ALG carrier is capable to protect insulin from degradation in the gastric environment and can enhance NP adhesion in the intestinal villi	[225]
Alginate nano particles	Aloe vera	Insulin	Diabetes	%EE- 47.3	• w/o/w emulsion and subsequent ionic gelation	Release profile not studied. In vivo or in vitro toxicity study was not done	Biocompatible ALG-aloe vera nanocarrier for oral delivery of insulin shows	[226]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
					• Better encapsulation efficiency (47%)		promise for enhanced intestinal cell transportation	
Alginate nano particles	DNA-nanocube Poly-L-Lysine	Vildagliptin (VI)	Diabetes	%EE- 89.23 (DNA) and 83.35 (VI). It shows superior oral antidiabetic effects with improved GLP1 and glycemic levels. In mice, nanoparticles reduced adverse events and better control of glycemic levels	• Nano scale size of the particles • Entrapment efficiency up to 90 % • Better hypoglycemic effect	• In vivo biodistribution and cytotoxicity studies were not done	ALG-DNA nano cube carrier showed uniform size distribution, less toxicity and better therapeutic delivery effect	[227]
Alginate nano particles	Layered double hydroxide nanoparticles (LDHs) CS Tripolyphosphate (TPP) CaCl2	BSA		%EE- approximately 60–65% (0.75 mg/ mg). RP- 40% of BSA-FITC was released from ALG-CHT-LDH rapidly in 10 min and then retained at pH 1.5 for 2 h. The ALG-CHT coating protected protein release at the acidic condition (pH 1.2).	• LDH based oral vaccine delivery • pH responsive delivery of protein/antigen in the intestine	• Short lifetime of encapsulation significant amount of drug loss • In in vivo study was done	ALG-CS coated LDH exhibited better protein internalization by the Caco-2 and macrophage cells	[228]
Alginate Hydrogel	[3-(Methacryloylamino) propyl] trimethylammonium chloride (MAPTAC) Methacrylic acid (MA) 2-Hydroxyethyl methacrylate (HEMA) N,N' –Methylenebisacrylamide (MBA) N,N,N ',N'-Tetramethylethylenediamine	Diclofenac sodium	Anti-inflammatory	%EE- 22.8%. RP- at pH 1.2, 4.5% of drug release in 3 h and at pH 7.0 95% of drug releases in 20 h. Formulation also showed antibacterial effect.	• Antibacterial and pH responsive properties • Sustained release in SIF	• No in vivo study was done to check the viability of the oral delivery system	ALG based pH responsive carrier showed great promises for oral drug delivery	[220]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
	(TEMED) Polyvinyl alcohol (PVA)							
Alginate Hydrogel	N/A	N/A	N/A	RP- The synthesized beads completely dissolved in 3h time	• Two methods were utilized to form two different ALG-ABA hydrogels • Direct amidation of ALG and ABA • Oxidation of ALG with $NaIO_4$ followed by reductive amination with BA and pic-BH_3	• No therapeutics was loaded on the beads • No in vivo study was done Drug release mechanism form bead and changes in morphology not conducted	• ALG-ABA hydrogels-based delivery cargo • The disintegration of the cargo depends on the rate of oxidation of ALG	[191]
Alginate Hydrogel	Gum Arabic (GA) Gelatin (GE) Stearic acid Tween-80 Tannic acid	Fucoxanthin (FX)	Anti-obese Anti-oxidation Anti-cancer	%EE- 71.11 (beads) and 80.62 (microcapsules) %DL- 0.32 (beads) and 0.93 (microcapsules). RP- in SGF microcapsules released 31.93 and beads releases only 3%. In SIF, 90% of the drug was released in the SIF in 4h.	• 70 % encapsulation of FX • Better protection in SGF • Better release profile in SIF	• No cytotoxicity study was done for the in vivo mouse model	FX loaded GA-GE microcapsule was prepared via sonication-mixing process which was further encapsulated in ALG hydrogel which showed better efficacy for oral administration of FX	[229]
Ca-alginate Hydrogel	GA, Gelatin (GE) Stearic acid Tween-80 Tannic acid	Perinereis aibuhitensis extract (PaE)	Antioxidant	CA hydrogel could protect PaE in stomach and sustain releases in intestine and make it maintain high antioxidant activity while incubated in SGF. After, 30 days of administration, the	• Antioxidant efficacy of the encapsulated drug is 1.8 folds than the free drug	• No in vivo study was done to test the oral delivery efficiency	Showed profound efficiency for decreasing oxidation stress after 30 days of treatment	[206]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
				mice of PaE:CA/GA/ GE-CCs group suffered significantly lower oxidative stress level than those of other groups,				
Alginate nanocomposite	Carboxymethyl CS	Purple sweet potato extract containing high anthocyanin	Type 2 diabetes	–	• Better targeting efficiency • Can lower blood glucose level than free extract	• No in vitro or in vivo study was done	CMCS-ALG carrier is suitable for delivering purple sweet potato extract to the circulatory system	[230]
Alginate Nanocomposite	Whey	Iron sulfate Bovine spray-dried blood cells (BC)	Anemia	%DL- 3 to 34 mg per matrix. RP- Iron was releases 2–11% in SGF, whereas it was in SIF 83–100% in 2h.	• Ionic gelation method • Controlled release of iron in the in vitro SIF whereas protects Fe in the gastric environment	• No in vivo toxicity study was done	The ALG-whey based carrier system could be potentially effective for oral iron supplement	[231]
Amphiphilic alginate	Vitamin B_{12} N, N'-dicyclohexylcarbodiimide Cholesterol	Insulin	Diabetes	%DL- 34%. RP- in SGF and SDF insulin releases less than 15% and in SIF it was 15%. Nontoxic to caco-2 cells. CSAD-VB12/INS nanoparticles induced more obvious reduction of blood glucose level by 54% compared with 25% for CSAD/INS group within 12 h at the same insulin dose of 70 IU/kg	• Nontoxicity to Caco-2 cell • Better permeability through Caco-2 cell • Better intestinal absorption efficiency	• Biodistribution of the carrier was not analyzed for the in vivo model The interaction with mucin not investigated	Amphiphilic ALG-VB_{12} carrier could be promising oral drug administration because of its better intestinal transporting efficiency	[232]
Alginate microparticles	Cyperus esculentus (Tiger nut) $CaCl_2$	Ibuprofen	Gastrointestinal irritation	%EE- 46.05–89.86%. RP- <8% in SGF in 6h. however, in SIF	• Better mucoadhesive property	• No in vivo study was done	The cross-linked starch-ALG carrier has the potentiality for sustain	[233]

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Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
				in 6h 83% of drug released.	• Better swelling property • pH dependent in vitro release of the drug		release of the drug in the GI tract	
Alginate microparticles	$CaCl_2$	Losartan Potassium	Hypertension	%EE- 73.06–79.06 %DL- 12.05 to 18.2 RB- 98.51% of the drug was released from F3 formulation in 12h.	• Ion tropic gelation to form microencapsulated drug • Controlled release of the drug • Drug loaded carrier size is approximately 0.61–0.77 mm • Better swelling properties	• In vitro or in vivo oral drug analysis was done	This study represents the formation ALG based microbead particle for oral delivery of hypertension drug	[234]
Alginate Microparticles	Arginine CS	Ivermectin Praziquantel	N/A	An in vivo study of oral administration to teleost fish revealed that the bioparticles attain the intestine mucus and further, the interaction with the intestinal mucosa is timely dependent. The in vivo study endorsed that the bioparticle provides high compliance	• Colloidal formation CS-N-ALG complex • pH responsive • Better mucoadhesive property	• No cytotoxicity study was done	The polygonal structure of the carrier could be useful in drug delivery	[235]
Alginate Microparticles	Folic acid (FA) Eudragit (S100)	Irinotecan hydrochloride trihydrate (IHT)	CRC	%EE- 76 (IRSLN3) and 72.6 (IRSLNF3). %DL- 36.3 (IRSLN3) and 35.2) (IRSLNF3) RP- In the case of EuBIRSLN3, the	• Dual targeting delivery cargo • pH responsive • Higher cytotoxicity effect	• In vivo cytotoxicity study was not done	IHT conjugated FA-SLNs encapsulated ALG-Eudragit carrier is highly efficient for delivering drug to colorectal tumor region	[236]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
				IHT release was detected to be 30.66% and for EuBIRSLNF3, it was 26.29 after 12h. The release of the drug in the intestinal region only (i.e., pH>7.0). The FA-coupled microbeads (^{99m}TcEuBIRSLNF3) distributed higher (19.62 ± 0.78%) amount of drug (i.e., ^{99m}Tc-IHT/g of tissue) as compared to uncoupled microbeads (^{99m}Tc-EuBIRSLN3, 7.63 ± 0.49%) in the colon tumor after 48 h.	• against COLO-205 cells • Higher anti-tumor effect against HT-29 cells			
Hybrid Alginate nanoparticle	PEG cholesteryl methacrylate (CMA) Palmitoyl-2-oleoyl-snglycero- 3-phosphocholine (POPC) 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-L-serine sodium (POPS)	N/A	N/A	–	• Micro penetrating particles • Better mucoadhesive property • Substantial release in the GI track	• Drug loading and its pharmacokinetics were not studied	PEG-lipid hybrid vesicle entrapped in ALG carrier can be a suitable cargo for oral drug delivery	[237]

Table 6

Pectin based mucoadhesive oral drug delivery system.

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		Co
Pectin Microparticles	High amylose starch and cellulose nanofibers	5-aminosalicilic acid	Inflammatory bowel disease	%EE- 16–98 % DL- 1.97–26.63 RP- 25% of 5-ASA in SGF, followed by 68% in SDF.	•	High encapsulation efficiency (16–98%) and drug loading (1.97–26.63%)	•	No in vivo study was carried out to test the specificity of the carrier system	En va
					•	Controlled monodispersed particles from 1–10 μm size	•	Particle size was in the micrometer range so	
Pectin Microparticles	Eudragit S 100 and hard gelatin	Sulfasalazine	Inflammatory bowel disease	%EE- 95.62 ± 1.21%. RP- drug release (91.12%) in SCF (pH 7.4) and 98.07 in rat cecal content (RCC, pH 7.4) for 24 h in a sustained manner. In vivo X-ray study shows the release of radio-opaque substance from Eudragit S 100 coated hard gelatin capsules.	•	The fabricated microparticles had high drug release profile of 91%	•	Large size particles	
					•	The long self-life of 3.3 years indicates high stability of the microparticles	•	In vivo cytotoxicity study was not done	
Pectin Microparticles	Gellan gum	Insulin	Reducing blood glucose levels	%DL- 0.65 – 0.99%. RP- 80% insulin release after 2h Lower amount of drug releases at pH 1.2 and pH 4.5 than in phosphate buffer pH 6.8 release 67%. Due to anionic polymers on tight junctions opened. oral administration to diabetic rats showed reduction of up to 51% of blood glucose levels.	•	The developed microparticles promoted an impressive protection of insulin (80%) after 120 min of incubation with trypsin and alpha chymotrypsin	•	Increased microparticle stability would be more effective in insulin delivery	Th sy pr ins
					•	In vivo study with rats showed reduction of up to 51% of blood glucose levels			
Methoxylated pectin microparticles	CS	Insulin	Reducing blood glucose levels	%EE- 62 RP- In SGF, 13% release in 120 min. In intestine at pH 6.8, 89.0% release in 120 min.	•	Polyelectrolyte complex system of chitosan-pectin nano- and	•	No in in-vitro and vivo study was done	

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Co
					microparticles was developed to encapsulate the hormone insulin • In simulated intestinal fluid (pH 6.8), controlled insulin release occurred over 2 h		
Low methoxylated pectin microparticles	Zinc acetate	Doxorubicin	Colorectal cancer	%EE- 906.8±90.1 μg/g bead. RP- in gastric condition in 2h nearly 60% DOX was released.	Microbeads containing thiolated pectin-DOX conjugate exhibited reduction-responsive in reducing condition	• No in vivo study was done	Th co res del
Pectin hydrogel	Oligochitosan and Ca^{2+} ions	Dextran	Colon cancer	%EE- 68.1 RP- 19% of FITC-CM-Dextran released within the SGF in 2 h, in SIF 30% releases in 2h, and in SCF 94% drug was released.	• cross-linking biopolymer Oligo chitosan and divalent cation Ca^{2+} stabilized the pectin-based hydrogel for passing though the gastrointestinal trac • at high pH the carrier released 94% drug indicating great potential for colonic drug delivery	• No in vivo testing was done	
Pectin (MW 30,000–100,000) hydrogel	Ethylene glycol Di methacrylate, Methacrylic Acid, and benzoyl peroxide	5-Fluorouracil	Colon cancer	RP- 58–60% drug release at pH 1.2 and more than 90% release at pH 7.4 after 12 h dissolution experiments.	• Hydrogels with higher amounts of pectin were prepared for complete degradation in the colon • Thermally stable, biocompatible, and colonically degradable hydrogel was prepared for oral delivery of drug with	• No in vivo cytotoxicity study was done	Pr pr tes

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		Co
						minimal upper gastrointestinal invasion			
Pectin (esterified 60% to 70%) hydrogel	Polyethylene glycol 300 and 7-dehydrocholesterol	Ca^{2+} with vitamin D / Fe^{2+} with vitamin C		%EE- vitamin D 99.1 and vitamin C 99.3. RP- below 20% releases in SGF pH 1.2 and nearly 100% releases SIF in 6h.	•	the hydrogel showed highest swelling in simulated intestinal fluid • Lowest release was observed for simulated gastric fluid	•	side effects not investigated	
Pectin with galacturonic acid ≥74% from citrus peel hydrogel	Alginate and egg yolk low density lipoprotein (LDL)	Curcumin	Inflammation	RP- Showing about 75% release in SGF and 100% cumulative release in 180 min.	•	Developed hydrogel beads exhibited pH dependent release of curcumin • Hydrogel showed limited swelling property and more sustained release of curcumin in simulated gastrointestinal conditions	•	No in vivo study was done to test the specificity or cytotoxicity	
Pectin nanocomposite	FA	Insulin	For controlling blood glucose level	%EE- 99.8 %DL- 23 RP- INS/FAN18 presented an initial burst release of 62.1% in pH 1.2 HCl, followed by a cumulative sustained release of 75.6% in pH 6.8 PBS (2–6 h) and 96.1% in pH 7.4 PBS at the end of 24 h. Significantly lowered the blood glucose levels in type I diabetic rats,	•	In vitro study showed that insulin release profile depended on −COOH/ADH molar ratio in the dual-crosslinking process • Decrease in Type I diabetic rats confirmed the effectiveness of this system for effective oral delivery of insulin	•	The LE was low for the drug carrier system. Initial burst releases 62% is too high amount of drug may loss need to control.	
Pectin nanocomposite	Trimethyl chitosan,	Celastrol	Colitis	%EE- 94.45 % DL- 1.26 RP- 20% of Cel was released during	•	Successful synthesis of colon targeting oral delivery	-		

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Co
				the first 12 h in SCF. Survival rate of Cel/PT-LbL Lipo group was significantly enhanced, compared with the Cel/Lipo group. Cel/Lipo and Cel/ TMC Lipo, Cel/PT-LbL Lipo had better pharmacodynamic effect, which were related to the TLR4/ MyD88/NF-κB signaling pathway.		system of celastrol • Cytotoxicity tests showed minimal effect on colon epithelial NCM460 cells	
Apple pectin nanocomposites	mucoadhesive liposomes	Amoxicillin	*Helicobacter pylori* pathogenicity	%EE- 66–83%. RP- After 1h almost 75% drug was released	•	The smart delivery system was able to prevent *H. pylori* from interacting with the stomach mucin	• drug releasing very fast it may have very low half-life. Half-life not studied. • No in vivo testing was carried out
Pectin nanocomposite	Zein and Eudragit S 100	Resveratrol	Ulcerative colitis and cancer	%EE- 3.8–4.0 % DL-84.8 RP- neutral medium with 30% ethanol 65% release in 3h. In acidic medium with 30% ethanol 84% releases in 3 h.	•	The hydrophilic pectin shell to significantly increased the dissolution rate of RSV in aqueous environments • Based on release study specific colon delivery of this drug was suggested	• No in vivo testing was carried out
Pectin nanocomposite	Gellan gum	Resveratrol (RVT)	Ulcerative colitis and cancer	%EE- >80 RP- only 3% of RES was released in acidic media over 2 h, and, in pH 6.8, the drug was released in a sustained manner, reaching 85% in 30 h. It showed high ability to interact with the intestinal tissue.	•	Achieved high drug loading (>80%) • Only 3% of resveratrol was released in acidic media over 2 h, and, in pH 6.8, the drug was released in a sustained manner,	• In vivo experiment was not done to test oral delivery

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Co
						reaching 85% in 30 h	
Pectin nanospheres {Citrus pectin (MW ~ 30,000 g/mol, degree of esterification = 27.3%, and the contents of galacturonic acid N(74%)]	3-aminopropyltriethoxysilane	5-fluorouracil	Colorectal cancer	%EE- 31.2 – 52.6 %DL- 14.1 – 16.6 RP- The drug release profile was 32.17%, 22.77% and 63.89% in the SGF, SIF, and SCF respectively.	•	Synthesized nanospheres showed highest drug release profile in the simulated colon fluid • In vivo testing is necessary to confirm specificity and cytotoxicity	
Citrus pectin with degree of esterification of 27.3%	Succinic anhydride and glutaric dialdehyde	Diclofenac sodium	Inflammation	%EE- 78.81 %DL- 7.78 RP- The drug release profile was 3.04, 3.66 and 79.43% in the SGF, SIF, and SCF, respectively.	•	Cytotoxicity results were also promising With the succinic anhydride and glutaric dialdehyde modification the instability of pectin-Ca^{2+} gels based oral colon-specific drug delivery system was overcome • Needs in vitro and in vivo testing for toxicity and release profile study	
Hybrid nanoparticle (Pectin with a galacturonic acid content of 74%)	Casein sodium	Curcumin	Inflammation	%DL- 93%. RP- in SGF, 35% of drug releases in 3h and 51.81% releases in SIF in 6h. Showed Highest antioxidant activity 46.7%	•	Synthesized nanoparticles had average size of 266.4 nm (polydispersity index = 0.193) and loading capacity of 93% • Needs in vivo analysis for confirmation. Anti0xidant potential in in- vivo not studied • simulated gastric fluid showed that pectin helped in prolonged release profile for the curcumin	
Pectin hybrid nanoparticles (Pectin from *Smilax china L.*)	Fluorescein-5-thioicarbazide and Cyanine7 amine			–	•	Showed oral absorption characteristics and mechanisms of pectin through the intestinal epithelium • This study did not report any specific drug loading	

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		Co
					•	In vivo study showed that pectin was in the small intestine and distributed in the liver and kidney after oral administration			
Pectin (Type LM-5206CS – DE < 50%	High amylose starch and CS	5-fluorouracil	Colorectal cancer	%EE- 21.4 RP- In pH 1.2 almost 91.1% drug was released in 2h and at pH 7.4 sustained release of drug observed in 7h. In vivo biodistribution confirmed the RS/P microparticles as potential carriers for delivering drug-loaded nanoparticles to the colon.	•	In vivo and in vitro studies showed drug release decreased by 53% in acidic media by the vehicle • Colon biota was intact indicating that the oral vehicle had target specific delivery	•	In the acidic condition of the stomach there is a chance that the drug carrier will degrade very quickly during oral delivery	Ve co of
Pectin (low-methoxy)	Multi-walled carbon nanotubes	Celecoxib	Colitis	RP- at pH 1.2, <10%, at pH 6.8, ~25%, and at pH 7.4 ~90% drug releases in 2h, 6h, and 10h, respectively. In presence of pectinase undergo enzyme degradation and release drug in the colon.	•	the multi-walled carbon nanotubes were able to load the drug through their porous structure • Has potential for colon specific delivery	•	No in vivo experiment was done to test the viability of the oral delivery proposal	

Table 7

Poly acrylic acid based mucoadhesive oral drug delivery system.

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
Poly (acrylic acid-co-acrylamide) P(AAc-co-AAm) Hydrogel	Acrylamide	Pyronine 4 (4sPy)	N/A	–	• pH dependent release of the drug • The carrier showed maximum swelling at pH 9	• No in vitro or in vivo study was done in this work	P(AAc-co-AAm) based could be efficient for jejunum targeting oral drug delivery	[284]
PAA Hydrogel	Graphene oxide (GO) Xanthan gum	Diclofenac potassium (DCFP)	Inflammation	DCFP release higher in SIF than SGF in 96 h. $t_{1/2}$ of DCFP in formulation increases from 2.03 to 10.71h. $AUC_{(0-t)}$ of the DCFP increases from 53.99 mg L^{-1} h^{-1} to 116.79 mg L^{-1} h^{-1}	pH sensitive • Hydrogel had better mechanical strength • High release in the intestine	• No in vitro or in vivo study was done in this work	The PAA-XG-GO carrier has potentiality to increase the bioavailability of the drug in the intestine	[283]
Ion conductive PAA hydrogel	Silicone	Florescent reagent	N/A	%EE- 84 %DL- 34 RP- When voltage was increased to 3, 5, and 7 V, the amount of drug released was 53, 88, and 96%, respectively.	• Electron beam irradiation technique was used to prepare the PAA-silicone cross linked hydrogel • High tensile strength • Voltage dependent drug release	• No in vivo study was done to see the voltage effect in biological system	This ion conductive polymeric matrix could be potential for oral drug deliveries its less cell toxicity and better targeting efficiency	[299]
Pluronic F127-co-poly (acrylic acid) (PF127-co-PAA) hydrogel	Pluronic F127 Ethylene glycol dimethacrylate (EGDMA)	Ivabradine	Heart failure	RP- at pH 1.2 nearly 10% of drug releases whereas at	• Free radical polymerization	• in vitro studied such as cellular	The PF127-PAA based pH dependent smart polymeric matrix showed controlled release of the drug upon	[300]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros		Cons		Comment	Ref
	Ammonium persulfite (APS) and sodium hydrogen sulfate (SHS)			pH 6.8 100%of drug releases in 24 h.	• The polymeric matrix is thermodynamically stable • pH dependent swelling behavior • Almost no toxicity to animal (rabbit)		• update not tested • Bioavailability also not studied		oral administration and showed no toxicity on healthy rabbit indicating its huge potentiality for oral drug delivery	
Acid (Zein-co-PAA) hydrogel	Zein AA N, N-methylene bisacrylamide, and ammonium persulphate	5-FU Rutin	Colorectal cancer Antioxidant	%EE- 12 (5-FU) and 10 (Ru) %DL-89 (5-FU) and 81 (Ru) RP- At pH 7.4, 5-FU 88.73% and Ru 74.54% was releases. At Ph 1.2, 72% and 69% of 5-FU and Ru was observed. Induced 50% cancer cell death in 24h.	• The copolymer was prepared by employing graft polymerization technique • In vitro cytotoxicity against breast cancer cells		• No in vivo testing was done		The copolymer vector ensured co-delivery of 5-FU and rutin to the breast cancer site and rutin delivery could be highly potential for minimizing the doses of 5-FU to reduce drug toxicity	[285]
PAA-PVP hydrogel	PVP PAA di-Ethylene glycol bis-allyl carbonate	–	–	–	• Interpenetrating polymer network synthesis • Better hemocompatibility and cell viability in contact with oral mucosa cell		• No in vivo testing was done		The PAA-PVP matrix is suitable for reducing cytotoxicity in mucosa cells indicating its potentiality for oral drug delivery	[301]
P(AAM-MAA) hydrogel	Acrylamide (AAM) Methacrylic acid (MAA) N, N-Methylenebis (acrylamide)	Theophylline	Lung disease	%DL- >98% RP- 19% of drug released in 90 min, accounting for gastric emptying, and potentially possessing 45% of the remaining	• A pH-responsive hydrogel system was prepared by free radical polymerization • The hydrogel had very good drug		• No in vivo or in vitro study was done		The versatile oral polymeric delivery platform could be used a good candidate for oral delivery of therapeutics	[302]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
	(MBA) Pluronic F-127			drug to be release once reaching the small intestines. Drug loading and release evaluation confirmed >98% drug loading capacity, with over 60% drug release in 24 h,	leading (98%) capability			
Collagen-grafted-P(AA-co- MAA) hydrogel	AA MAA MBA TEMED	Insulin Methylene blue (MB)	Diabetes	%DL- approximately 50%. RP- Payload release was observed only in neutral media	• The synthesized hydrogel showed water absorbency based on both pH and temperature • Hydrogel released the drug at pH 6.8 but not at pH 1.2	• No in vivo or in vitro study was done	• In vivo and in vitro testing should have been carried out for better understanding of the toxicity and release profile	[303]
Carboxymethyl CS-grafted-PAA hydrogel	Carboxymethyl CS AA $K_2S_2O_8$	Insulin	Diabetes	%EE- 216 mg/g RP- 16.3 ± 2.6% of INS was released at pH 1.2, while over 93.2 ± 3.8% of INS was diffused into PBS (pH 7.4). In vivo studies showed effective hypoglycemic effect.	• The hydrogel showed excellent pH responsiveness • In vivo testing showed hydrogel had a persistent and effective hypoglycemic effect	• In vivo cytotoxicity study was not done • Drug LE was analyzed	Shows promise as a site-specific delivery system for insulin	[304]
PCL-PAA hydrogel	PCL PAA Azo-isobutyronitrile N, N'-Methylene bisacrylamide	Gliclazide (Glz)	Diabetes	RP- After 24h the release profile was 6 mg/g for pH 1.2 and 18 mg/g at pH 7.4 blood sugar level reduced to 67.14 and 57.55% showed zone of inhibition 20 mm with bacteria *E. coli.*	• The PCL-PAA system improved solubility and bioavailability of the Glz • Animal testing also suggested that this vehicle was very effective in	• Biodistribution study was not done for the in vivo experiment	PCL-PAA could be effective for treating type 2 diabetes by delivering Glz	[305]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
						lowering blood glucose level		
PAA hydrogel	AA	Triamcinolone acetonide	Skin Condition	RP- initial 60 min release percentage of drug is high and in 5h almost 95% drug was released in PBS	• The drug delivery system was successfully prepared • The carrier was prepared using electron beam crosslinking	• In vivo study was not done	A bio adhesive drug delivery system was developed that could adhere to the wet mucosa surface of a mucosa membrane	[306]
PF 127-PAA hydrogel	PF 127 AA MBA TEMED APS	Epirubicin (Epi)	Colon adenocarcinoma	RP- formulation showed sustained drug release up to 96h. It showed very good inhibition efficacy of in vivo tumor growth mice. Plasma concentration (T_{max}) achieved in 4.39h.	• Pluronic (Plu) and polyacrylic acid (PAA) based epirubicin drug delivery vehicle was developed • It had sustained drug release characteristics for 96 h and high permeability	• In vivo cytotoxicity study was done	Viable candidate for solution based oral delivery of drugs to the colon	[307]
PVA-PAA Bilayer hydrogel	PVA EGDMA APS SDS	Vancomycin hydrochloride		RP- After 10h the release was nearly 60% From hydrogel drug releases at pH 2 70% and pH 9 75% and at pH 7 only 65% of drug releases. Drug releases 70% from PVA in 10h irrespective of medium. From IDN drug release percentage increases	• Inverse double network (IDN) bilayer synthesis • pH sensitive drug release • Improved mechanical strength of IDN • Mucoadhesive property	• In vivo study was not done	IDN structured hydrogel could be potential for preparing soft hydrogels, hydrogel driven origami for improved drug delivery	[308]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
				from 35% to 70% with increase of pH.				
Acrylate grafted-carboxymethyl starch (CMS-g-AA) and iBAA Hybrid microgel	Carboxymethyl starch (CMS) AA iBAA α-Amylase	Insulin	Diabetes	%DL- 2.5 – 15 RP- For all formulations 75% insulin was released in 2h presence of α-amylase.	• Microgel preparation via aqueous dispersion copolymerization • Highly pH sensitive • Intestinal decomposition of microgels via chromogenic reaction involving amylase	• In vivo biodistribution study was not done • Insulin retention of the formulation was minimal	A systemic intestinal targeting nanocarrier has been developed which had the potential of accelerating the release of insulin in the intestine via degradation of CMS in presence of amylase in the small intestine	[286]
Carboxymethyl CS-co-PAA Hybrid gel	Carboxymethyl CS PAA N, N MBA Benzoylperoxide (BPO)	5-FU	Colorectal cancer	%DL- 65–85%. RP- drug released at pH 1.2 is range from 17–24% and at pH 7.4 89–96% in 36h. Maximum absorption achieved at pH 7.4 in rabbit.	• Cross-linked polymeric system • pH responsive property • Better swelling and drug release profile	• The formulation with the highest drug LE did not show best RB	Both in vivo and in vitro studies confirmed the potentiality of the carrier for better colonic targeting drug delivery	[309]
Gelatin/ polyvinylpyrrolidone-co-poly (Acrylic acid) (GE/PVP-co-PAA) Hybrid hydrogel	Gelatin PVP EGDMA Ammonium Peroxodisulphate/ sodium hydrogen sulphite	5-FU	Colorectal cancer	%EE- 361 to 443 %DL- 74 – 87 RP- In pH 1.2 solution less than 20% was released while in pH 7.4 nearly 60% drug was released after 36h	• A novel pH sensitive chemically cross-linked interpenetrating network was developed for oral delivery of 5-FU to colon • The hydrogel showed much greater swelling for drug release at higher pH	• Particle size determination would have been helpful	This formulation could be used for oral administration of 5-FU	[310]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
Carboxymethyl cellulose-PAA HYDROGEL	Carboxymethyl cellulose AA APS TEMED	Insulin	Diabetes	%DL-16–25%. RP- Almost 70% drug release after 6h	• Biodegradable and pH-responsive hydrogel was produced • Within 6h of oral delivery the blood glucose level decreased in rats	• Stability in low and high pH condition was not checked	Good bioavailability of insulin after delivery to the rabbits makes it an excellent candidate for oral delivery of insulin	[311]
Barley-grafted-PAA Nanocomposite	Barley AA Ceric ammonium nitrate (CAN) PVP	5-Amino salicylic acid (5-ASA)	Inflammatory bowel disease (IBD)	RP- In pH 1.2 after 12h almost 60% and in pH 7.4 after 12h nearly 90% drug was released.	• A novel system that utilized Barley was developed for colon targeted delivery of 5-ASA • The mechanism of the drug delivery was also analyzed	• Low stability of the drug formulation in acidic condition	• The knowledge regarding colon specific delivery of 5-ASA would help future researchers • In vivo study is necessary to understand the complete mechanism of the drug delivery process	[292]
Pluronic-PAA-Cysteine-co-Pluronic L121 Micelle	PF 127 Pluronic L121 (PL 121) PAA L-Cysteine hydrochloride	Paclitaxel (PTX)	Anti-tumor	RP- In pH 1.2 after 12h almost 60% and in pH 7.4 after 12h nearly 90% drug was released	• Synthesized micelle showed effectiveness as an oral drug delivery system for paclitaxel • Presence of verapamil and Pluronic both improved the intestinal	• No in vivo study was done	The designed vehicle could be a viable candidate for commercial delivery of PTX	[297]

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), % of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	Comment	Ref
					permeability of paclitaxel			

Table 8

Carboxymethyl cellulose based mucoadhesive oral drug delivery system.

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	C
High purity CMC Microparticles	Chitosan and pectin	Iron from natural vegetable source	Iron deficiency	RP- Iron was released by almost 90% within 50 minutes	• Formation of microparticles and orally disintegrating films • formation of hydrophilic systems with fast disintegrating times (<50 s)	• No in vivo study was done	
CMC Microparticles	Chitosan, gelatin, or PAH and PSS	Esculin	Cytotoxicity effect on human gingival fibroblasts	%EE- 58–61 %DL- 19–20 RP- After 2h almost 50% of the drug was released when in pH 2.0 medium	• Formation of microparticles with pH dependent release mechanism • Minimal cytotoxicity and transport through gastrointestinal tract	• No in vivo cytotoxicity or biodistribution study was done	
CMC 6000 fine powder of 8%, 10%, and 12% in aqueous solution Hydrogel	glycerol	Diluted red food degradable colorant		RP- 12% of drug releases in 24h	• Successfully 3D printing of capsules for oral delivery without deformation • CMC hydrogels from 8% to 12% forms most stable gel • Promising dissolution test result with the food colorant	• No actual drug was tested for delivery	
CMC hydrogel	Gelatin, glutaraldehyde, and acetic acid	5-FU	Skin cancer	RP-56%, 49%, and 36% of drug releases at pH 1.2, 5.5, and 7.5 in 24h. Toxicity of drug reduced after encapsulation. Acute oral toxicity in rabbits confirmed	• Development of novel pH-sensitive biocompatible hydrogel delivery system	• Drug LE and EE was not studied not studied 100% drug release profile	

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	C
				that hydrogels is biocompatible	• Hydrogel solution was safe up to 4000 mg/kg body weight		
CMC with CP 300–800 mPas hydrogel	Iron (II) chloride, iron (III) chloride, and acrylic acid	Doxorubicin hydrochloride and 5-fluorouracil	Different cancer cells including skin and colon cancer	%DL- 62% (5-FU) and 75% (Dox) RP- At pH 1.2 DOX and 5-FU had 20% and 25% release while at pH 7.4 both had nearly 60% release rate	• Fabrication of oral drug delivery beads for cancer therapeutic transport • Good stability in the acidic environment	• No in-vitro and in vivo analysis was done	
CMC and poly (methacrylic acid) hydrogel	NNMBA, TEMED, and APS	Insulin	For controlling blood glucose level	%DL- 26.4 RP- At pH 1.2 nearly 46% was released in 14h and at pH 6.8 nearly 85.86% was released in 6h.	• Synthesis of pH responsive oral insulin delivery system • Low cytotoxicity of the hydrogel	• No biodistribution or toxicity study for the in vivo system was done	
CMC hydrogel	Poly (lactic acid)	Curcumin		%EE- 77% RP- In 8h almost 8 mg/L drug was released in the neutral PBS.	• Prepared CMC film was able to dissolve curcumin • Showed good pH dependent release profile for the loaded therapeutics	• No in vivo study was done	
CMC hydrogel	cyclohexyl isocyanide, benzaldehyde, and ethylenediamine	Gentamicin	Antibacterial activity	%DL > 90 RP- at Ph 1.2 and 6.8 drug release is less than 25% but at pH 7.4 almost 85% drug was released in 8h Formulation showed antibacterial activity toward *S. aureus* and *E. coli*.	• Prepared hydrogel showed good antibacterial activity against *S. aureus* and *E. coli* bacteria • Had low toxicity towards healthy HUVEC cells	• No in vivo study was done	
CMC hydrogel	Metal ions and layered double hydroxides	Amoxicillin	Colonic bacterial infections treatment	%DL- 55–73 RP- at pH 1.2 and 6.8 the drug release ranges from 42 to 65 but at pH 7.4	• Successful synthesis of hydrogel beads with different content of layered	• Only a single cell line was used	

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	C
				59% to 88% of drug released in 8h. All drug loaded formulation showed antibacterial activity against *S. aureus* and *E. coli*.	double hydroxides • Low toxicity towards HUVEC cells • Good drug release profile	• No in vivo testing was done	
CMC hydrogel	Graphene quantum dots	Doxorubicin	Human colon adenocarcinoma	%DL- 2.6 RP- drug release 20% at pH 2 and 57% at pH 7.4 in 24 h.	• Graphene quantum dots would provide better imaging and tracking capability of the drug carrier • Prepared hydrogel showed good site-specific delivery of drug	• No in vivo study was done	
CMC (Mw = 250,000) hydrogel	NaOH, epichlorohydrin, chitosan, magnetic Fe_3O_4, and β-Cyclodextrin	Methotrexate	Cancer Treatment	%DL- 85 RP- At pH 1.2 around 15% and at pH 7.4 around 90% in 30 h.	• Magnetic drug delivery system showed possibility for high specificity and release profile	• No in vitro or in vivo study was done	
CMC hydrogel	layered double hydroxide (LDH)	5-FU	Colon anticancer	%DL- 87%. RP- at pH 1.2 20%, at pH 6.8 60% and at pH 7.4 80% of drug releases after 8h. MTT analysis confirm the formulation is safe for oral delivery.	The hydrogel system showed promising swelling, drug loading, drug- releasing, and MTT assay results	• No in vivo study was done • Only a single cell line was tested	H ha dc ca
CMC Nanofiber	$Fe(NO_3)_3$-$9H_2O$ and N,N-dimethylformamide	Tetracycline	Skin treatment for harmful bacterial infection	%DL- 99.6 ± 0.5%. RP- Almost 60% drug was released in pH 7.4 after 384h. Formulation showed low cytotoxicity and sittable for drug delivery	• Highly prolonged drug release profile of 384 h • Effective against skin fibroblast and bacterial treatment	• Only in vitro study was done	
CMC Nanocomposite	Graphene Oxide (GO) and Zn-based MOF-5	Doxorubicin	Cancer treatment	%DL- 6.2 RP- 0.225 mg of drug releases at pH 7.4 in 480 h. After 72h incubated, IC_{50} values were respectively 28.1, 15.7, 13.4, and 12.1 ng/mL of GO,	• Successful improvement of surface charge, solubility, and drug loading capacity of GO • The carrier showed increased	• No in vivo testing was done	

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	C
				CMC/MOF-5/GO, DOX@GO, and DOX@CMC/ MOF-5/GO.		release profile at pH 5 of tumor microenvironment	
CMC nanocomposite	Bilayer alginate-chitosan hydrogel	Dexamethasone	Treatment of acute and chronic ocular disorders, popliteal artery disease, inflammatory diseases such as asthma, meningitis, and rheumatoid arthritis	$DL- 0.78–5.53%; RP- Almost 25% drug was released after 12h in pH 7.4	•	Synthesis of CMC based nanocarrier with excellent pH-sensitive drug release profile • Characterization of the drug carrier with different techniques	• No in vitro or in vivo testing was carried out
CMC nanocomposites	Graphene quantum dots (GQDs) and CS	Sodium salicylate		RP- Around 70% in pH 7.4 after 8h. Formulations CS-GQD, CS-GQD/SS, SS@CMC and CS-GQD/SS@CMC shows cell viability 80.6, 71.6, 70.3 and 70.8, respectively. Hence, they are cytocompatibility.	•	In vitro tests showed promising results for site specific delivery • Synergistic effects of CMC and CS enhanced the stability of drug dosing for a long time	• No in vivo study was done
CMC nanocomposite	Graphene oxide	Methotrexate	Cancer treatment	%EE- 8–29 %DL- 16–39 RP- At pH 7.4 nearly 82% drug was released in 48 h. MTX/CMC-GO does not showed any damage to the organs of mice. MTX/CMC-GO-treated group showed inhibition rate of live metastasis was 83.3%.	•	pH-sensitive and controlled drug-release properties were developed • low cytotoxicity against NIH-3T3 cells and low in vivo toxicity was observed	• In vivo biodistribution study was not done
CMC Hybrid nanoparticle	MOF-5	5-fluorouracil	Colon cancer	%EE- 84.1 RP- At pH 1.2 and 6.8, and 7.4 drug rleaase 20%, 60% and 70%, respectively in 8 h.	•	Showed promise for site specific delivery of loaded drug through oral delivery • The drug loaded cells showed high toxicity against HeLa cells	• No in vivo testing was done
CMC (MW = 90,000) hybrid nanoparticles	PEG, Fe_3O_4, CS,	Diclofenac	Inflammation	%EE- 55–80 RP- formulations showed pH	•	Synthesis of pH sensitive CMC based magnetic	• No in vitro or in vivo testing

Mucoadhesive drug delivery system	Other composition used	Drug	Therapy for disease	% Of Encapsulation efficiency (EE), %of drug loading (DL) and Release Profile (RB), Drug efficacy (DE), in-vitro, Ex-vivo, In-vivo, Pharmacokinetics (PK) and Pharmacodynamics (PD)	Pros	Cons	C
				responsive release of drug. Nearly 80% drug was released in SIF.	•	polyelectrolytic Oral drug carrier • Characterization of the drug carrier with different techniques	was carried out