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Review

Carbohydrate polymers: Applications and recent advances in delivering drugs to the colon

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ABSTRACT

Colon specific delivery gained increasing importance for the treatment colonic diseases, such as colorectal cancer, amebiasis, ulcerative colitis and Crohn's disease. Different strategies are used for targeting drugs to the colon include enzymatically degradable polymers, prodrug based approach, coating with time or pH-dependent polymers, osmotically controlled and pressure-controlled drug delivery systems. Polysaccharides that are precisely activated by the physiological environment of the colon hold great promise, as they provide improved site specificity and meet the desired therapeutic needs. The colon specific delivery systems based on a single polysaccharide do not efficiently permit targeted release. The pH and transit time can vary depending on the individual and the particular disease state. The conventional approaches give rise to premature drug release. The combination/chemically modified forms of polysaccharides eliminated the drawbacks associated with the use of single polysaccharide. This review focus on approaches to emerging discipline, revisits the existing technologies and future development.

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Abbreviations: AcGGM, O-acetyl-galactoglucomannan; AELC-PAD, anion exchange liquid chromatography with pulsed amperometric detection; AG, arabinogalactan; CAP, cellulose acetate phthalate; CSA, chitosan acetate; Dex-MA-SA, methacrylated and succinic derivative of dextran; DMF, drug master file; EC, ethyl cellulose; FDA, Food and Drug Administration; GLARS, geometrically long absorption regulated system; GMP, good manufacturing process; GRAS, generally recognized as safe; HEC, hydroxy ethyl cellulose; HEMA, 2-hydroxyethylmethacrylate; HPC, hydroxy propyl cellulose; HPMC, hydroxy propyl methyl cellulose; HPMCP, hydroxy propyl methyl cellulose phthalate; MCC, micro crystalline cellulose; NaCS, sodium cellulose sulfate; NDA, new drug application; PC, pectin; PEC, polyelectrolyte complex; SEC-MALLS, size exclusion chromatography with multi-angle laser light scattering; WGA, wheat germ agglutinin.

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1. Introduction

Carbohydrates also called as 'hydrates of carbon'. They consist of simple sugars having the empirical formula $C_nH_{2n}O_n$, where n is Z3, indicating that carbon atoms are in some way combined with water. In contemporary medicine and chemistry carbohydrate-based drug development has emerged as a highly promising and exciting area as a result there has been a significant increase in the number of reviews that address the general field of carbohydrate medicinal chemistry. This indicates the increasing importance of these new developments in carbohydrate-drug design, with a major focus on novel synthetic pathways and application in colon specific delivery (Huang & Fu, 2010; Witczak, 2006).

Carbohydrate polymers of monosaccharide are found in abundance and are inexpensive thus attracting a lot of attention for targeting drugs to the colon. The use of natural polymers for colon-targeted delivery is based on the fact that anaerobic bacteria in the colon are able to recognize the various substrates and degrade them with the enzymes. The natural polymers has also attracted lot of attention because of their unique quality as they are stable in the gastric environment of the upper GIT and thus preferred for colon-targeted delivery.

The colon specific delivery systems based on a single polysaccharide do not efficiently permit targeted release. The pH and transit time can vary depending on the individual and the particular disease state. Drug release can be premature or even non-existent in these cases. The combination/chemically modified forms of polysaccharides eliminated the drawbacks associated with the use of single polysaccharide. The industrial researches are going on with the use of mixtures of polysaccharide and their structurally/chemically modified forms. In this review emphasis is given on the application and properties of combination/modified forms of carbohydrate polymers employed for colon specific delivery (Kopeek, 2010; Nichifor & Mocanu, 2006).

2. Colon specific delivery

The aim of drug delivery to colon is to protect the drug from degradation in stomach and small intestine, to release maximum drug load to the colonic region. The benefit of colon specific delivery includes, lower dose, minimizing the side effects. Colonic diseases such as ulcerative colitis, Crohn's disease, colorectal cancer, constipation, spastic colon and irritable bowel syndrome could be effectively treated by delivery drug locally to the colon. The colonic drug delivery include systems using pH sensitive polymers as enteric coatings, those based on increasing of luminal pressure within the GIT either on transit time or and enzymatically controlled (Basit, 2005; Jung & Kim, 2010; Shah, Shah, & Amin, 2011; Van den Mooter, 2006). Oral route if mostly preferred for colon delivery, but rectal route can also be used, for example suppositories and enemas. There is high variability were reported while using these dosage forms (Adkin, Davis, Sparow, & Wilding, 1993; Jain & Jain, 2008; Kesisoglou & Zimmermann, 2005; Mc Connell, Liu, & Basit, 2009).

3. Carbohydrate polymers

Carbohydrate polymers have created a great attention to pharmaceutical industries and researches for developing drug delivery system/technology to colonic region. Since they are easily available, cost effective and can be modified to more advanced form. The single carbohydrate is not as much effective as their modified form/combination with other polymer. Carbohydrate polymers like guar gum, pectin, chitosan, etc. can be cross-linked with suitable cross-linking agent. The cross-linked polymers control the release of drug in a desirable manner (Fig. 1). Different carbohydrate polymers along with their source, structural unit are described in Table 1 (Jain & Jain 2008; Shukla, Trivedi, Ramteke, & Tiwari, 2011; Shukla & Tiwari, 2011; Tiwari, Ramteke, Dahima, & Shukla, 2011).

3.1. Polysaccharide modification

The modification/substitution in carbohydrate polymers leads to enhancement in targeting efficiency of therapeutic drug candidates. Substitutions in general greatly influence the physicochemical behavior of polysaccharides (Liang et al., 2008; Sanli, Ay, & Işiklan, 2007; Westedt et al., 2006). The modification can be brought by grafting of some polymers (PVA grafted guar gum),

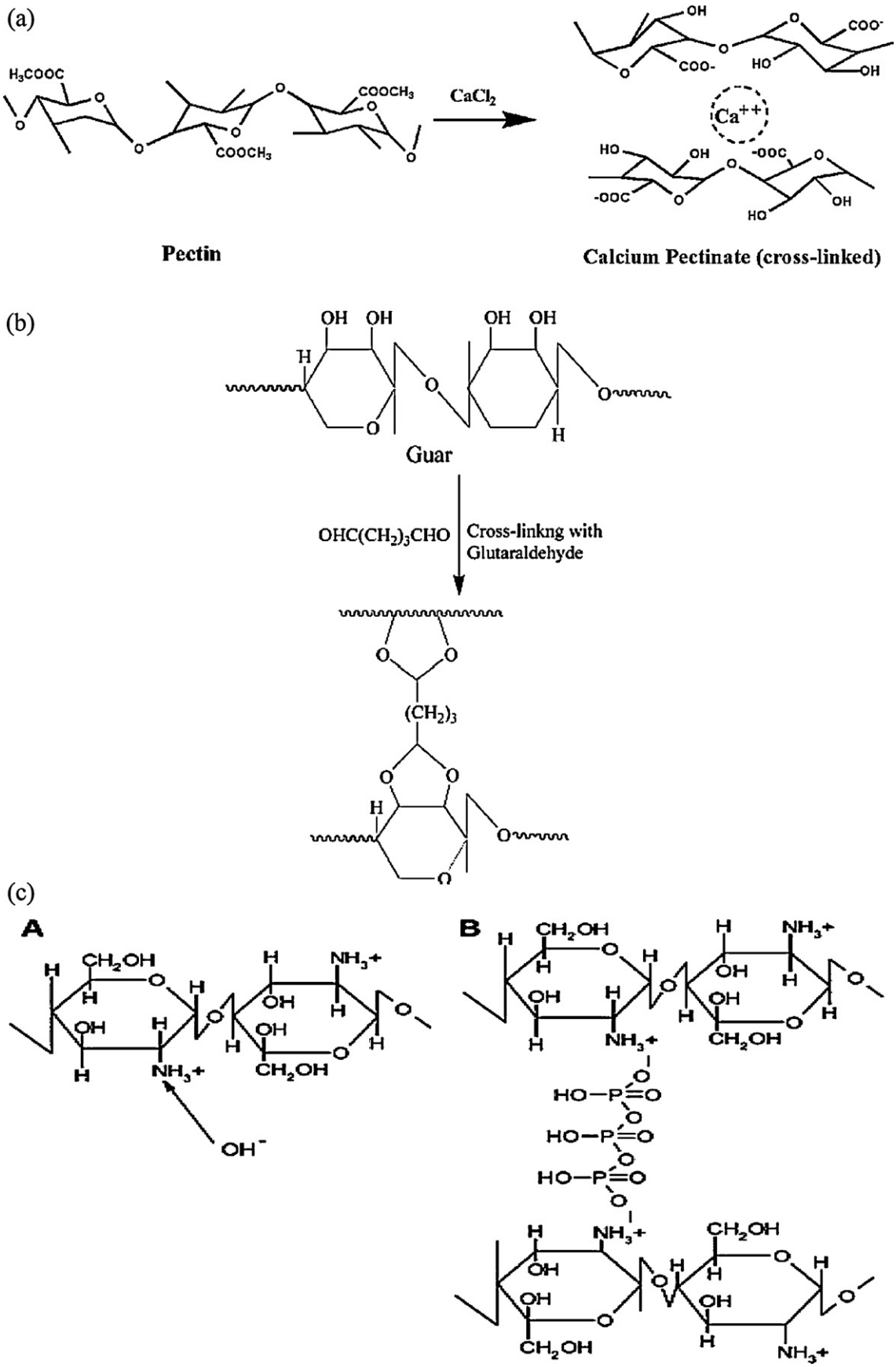


Fig. 1. (a) Cross-linking; Pectin. (b) Cross-linking; Guar gum. (c) Cross-linking, Chitosan by tripolyphosphate. (d) Cross-linking, methacrylated and succinic derivative of dextran (Dex-MA) with a methacrylated and succinic derivative of α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA), PHM-SA.

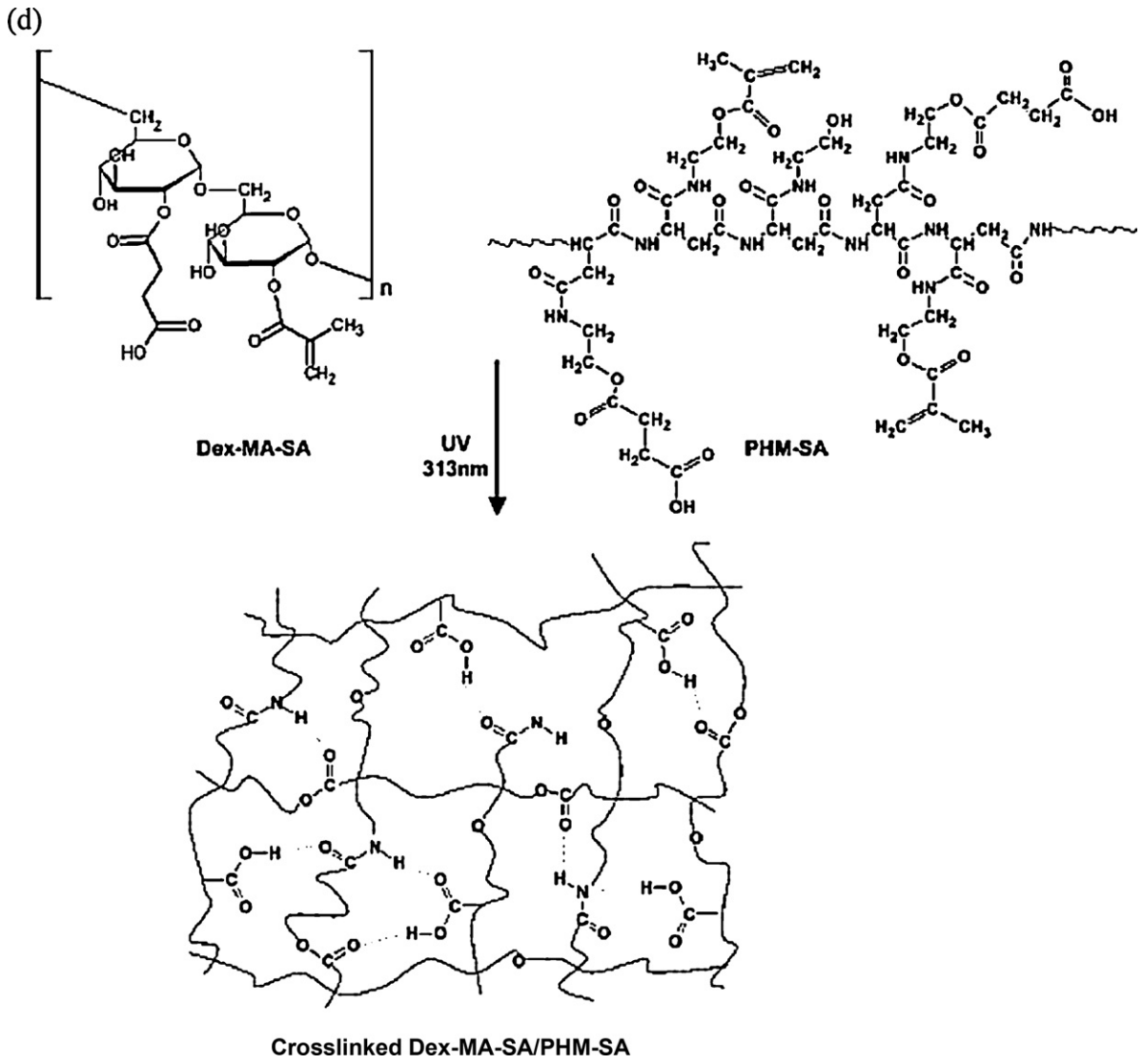


Fig. 1. (*Continued*).

chemical reaction, (amidation of pectin, acetylation of guar gum) or derivative formation (succinic acid derivative of dextran), etc. (Table 2) (Liu, Fishman, Kost, & Hicks, 2003; Mourya & Inamdar, 2009; Paños, Acosta, & Heras, 2008). This section focuses on some research based on modification of important carbohydrate polymers (Rinaudo, 2006; Vaidya, Agarwal, Jain, Agrawal, & Jain, 2011).

3.1.1. Guar gum

The high molecular weight of guar gum provides a highly viscous solution in cold water. Guar gum is soluble in cold water, hydrate rapidly to produce viscous pseudoplastic solutions that although shear-thinning generally have greater low-shear viscosity than other hydrocolloids. The gelling of guar gum retards release of the drug and it is susceptible to degradation in the colonic region. The modified products are having better swelling and enzymatic degradation properties. Guar gum was reacted with glutaraldehyde under acidic conditions to obtain different products with increasing crosslinking densities (Fig. 1). To prevent premature drug release, guar gum with low swelling index was manufactured by crosslinking it with trisodium trimetaphosphate, glutaraldehyde, which was capable of delivering drug to the colon (Shukla et al., 2011).

The good manufacturing process (GMP) has been developed for manufacturing DAVANAT®, a modified galactomannan from *Cyamopsis tetragonoloba*, or guar gum. DAVANAT® is being developed by Pro-Pharmaceuticals, Inc. DAVANAT® is a galactomannan, whose backbone is composed of (1 → 4)-linked β-D-mannopyranosyl units to which single α-D-galactopyranosyl residues are periodically attached via a (1 → 6)-linkage, with an average repeating unit of 17 β-D-Man residues and 10 α-D-Gal residues, and an average polymeric molecule containing approximately 12 such repeating units (Fig. 2). In April 11, 2007 Pro-Pharmaceuticals received letter from the Food and Drug Administration (FDA) for new drug application (NDA) for DAVANAT®/5-FU. In Dec 2008, Pro-Pharmaceuticals submitted data to FDA for DAVANAT® NDA to treat advanced colorectal cancer and announced submission of drug master file (DMF) for DAVANAT® to FDA (Miller, Klyosov, & Mayo, 2009).

The material was structurally identified and characterized by standard analytical techniques as well as by the following methods: ^{13}C nuclear magnetic resonance (^{13}C NMR); size exclusion chromatography with multi-angle laser light scattering (SEC-MALLS) for absolute molecular weight determination; and anion exchange liquid chromatography with pulsed amperometric detection (AELC-PAD) for carbohydrate composition and to verify the uniformity and purity of the final products. Preclinical studies with 5-fluorouracil, doxorubicin, irinotecan and cisplatin have shown significant degrees of efficacy enhancement both in colon and breast cancer models in nude mice (Platt, Klyosov, & Zomer, 2006).

Table 1
Carbohydrate – sources and structural units.

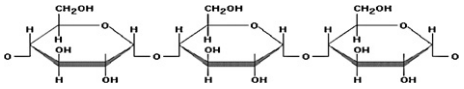
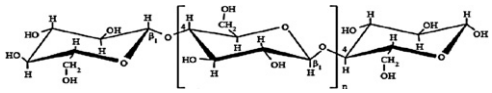
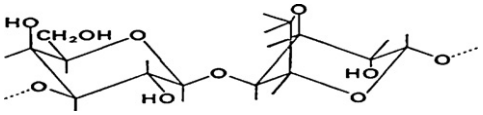
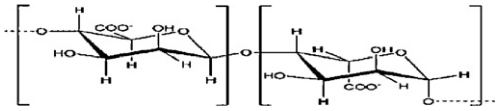
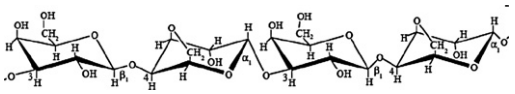
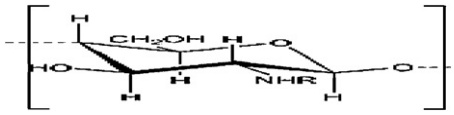
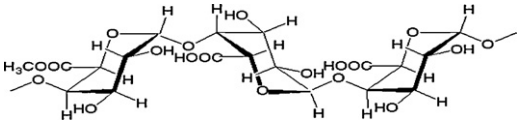
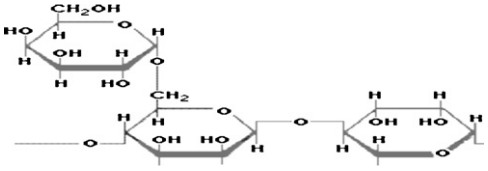
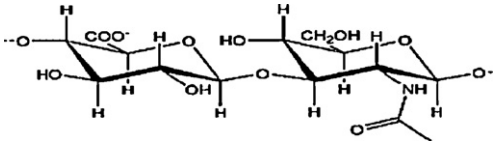
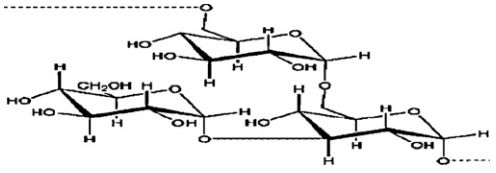
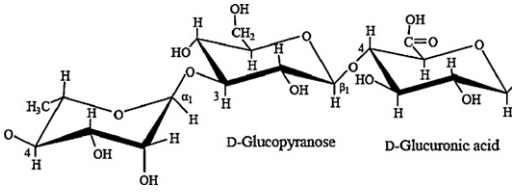
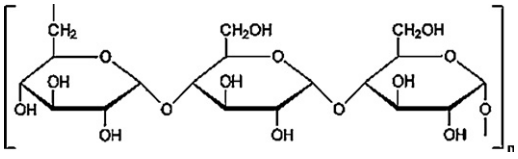
Carbohydrate	Source	Structural units	Image
Starch	Plant (e.g. Corn, rice, potato, wheat, tapioca, etc.) (Svensson et al., 2005).	α-(1/4)-linked glucose residues.	
Cellulose	Plant (cotton, wood, straw, etc. microbial (bacterial cellulose, e.g. *Acetobacter xylinum*) (Mano et al., 2007).	D-glucose units linked by β-(1/4) glycosidic bonds.	
Arabinogalactan (larch gum)	Plant (extracted from the eartwood of the western larch *Larix ccidentalis*) (Mano et al., 2007).	β-(1/3)-linked D-galactose units.	
Alginic acid	Brown algae (Phaeophyceae, mainly Laminaria); microbial (bacteria *Pseudomonas mendocina*, *Azotobacter vinelandii*) (Mano et al., 2007)	β-(1/4)-linked D-mannuronic acid and α-(1/4)-linked L-guluronic acid.	
Agar	Red algae: Rhodophyceae (*Gelidium* and *Dracilaria* spp) (Mano et al., 2007).	(1/3)-β-D-galactopyranose-(1/4)-3,6-anhydro-α-L-galactopyranose.	
Chitin	Animal (crustacean shells, exoskeletons of insects and other arthropods); microbial (fungal cell walls) (Mano et al., 2007).	β-(1/4)-linked N-acetyl-D-glucosamine residues.	
Pectin	Dried citrus peel or apple pomace (Itoh et al., 2007).	(1 → 4)-linked α-D-galacturonic acid residues.	
Guar gum	Seeds of *Cyamopsis tetragonolobus* (Tiwari & Prabaharan, 2010).	(1 → 4)-β-D-manopyranosyl units with α-D-galactopyranosyl units attached by (1 → 6) linkages.	
Hyaluronic acid	Animal (synovial fluid, vitreous humour of the eye, umbilical tissue; microbial (fermentation *Bacillus subtilis*) (Widner et al., 2005).	D-glucuronic acid and N-acetyl-D-glucosamine (GlcNAc) linked by β-(1/3) bond.	
Dextran	Microbial (bacterium *Leuconostoc mesenteroides*) (Naessens, Cerdobbel, Soetaert, & Vandamme, 2005).	α-(1/6)-linked D-glucose residues with some degree of branching via α-(1/3) linkages.	
Gellan gum	Microbial (bacterium *Sphingomonas elodea*) (Coutinho et al., 2010).	Tetrasaccharide, (1/4)-Lrhamnose-α-(1/3)-D-glucose-β-(1/4)-D-glucuronic acid-β-(1/4)-D-glucose as a repeating unit.	
Pullulan	Microbial (fungus *Aureobasidium pullulans*) (Wang, Jonathan, Robert, & Linhardt, 2002).	Maltotriose (α-(1/4)-linked) joined by α-(1/6) linkages.	

Table 2
Chemically modified carbohydrate polymers in colon specific drug delivery applications.

Polymers used	Modification in polymer	Drug delivery system prepared	Bioactive studied	Purpose/outcome of study	Reference
Guar gum	Acetyl derivative; O-acetyl-galactoglucomannan was prepared	Hydrogel	BSA	Modified AcGGM decreased the hydrolysis rate and maximum hydrolysis, indicating steric hindrance of the enzyme by the acrylate side group.	Roos et al. (2008)
Arabinogalactan	Tethering with folic acid	Biomacromolecular nanovehicle	Methotrexate	The FA-AG-GFLG-MTX drug conjugate displayed 6.3-fold increased cytotoxic activity to FR-overexpressing cells compared to their FR-lacking counterparts.	Pinhassi et al. (2010)
Pectin	Oxidized citrus pectin	In situ hydrogels	Doxorubicin	Oxidized pectin hydrogels have the potential to prevent both progression of primary cancer by the released Doxorubicin and generation of metastatic cancer by the released Oxidized pectin.	Takei, Sato, Ijima, and Kawakami (2010)
Chitosan	Folate complex prepered	Microcapsule	Camptothecin	The chitosan-folate microcapsules loaded with camptothecin significantly reduced the proliferation of HeLa tumor cells, while they have a negligible effect on fibroblasts.	Galbiati et al. (2011)
Dextran	Methacrylated and succinic derivative prepared	Hydrogel	2-Methoxyestradiol (Model drug)	In vitro cell compatibility studies indicated the absence of toxic effects. Potential mucoadhesive behavior of the hydrogel promoted drug release in the site of action for a prolonged time.	Casadei et al. (2008)

DAVANAT® is being developed to enhance the efficacy of anti-neoplastic drugs by targeting specific receptors, possibly, but not necessarily, galectins, present on cancer cells. Since DAVANAT® consists of a polymeric mannose backbone carrying galactose side chains, and therefore allegedly capable to interact with some galectins, that is receptors specific for galactose residues (both β- and α-galactose, as it was recently shown), the initial idea was to use DAVANAT® as a kind of chaperon along with 5-fluorouracil (5-FU) to facilitate its delivery into the cancer cell. A choice of 5-FU as a chemotherapy drug in a combination with DAVANAT® was based on a fact that or over 40 years 5-FU has been the standard first-line agent in the treatment of metastatic colorectal cancer. Preliminary animal studies with a variety of soluble galactomannan oligomers from various plant sources have shown promising response to the combination therapy of 5-FU (Abubaker et al., 2005; Klyosov, Zomer, & Platt, 2006).

The O-acetyl-galactoglucomannan (AcGGM) hydrogel of bovine serum albumin (BSA) was prepared by Roos et al. The degree of substitution (DS) of AcGGM was modified enzymatically with α-galactosidase, and chemically with an acrylate derivative, 2-hydroxyethylmethacrylate (HEMA). The hydrolysis of AcGGM with β-mannanase increases with decreasing DS. The addition of β-mannanase significantly enhanced the BSA release from hydrogels with a DS of 0.36, reaching a maximum of 95% released BSA after 8 h compared to 60% without enzyme (Roos, Edlund, Sjöberg, Albertsson, & Stålbrand, 2008).

Pinhassi and co-workers investigated that tethering of both FA and methotrexate (MTX) to arabinogalactan (AG), a highly branched natural polysaccharide resulted in a targeted biomacromolecular nanovehicle with unusual water solubility. This nanovehicle can differentially deliver a cytotoxic cargo into FR-overexpressing cells. They demonstrated a target-activated release mechanism. The C5-FRR cells were incubated in the presence of excess free FA (50 μM). In this case, a 6.3-fold higher cytotoxicity was also obtained for C5-FRR cells incubated in FA-free medium relative to cells incubated with excess FA. The average IC50 values obtained for C5-FRR cells in FA-lacking medium and in medium supplemented with 50 μM FA were 400 ± 13 and 2500 ± 65, respectively. The FA-AG-GFLG-MTX drug conjugate showed 6.3-fold increased cytotoxic activity to FR-overexpressing cells compared to their FR-lacking counterparts. These findings established a novel FA-tethered polymeric nanoconjugate for the targeted delivery of antitumor agents into cancer cells overexpressing FR (Pinhassi et al., 2010) (Fig. 3).

3.1.2. Pectin

The most desirable property of pectin is that it is gastric resistance and degradable by colonic bacteria. Pectin contains varying degrees of methyl ester substituents, which depend upon the plant source and preparation. For pronounced shielding effect, solubility of pectin can be decreased by forming its calcium salt, calcium pectinate. The solubility and gelation of pectin are also affected by the methyl groups. Higher methoxy pectins require a less soluble solids and a pH about 3 to form gels. While the low methoxy pectins require the presence of a controlled amount of calcium ions for gelation and need neither sugar nor acid. When the degree of esterification is less than 50%, pectins form rigid gels by reacting with calcium salts or multivalent cations, which crosslink the galacturonic acids of the main polymer chains. Calcium pectinate is obtained by the formation of an ionic bond between the carboxylic acid groups of the pectin molecules and the calcium ions. The resulting structure has the form of an 'eggbox' (Fig. 1) (Jain, Gupta, & Jain, 2007; Liu et al., 2003; Tiwari et al., 2011).

The methoxy content of pectin affect the drug release from polymer matrix. Muhidinov et al. prepared new microcapsular system delivery from pectins obtained from various sources, with different molecular weight and the degree of esterification for colon delivery. Predsinolone was studied as model drug. They investigated the

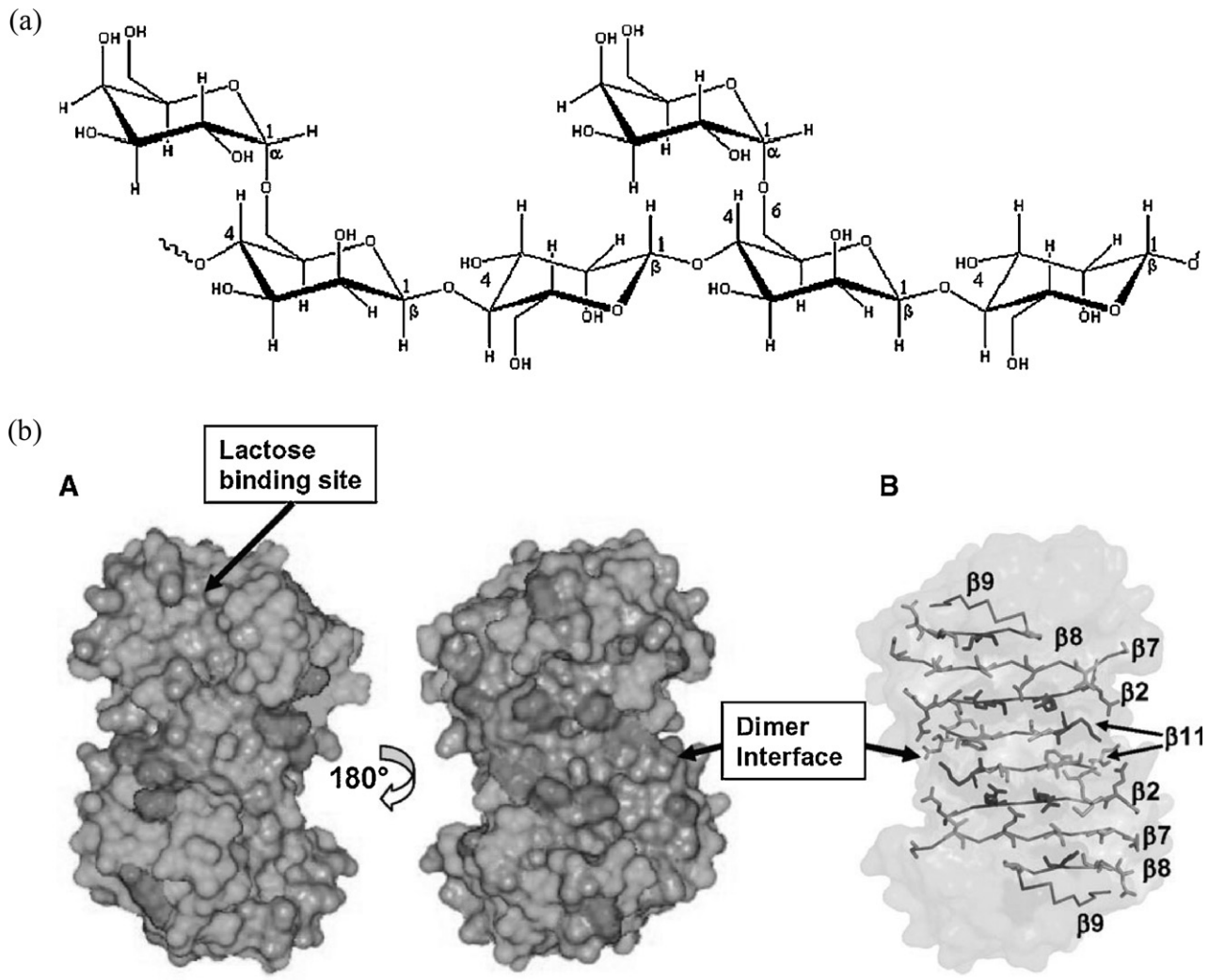


Fig. 2. (a) Chemical structure of the repeat unit in Davanat. Davanat is a galactomannan, whose backbone is composed of (1 → 4)-linked β-D-mannopyranosyl units to which single α-D-galactopyranosyl residues are periodically attached via a (1 → 6)-linkage, with an average repeating unit of 17 β-D-Man residues and 10 α-D-Gal residues, and an average polymeric molecule containing approximately 12 such repeating units. Adopted with permission from Miller et al. (2009). (b) Davanat binding domain on gal-1. (A) Residues on the folded structure of gal-1 that have been most affected by binding to Davanat are highlighted in red and orange as discussed in the text. The orientation at the left shows the face of the dimer where Davanat binds. The gal-1 dimer interface is also indicated. The orientation at the right shows the opposite side of the dimer where lactose binds. (B) Illustration of gal-1 residues in the Davanat binding domain. Polar, positively charged, and hydrophobic residues are colored in orange, blue, and green, respectively. For reference, the lactose molecule in its binding site is shown in purple. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Adopted with permission from Miller et al. (2009). The α-galactomannan Davanat binds galectin-1 at a site different from the conventional galectin carbohydrate binding domain. *Glycobiology, 19*(9), 1034–1045, Copyright Oxford University Press.

release kinetics of poor water soluble drug from the pectin microcapsules. The highest value of drug dissolution/diffusion number was obtained for microcapsule from high methoxylated apple pectin in the presence of anionic surfactants and calcium ions, rather than for the systems of highly charged citrus pectin. Capsules prepared by the use of ethyl acetate also showed retarded drug release, however the amount of drug encapsulated was much less than those from other emulsion systems. The study suggested the application of biodegradable pectin polysaccharides in the production of vastly diverse drug carrier systems for colon-specific drug delivery (Muhidinov et al., 2008).

3.1.3. Chitosan

The number fraction (%) of GlcNAc residues in the polymer chain is designated by the degree of acetylation that significantly influences the chitosan physico-chemical properties such as solubility, reactivity, biodegradability and cell response. Most of them are acid soluble, water-soluble derivatives (e.g. carboxylated derivative) can also be obtained. Chitosan is produced commercially by deacetylation of chitinin. It is hydrophilic, cationic and crystalline polymer that demonstrates film forming ability and gelation characteristics (Paños et al., 2008).

The ability of chitosan to prolong residence time in the gastrointestinal tract through mucoadhesion, and its ability to enhance absorption by increasing permeability have all been major factors contributing to its widespread evaluation as a component of oral dosage forms. Despite the outstanding scientific progress being made in the application of chitosan in drug delivery systems, no chitosan-based drug delivery systems have been launched to the market yet. However, since clinical trials are ongoing for a wide range of pharmaceutical formulations, chitosan-based products can be expected in the near future and it has already been proposed that chitosan may be the carrier material of the 21st century in drug delivery devices (Rinaudo, 2006).

Wang et al. prepared polyelectrolyte complex (PEC) of sodium cellulose sulfate (NaCS) and chitosan. FTIR data indicated that the NH_3^+ of the chitosan had reacted with the SO_4^- of the NaCS. NaCS–chitosan complex released about 80% of the drug in the SCF

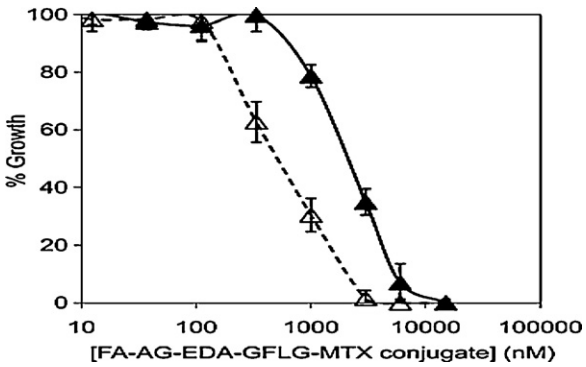


Fig. 3. Cytotoxicity of FA-AG-EDA-GFLG-MTX conjugate to C5-FRR cells incubated in FA lacking medium (empty triangles) or in 50 μM FA-containing medium (solid triangles). The experiment was conducted in pentaplicates. Error bars represent standard error. A 6.3-fold higher cytotoxicity was obtained for cells incubated in FA free medium relative to cells incubated with excess FA. The average IC50 values measured for FRR cells in the absence or presence of 50 μM of FA were 400 ± 132,500 ± 65.

Adopted with permission from Pinhassi et al. (2010). Arabinogalactan–folic acid–drug conjugate for targeted delivery and target-activated release of anticancer drugs to folate receptor-overexpressing cells. *Biomacromolecules, 11*(1), 294–303.

during 4 h. The study suggested that the NaCS–chitosan complex showed excellent behavior for colon specificity. The system could be a potential material for a colon-specific drug delivery system (Wang, Xie, Zheng, & Yao, 2009).

Smoum et al. prepared chitosan–pentaglycine–phenylboronic acid conjugate for colonic delivery of calcitonin. Three types of conjugates were prepared. In the first, 4-formylphenylboronic acid was directly linked to chitosan. The other two conjugates employed glycylglycine and pentaglycine spacers. Enzyme-inhibition assays toward trypsin and elastase, in the presence of the enzyme chitosanase, demonstrated a strong inhibitory effect for the chitosan–pentaglycine–phenylboronic acid conjugates, while no inhibitory effect was detected without chitosanase. The chitosan–pentaglycine–phenylboronic acid conjugate with the highest degree of substitution of 4-formylphenylboronic acid was able to decrease the salmon calcitonin degradation rate by trypsin. It is concluded that chitosan–pentaglycine–phenylboronic acid conjugates are a potential multifunctional, colon-specific vehicle for orally administered salmon calcitonin (Smoum, Rubinstein, & Srebnik, 2006).

3.1.4. Dextran

Dextran is water soluble and easily functionalized through its reactive hydroxyl chemistries. Biodegradation occurs through natural enzymatic splitting of polysaccharides bonds by dextran–1,6-glucosidase found in liver, spleen, lungs, brain and by dextranases expressed by bacteria in the colon. The dextran resists protein and lacks nonspecific cell binding, which has increased its use as a biomaterial. The hydroxyl functionality for chemical modification of dextran and relatively low cost, availability has increased the utilization of dextran in the field of polysaccharide polymer conjugates for biomaterials (Hu & Jing, 2009; Lee, Jeong, Kang, Lee, & Park, 2009).

A novel pH-sensitive and biodegradable composite hydrogel, based on a methacrylated and succinic derivative of dextran, named Dex-MA-SA, and a methacrylated and succinic derivative of α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA), named PHM-SA was prepared. The goal was to obtain a colon-specific drug delivery system, exploiting both the pH-sensitive behavior and the colon-specific degradability. The hydrogel was prepared with a suitable ratio between the polysaccharide and the polyaminoacid. It was characterized regarding its swelling behavior in gastrointestinal simulated conditions, chemical and enzymatic degradability, interaction with mucin, and cell compatibility on $CaCo_2$ cells. In vitro drug release studies, performed using 2-methoxyestradiol as a model drug, showed that Dex-MA-SA/PHM-SA based hydrogel was able to release the drug in simulated intestinal fluid, especially in the presence of dextranase and esterase. Furthermore, the potential mucoadhesive behavior of the hydrogel promoted drug release in the site of action for a prolonged time. The obtained results show that this polysaccharide/polyaminoacid hydrogel is potentially useful for the oral treatment of colonic cancer (Casadei, Pitarresi, Calabrese, Paolicelli, & Giammona, 2008).

Larrosa et al. explored the efficacy of different resveratrol prodrugs and pro-prodrugs to ameliorate colon inflammation in the murine dextran sulfate sodium (DSS) model. Mice fed with a very low dose (equivalent to 10 mg for a 70 kg-person) of either resveratrol-3-O-(6′-O-butanoyl)-β-D-glucopyranoside (6) or resveratrol-3-O-(6′-O-octanoyl)-β-D-glucopyranoside (7) did not develop colitis symptoms and improved 6-fold the disease activity index (DAI) compared to resveratrol. The study indicated that these pro-prodrugs exerted a dual effect: (1) prevention of rapid metabolism of resveratrol and delivered higher quantities of resveratrol to the colon and (2) reduction in mucosal barrier imbalance and prevented diarrhea, which consequently facilitated the action of the delivered resveratrol in the colon mucosa (Larrosa et al., 2010).

3.1.5. Alginate

The gel formation of polysaccharides in the gastric medium retards drug the release from the core. The presence of calcium ions is necessary since alginates do not gel because they have rigid poly (L-guluronic acids), which gel in the presence of calcium ions. Alginate gelation takes place when divalent cations (usually calcium ions) interact ionically with blocks of guluronic acid residues, resulting in the formation of a three-dimensional network that is usually described by an ‘egg-box’ model. It is the ion exchange process between sodium and calcium ions that is supposed to be responsible for the swelling and subsequent degradation of sodium alginate in the colon. The swelling and mechanical properties of alginate, produced by ionic crosslinking with cations, depend on ionic properties. For example, monovalent cations and magnesium ions do not induce gelation whereas barium ions produce stronger beads than calcium ions (Shah et al., 2011).

4. Carbohydrate mixtures

The combination of polysaccharide is more effective as compared to single polysaccharide. In this section we have discussed some important carbohydrate polymers and their combinations employed for colonic specific delivery.

4.1. Cellulose derivatives

Cellulose is the structural component of the primary cell wall of green plants, many forms of algae and the oomycetes. Some species of bacteria secrete it to form biofilms. Cellulose is the most common organic compound on the earth (Mandal et al., 2010). About 33% of all plant matter is cellulose (the cellulose content of cotton is 90% and that of wood is 40–50%). Cellulose consists of a linear chain of several hundred to over ten thousand D-glucose units which in contrast to starch are β-1,4 linked. This β-1,4 linkages make cellulose linear, highly crystalline and indigestible for humans (Al-Tabakha, 2010; Caraballo, 2010; Li, Martini, Ford, & Roberts, 2005).

Since cellulose is not absorbed systemically following oral administration, it has little toxic potential and is thus also a generally recognized as safe (GRAS) listed material. Cellulose is one of the most important pharmaceutical excipients and food additives.

Cellulose is a frequently used as tablet excipients (Liu et al., 2003; Raymond, Paul, & Siân, 2006; Sarfaraz, 2004)

Cellulose esters can be distinguished into two categories, non-enteric and enteric. Non-enteric esters, like cellulose acetate, cellulose acetate butyrate (CAB) and cellulose acetate propionate do not show pH-dependent solubility characteristics and (with no commercial exceptions) are insoluble in water. The non-enteric cellulose esters can be used to sustain drug release from oral delivery systems either by formation of a matrix or an insoluble but permeable film. Enteric esters are those, such as cellulose acetate phthalate (CAP) or hydroxypropylmethyl cellulose phthalate (HPMCP) which are insoluble in acidic solutions but soluble in mildly acidic to slightly alkaline solutions. The dissolution pH of these polymers depends upon the degree of esterification. The different HPMCP types dissolve within the pH range of 4.5–5.5 that is the pH values in the upper small intestine portion of GIT. While CAP dissolves at somewhat more neutral pH (pH >6) which indicate that drug release from CAP coated dosage forms occurs in the jejunum, the mid-part of the small intestine (Bassi & Kaur, 2010; Kosaraju, 2005).

4.1.1. Cellulose acetate phthalate

CAP is used as an enteric polymer and for oral controlled release formulations. It is a cellulose polymer where about half of hydroxyls groups are esterified with acetyls, a quarter are esterified with one or two carboxyls of a phthalic acid, and the remainder is unchanged. CAP has pH dependent solubility and has been used for several decades as pharmaceutical excipients. CAP coated formulations are resistant to acidic pH (gastric fluids), but easily soluble in mildly alkaline medium (intestine). The pH dependent solubility of CAP is mainly determined by the degree of substitution, i.e. the average number of substituent groups bound to an anhydroglucose unit, as well as by the molar ratio (acetyl and phthaloyl groups). These two important structural properties CAP are dependent on the method employed for its synthesis (Mandal et al., 2010; Siepmann, Siepmann, Walther, MacRae, & Bodmeier, 2008).

4.1.2. HPMC

Hypromellose (INN), (HPMC) is a solid, and is a slightly off-white to beige powder in appearance and may be formed into granules. Hypromellose in an aqueous solution, unlike methylcellulose, it does not exhibit thermal gelation property. The methoxy content determines the inflexibility/viscosity of HPMC solution. The higher methoxy content, the more viscous or less flexible will be the solution (Caraballo, 2010).

4.1.3. HPMCP

HPMCP was introduced into the market in 1971 as an enteric coating polymer. Shin estu chemical company has made 3 enteric polymers available commercially. These are derived from hydroxyl propyl methyl cellulose N.F. by esterification of with phthalic anhydride and are marketed as HPMCP 50, 55 and HP-55-S HPMCP is the trade name for hydroxyl propyl methyl cellulose phthalate. These polymers dissolve at loser pH 5–5.5 than CAP or acrylic polymers (Li et al., 2005).

4.2. Pectin–HPMC

Ugurlu et al. prepared compression coated tablets of nisin using different combinations of pectin/HPMC. Pectin alone was insufficient to protect the nisin containing core tablets. At the end of the 6 h 40% degradation was observed for 100% pectin tablets. HPMC addition required to control the solubility of pectin, a 5% increase in HPMC ratio in pectin/HPMC mixture provided a 2 h lag time for nisin release. Eighty percent pectin–20% HPMC appeared to be an optimum combination for further evaluation. Tablets maintained their integrity during the 6-h dissolution test, approximating the colon arrival times. The polymer hydration affected the enzymatic degradation of pectin (Ugurlu, Turkoglu, Gurer, & Akarsu, 2007).

The pectin–HPMC compression coated tablet labelled with 4MBq (99m)Tc-DTPA was developed by Hodges et al. Authors studied the in vivo behavior of tablet in six healthy male volunteers three in the ascending colon (AC) and three in the transverse colon (TC). Prolonged residence at the ileocaecal junction (ICJ) was assumed to have increased hydration of the hydrogel layer surrounding the core tablet. Inadequate prior hydration of the hydrogel layer preventing access of pectinolytic enzymes and reduced fluid availability in the TC may have retarded tablet disintegration and radiolabel diffusion (Hodges et al., 2009).

4.3. HPMC–NaCMC

Chaudhry et al. prepared microporous bilayer osmotic tablet of dicyclomine hydrochloride and diclofenac potassium for colon specific delivery. The HPMC and Na-CMC were used as osmogen. The number of pores was dependent on the amount of the pore former in the semipermeable membrane. In vitro dissolution results indicated that system showed acid-resistant, timed release and was able to deliver drug at an approximate zero order up to 24 h (Chaudhary, Tiwari, Jain, & Singh, 2011).

4.4. Chitosan–HPMC

Chitosan acetate (CSA) and HPMC can be applied at compression coat. Nunthanid et al. prepared the tablet of 5-ASA using spray drying CSA and HPMC new compression-coats. They studied the effect of pH and enzymatic degradation of the tablet for suitability in colon delivery. The degradation of CSA by β-glucosidase in the colonic fluid enhanced the drug release while adding the disintegrant or the osmotic agent in the core tablets would affect the drug release (Nunthanid et al., 2008).

Priscileila et al. prepared the enteric coated chitosan based drug delivery system for colon specific delivery of metronidazole. Enteric polymers, namely CAP and HPMCP, were incorporated, due to their insolubility in environments presenting low pH values. The results demonstrated that it is possible to prepare relative simple drug carrier systems able to reach the colonic environment, since their swelling capacity can be controlled by varying the composition (Priscileila, Giselle, Flávia Cristina, & Raul, 2009).

4.5. Alginate–chitosan

Mennini Mennini, Furlanetto, Cirri, and Mura (2012) designed a multiparticulate system, for colon-specific delivery of celecoxib for both systemic (in chronotherapic treatment of arthritis) and local (prophylaxis of colon carcinogenesis) therapy. The system comprised of ternary complexation with hydroxypropyl-β-cyclodextrin and PVP (polyvinylpyrrolidone), to increase drug solubility, and vectorization in chitosan-Ca-alginate microspheres, to exploit the colon-specific carrier properties of these polymers. Statistical experimental design was employed to investigate the combined effect of four formulation variables, i.e. % of alginate, $CaCl_2$, and chitosan and time of cross-linking on microsphere entrapment efficiency and drug released after 4 h in colonic medium. Design of experiment was used in the context of Quality by Design (QbD), which requires a multivariate approach for understanding the multifactorial relationships among formulation parameters. The desired goals were achieved for both systemic and local use of celecoxib. These results indicated that effectiveness of the proposed jointed use of drug cyclodextrin complexation and chitosan-Ca-alginate microsphere vectorization.

4.6. Ethyl cellulose–starch combination

Freire et al. prepared the colon targeting pellets coated with a dispersion of high amylose starch (Hylon VII) and ethylcellulose (Surelease) (1:2, w/w) of (5-aminosalicylic acid; 5-ASA). Developed formulation was evaluated in vivo in rabbits. The coated tablets were able to resist the drug release in stomach and small intestine and were able to deliver maximum load to the colon (Freire et al., 2010).

A novel polymeric film for the site-specific delivery of drugs to the colon of patients suffering from inflammatory bowel diseases was developed. Ethylcellulose (EC) was blended with different types of bacteria-sensitive starch derivatives. The water uptake and dry mass loss kinetics of the systems were monitored upon exposure to media simulating the contents of the stomach, small intestine and colon (including fresh fecal samples from Crohn's disease and Ulcerative Colitis patients). Importantly, EC: Nutriose FB 06 and EC: Peas starch N-735 films showed highly promising water uptake and dry mass loss kinetics in all the investigated media, indicating their potential to minimize premature drug release in the upper gastro-intestinal tract, and allowing for controlled release once the colon is reached (Karrout et al., 2009a, 2009b).

Karrout et al. studied the film coated pellets of Eurylon 6 HP-PG (a hydroxypropylated and pregelatinized high amylose starch) and ethyl cellulose for inflammatory bowel diseases. 5-ASA release could effectively be suppressed in 0.1 N HCl and phosphate buffer pH 6.8, optionally containing pepsin or pancreatin, but occurred as soon as the pellets came into contact with culture medium inoculated with fecal samples from inflammatory bowel disease patients. This can be attributed to the partial degradation of the starch derivative by enzymes secreted by bacteria present in the colon of patients. The developed formulation can be adapted to the pathophysiological conditions in inflammatory bowel disease patients. Furthermore, drug release remained unaltered upon 1 year open storage (Karrout et al., 2009a, 2009b).

Further this group studied the 5-ASA loaded beads prepared by extrusion–spheronization and coated with different Nutriose:EC blends. Interestingly, the release of 5-ASA could effectively be suppressed upon exposure to release media simulating the conditions in the upper GIT, irrespective of the degree of agitation and presence or absence of enzymes. But as soon as the pellets came into contact with fecal samples of inflammatory bowel disease patients, the release rate significantly increased and the drug was released in a time-controlled manner (Karrout et al., 2010).

4.7. Ethyl cellulose–carbopol combination

Ali et al. prepared the matrix tablet of indomethacin for colon cancer, using different combination of ethyl cellulose and carbopol. The presence of ethyl cellulose in a hydrophilic polymer matrix resulted in a sigmoidal in vitro drug release pattern with negligible-to-very low drug release in the initial phase (0–6 h) followed by controlled release for 14–16 h. The decrease in initial release can be due to the ethyl cellulose that controls the swelling of hydrophilic polymer(s), while in the later portion, polymer relaxation at alkaline pH due to the ionization of acrylic acid units on carbopol and polycarbophil resulted in improved indomethacin release. A sigmoidal release pattern was obtained that could be ideal for colonic delivery of indomethacin in the potential treatment of colon cancer (Ali Asghar, Azeemuddin, Jain, & Chandran, 2009).

4.8. Pectin–chitosan

Bigucci et al. examined the release behaviors of vancomycin from poly electrolyte complex of pectin–chitosan. Moreover, the particular composition of these complexes improved vancomycin availability at alkaline pH on the bases of an enzyme-dependent degradation as confirmed from release studies performed in presence of beta-glucosidase (Bigucci et al., 2008)

Further this group extended the research and prepared hydrogels system of vancomycin using pectin and chitosan. Their study suggested that pectin/chitosan microspheres were able to limit the release of vancomycin under acidic conditions and release it under simulated colonic conditions, confirming their potential for a colon-specific drug delivery system (Bigucci, Luppi, Monaco, Cerchiara, & Zecchi, 2009).

4.9. Amidated pectin–chitosan–enteric polymers

Giselle et al. prepared the multiparticulate colon specific delivery system of triamcinolone using chitosan and amidated pectin. HPMCP and CAP were successfully incorporated into the system and aided the target action of the carbohydrates. The in vitro drug release studies showed that the addition of both enteric polymers, CAP and HPMCP, to the PC:CS:TC particles resulted in higher control over drug release in all media analyzed. Particles from all charges also exhibited enzyme-controlled drug release properties in simulated colonic medium. The addition of CAP and HPMCP resulted in the highest control over the drug release in all media. CAP:TC formulation presented the slowest drug release rate, of only 1.33%, in acidic medium after 2 h, while the control formulation released 45.52% after the same time (Giselle, Priscileila, Livia, & Raul, 2010).

4.10. Guar gum–chitosan

Celecoxib loaded polysaccharide films of guar gum and chitosan for local adjuvant or neoadjuvant therapy of colorectal cancer was developed. The impact of a single high dose was evaluated and compared with a repeating low-dose regimen. In vivo dosing experiments with Cx were performed in the perfused intestine of the anaesthetized rat. The study suggested maximum therapeutic efficiency in the context of minimal healthy tissue exposure for utilizing a local delivery system such as the proposed adhesive, biodegradable polysaccharide composites (Haupt, Zioni, Gati, Kleinstern, & Rubinstein, 2006).

Ravi et al. prepared novel colon targeted tablet formulation using natural polysaccharides such as chitosan and guar gum as carriers and diltiazem hydrochloride as model drug. In vitro studies revealed that the tablets coated with inulin and shellac have controlled the drug release in stomach and small intestinal region and released maximum amount of drug in the colonic environment. The study revealed that polysaccharides as carriers and inulin and shellac as coating materials can be used effectively for colon targeting of drugs for treating local as well as systemic disorders (Ravi and Pramod Kumar, 2008).

4.11. Guar gum–alginate

A matrix tablet of guar gum and alginate for colon specific delivery of ondasatron for the treatment of IBD was prepared by Tugcu. The developed formulation was system able to reduce the visceral sensitivity and inhibition of motor activity in irritable bowel syndrome (IBS) (Tugcu-Demiröz, Acartürk, & Takka, 2006).

4.12. Chitosan–alginate

Lectin-conjugated chitosan-Ca-alginate microparticles (MPs) loaded with acid-resistant particles of 5-fluorouracil (5-FU) for efficient local treatment of colon cancer were prepared by Glavas et al. Microparticles were prepared by a novel one-step spray-drying technique and after wheat germ agglutinin (WGA) conjugation. The retention of biorecognitive activity of WGA after covalent coupling

to MPs was confirmed by haemagglutination test. Functionalized MPs showed excessive mucoadhesiveness in vitro, due to the positive surface charge, pH-dependent swelling of the matrix and lectin–sugar recognition (Glavas Dodov et al., 2009).

Laroui et al. studied nanoparticles (NPs) to deliver an anti-inflammatory tripeptide Lys-Pro-Val (KPV) to the colon and assessed its therapeutic efficacy in a mouse model of colitis. To target KPV to the colon, loaded NPs (NP-KPV) were encapsulated into a polysaccharide gel containing 2 polymers: alginate and chitosan. The effect of KPV-loaded NPs on inflammatory parameters was determined in vitro as well as in the dextran sodium sulfate-induced colitis mouse model. The studied suggested that by using NPs, KPV can be delivered at a concentration that is 12,000-fold lower than that of KPV in free solution, but with similar therapeutic efficacy. Administration of encapsulated drug-loaded NPs can be a novel therapeutic approach for IBD (Laroui et al., 2010).

4.13. Dextran–chitosan

A polyelectrolyte complex (PEC) consisting porous chitosan (CS) hydrogel microsphere of ibuprofen were prepared via either wet phase-inversion or ionotropic crosslinking with sodium tripolyphosphate (Na^+-TPP) and dextran sulfate (DS). The CS/TPP/DS microspheres resisted hydrolysis in strong acid and biodegradation in enzymatic environments. The swelling kinetics for CS microspheres was close to Fickian diffusion, whereas those for CS/TPP and CS/TPP/DS were non-Fickian. The release profiles of ibuprofen from CS/TPP/DS microspheres were slow in simulated gastric fluid (SGF, pH 1.4) over 3 h, but nearly all of the initial ibuprofen content was released in simulated intestinal fluid (SIF, pH 6.8) within 6 h after changing media. Overall the results indicated that CS/TPP/DS microspheres could successfully deliver a hydrophobic drug to the intestine without drug degradation in the stomach, and hence could be potential candidates as an orally administered colon drug delivery system (Lin, Yu, & Yang, 2005).

5. Carbohydrate–Eudragit mixtures

The carbohydrate–Eudragit mixtures can be a better promising approach for colon delivery. Eudragit series is available with different form. The different Eudragit polymers have the property of dissolving at specific pH value. Different combinations of carbohydrate polymers with Eudragit are described in this section.

5.1. Guar gum–Eudragit

Ji et al. prepared pH and enzyme-dependent colon-targeted multi-unit delivery system of indomethacin by coating guar gum and Eudragit FS30D sequentially onto drug-loaded pellets in a fluidized bed coater. Pharmacokinetic study in beagle dogs showed that fastest absorption with the smallest T_{max} and T_{lag} was observed for uncoated pellets. The T_{max} and T_{lag} of Eudragit FS30D-coated pellets were postponed to about 2.5 and 1 h, respectively. After a further guar gum coating, T_{lag} was further postponed to about 2.8 h, about 2 h of additional lag time on the basis of Eudragit FS30D coating. The results indicated that the guar gum/Eudragit FS30D-coated system has potential to be used to deliver drugs to the colon (Ji, Xu, & Wu, 2007).

The chronotherapeutic based colon-targeted drug delivery system of theophylline (THEO) exploiting pH-enzyme sensitive property was prepared the prevention of episodic attack of asthma in early morning. Guar gum microspheres of theophylline were prepared by emulsification technique. Coating of microspheres was performed using solvent evaporation method with pH sensitive Eudragit® polymers. The controlled release of THEO after a lag time was achieved with developed formulation for chronotherapeutic delivery. The pH dependent solubility behavior of Eudragit and gelling properties of guar gum are found to be responsible for delaying the release (Soni et al., 2011).

Ji et al. prepared colon specific guar gum-based multi-unit pellet system. The guar gum was coated by pH-sensitive polymer Eudragit FS30D sequentially around drug-loaded non-pareil cores in a fluid-bed coater. The outer Eudragit FS coating protects the system against gastrointestinal environment and dissolves rapidly in distal small intestine, where a lumen pH of over 7 triggers the dissolution of the enteric polymer. The inner guar gum coating works as a time-controlled retardant and offers additional protection of the pellets until it is degraded by microbial enzymes at the proximal colon. In vitro results indicate that guar gum is a feasible coating material to achieve timed and enzyme-triggered fluorouracil release. Pharmacokinetic study in beagle dogs shows delayed absorption of about 5 h and limited absorption fraction as a result of guar gum and Eudragit FS coating (Ji, Xu, & Wu, 2009).

5.2. Pectin–Eudragit

The Eudragit S-100 based microsponges bearing dicyclomine for colonic delivery was developed. The colon-specific tablets were prepared by compressing the microsponges followed by coating with pectin:HPMC mixture. In vitro release studies exhibited that compression-coated colon-specific formulations started releasing the drug at the sixth hour corresponding to the arrival time at colon. The study presented a new approach for colon-specific drug delivery (Jain, Jain, Ganesh, Barve, & Beg, 2010).

5.3. CAP–Eudragit

Kotagale et al. prepared polymer-coated polysaccharide tablets for colon specific delivery of azathioprine. Tablets were prepared by direct compression method using different ratios of avicel-Micro Crystalline Cellulose (MCC), inulin and triacetin. Eudragit-S, Eudragit-L and cellulose acetate phthalate (ES, EL and CAP) were used for coating. Drug release increased with the plasticizer (triacetin) concentration. Increase in the concentration of inulin and citric acid above 5% (w/w) increases the drug release. The addition of inulin in the formulation with coating level 28% (w/w) demonstrated increased drug release in presence of rat cecal content. The results revealed that inulin containing ES, EL and CAP (1:1:1) polymer-coated formulation system can be used for the targeted delivery of azathioprine with desired release pattern (Kotagale, Maniyar, Somvanshi, Umekar, & Patel, 2010).

5.4. Chitosan–Eudragit

Hyaluronic acid-coupled chitosan nanoparticles bearing oxaliplatin (L-OHP) encapsulated in Eudragit S100-coated pellets were developed for effective delivery to colon tumors. In murine models, the drug delivery system showed relatively high local drug concentration in colonic tumors with prolonged exposure time, which provides a potential for enhanced antitumor efficacy with low systematic toxicity (Jain, Jain, Ganesh, et al., 2010; Jain, Jain, & Singh, 2010).

Ibekwe and co-workers reported a novel dual-triggered colonic delivery system with improved site-specificity over the pH-responsive systems currently used for ulcerative colitis. The system consisted of a mixture of pH-responsive Eudragit S and resistant starch in a single layer matrix film. Tablets were administered in a three-way crossover study to eight healthy volunteers. The site of intestinal disintegration was assessed using gamma scintigraphy. The coated tablets were able to resist breakdown in the stomach and small intestine. The dual pH- and bacterially-triggered

coating was applied to tablets and dosed a total of 23 times in healthy volunteers under three different feeding conditions (i) without food, (ii) with breakfast or (iii) 30 min before breakfast. The tablet did not empty from the stomach during the study period, but of those 22 tablets that emptied, disintegration occurred at the ileo-caecal junction or in the large intestine confirming successful targeting with this system. The independent triggers of a bacterially-triggered component within a pH-responsive polymer are effective, complementary and act as failsafe mechanisms for each other (Ibekwe, Khela, Evans, & Basit, 2008).

Eudragit L100 (EuL)-coated chitosan (Ch)-succinyl-prednisolone (SP) conjugate microspheres (Ch-SP-MS/EuL), were developed for IBD. Efficacy of these microspheres was dose-dependent and the greatest in the order Ch-SP-MS/EuL > Ch-SP-MS > prednisolone (PD) alone, and Ch-SP-MS/EuL showed excellent recovery of colitis states. Toxicity was the greatest in the order PD > >Ch-SP-MS > Ch-SP-MS/EuL. Ch-SP-MS and Ch-SP-MS/EuL reduced significantly the thymic atrophy caused by PD. It was demonstrated that Ch-SP-MS/EuL enhanced effectiveness of PD and reduced toxic side effects of PD greatly. Also, these results established the prediction by previous in vitro and in vivo studies (Onishi, Oosegi, & Machida, 2008).

The Eudragit-S-100 coated chitosan microspheres for 5-ASA and camylofine dihydrochloride for the treatment of ulcerative colitis was prepared by Dubey et al. In vivo data showed that microspheres delivered most of its drug load (76.55 ± 2.13%) to the colon after 9 h, which reflects its targeting potential to the colon. The study suggested that orally administered microspheres of both drugs can be used together for the specific delivery of drug to the colon and reduce symptoms of ulcerative colitis (Dubey, Dubey, Omrey, Vyas, & Jain, 2010).

6. Prodrugs

Polysaccharides are used either glucuronic or glycosidic prodrugs which are specifically degraded by colonic β-glucuronidases and glycosidases. The most widely used polysaccharide of this type is dextran, dextran derivatives, starch, hydroxyethyl starch, alginates, glycogen, pullullan, agarose, cellulose, chitosan, chitin and carrageenan (Dhaneshwar & Vadnerkar, 2011).

The budesonide–dextran conjugate as novel prodrugs of budesonide was developed for oral controlled delivery to the colon without needing to coat the pellets of the drug. The in vivo efficacy was evaluated against acetic acid-induced colitis in rats. The results indicated that budesonide–dextran conjugate was effective in improving signs of inflammation in experimental model of colitis through selective delivery of the drug to the inflamed area (Varshosaz et al., 2010).

Dextran–nalidixic acid ester (dextran–NA) was synthesized with a various degree of substitution (DS) as a colon-specific prodrug of nalidixic acid (NA). The dextran–NA was chemically stable during the transit through the gastrointestinal tract. When dextran–NA (equivalent to 50 μg of NA) with a DS of 7 or 17 was incubated with cecal contents (100 mg) of rats at 37 °C, the extent of NA released in 24 h was 41% or 32% of the dose, respectively. NA was not liberated from the incubation of dextran–NA with the homogenate of tissue and contents of the small intestine (Lee et al., 2011).

Further this group extended the research and investigated the dextran–flufenamic acid ester (Dex–FFA) as a polymeric colon-specific prodrug of flufenamic acid, an anti-inflammatory drug, for chronotherapy. The plasma level for FFA became greater around 6 h after administration of Dex–FFA than free FFA and it was maintained throughout the period of 24 h-experiment. Dex–FFA markedly attenuated gastric ulcerogenicity of FFA. Taken together, Dex–FFA could be useful as a colon-specific prodrug which possesses anti-inflammatory properties and offers opportunities as a chronotherapeutic approach for the treatment of arthritis (Lee et al., 2011).

Zou and collegues studied the polysaccharide prodrugs of 5-aminosalicylic acid as potential colon-specific delivery systems. They prepared several polysaccharide prodrugs of 5-ASA to examine the effect of solubility of prodrugs on the release characteristics of 5-ASA in the gastrointestinal contents of rats. The amide prodrug, chitosan-5-ASA (ChT-5-ASA), did not release the 5-ASA in the cecal and colonic contents. The ester prodrugs, hydroxypropyl cellulose-5-ASA (HPC-5-ASA), being poor solubility in acetic acid solution also did not release the 5-ASA in any of gastrointestinal contents of rats. Whereas the 5-ASA release from cyclodextrins-5-ASA (CyDs-5-ASA) in cecal and colonic contents was significantly higher than that in stomach and small intestine contents. Furthermore, with the decrease in the degree of substitution, the solubility of CyD-5-ASA increased, and the release of 5-ASA in the gastrointestinal contents was also higher at the same time interval of incubation. When the ratio of cyclodextrin (CyD) and 5-formylaminosalicylic acid (5-fASA), a precursor of 5-ASA prodrugs, was 1:10, CyD-5-ASA was very slightly soluble, and no release of 5-ASA was observed within 48 h in gastrointestinal contents. The study suggested that the ester prodrugs of 5-ASA with certain solubility could release 5-ASA in the cecal and colonic contents of rat (Zou et al., 2005).

Budesonide conjugates were prepared using glutarate spacer and different molecular weights of dextran and their degree of substitution, solubility, and stability were examined. The conjugates were stable in HCl 0.1 N, phosphate buffer solutions pH 6.8, and 7.4 incubated at 37 °C within 6 h and degradation rate constants were $<0.009\ h^{-1}$. Less than 10% of budesonide was released in contents of stomach and small intestine and it was increased significantly after incubating with colonic contents. The conjugate prepared using dextran 70,000 was studied for in vivo studies that decreased the macroscopic and microscopic scores of induced colitis compared with mesalasine and budesonide suspension (Varshosaz et al., 2011).

7. Industrial patents and marketed preparations

There are only few carbohydrate based marketed preparation available in the market for colon specific delivery as shown in Table 3. There has been tremendous interest in developing colon targeted drug delivery systems over the last decade, but only enteric-coated colonic tablets have been able to hit the market so far. Nowadays chronotherapeutic approach is being given consideration. The scientists in pharmaceutical industry always decide their product development pathway on considering the regulatory requirements. The regulatory issues include pre and post-approval considerations (Marroum, 2009).

In pre FDA approval stage, it becomes difficult to demonstrate chronotherapeutic advantage of controlled release or modified release formulations in clinical studies. The major issues include the lack of truly rhythmic biomaterials and drug delivery systems and rhythm engineering and better prediction tools. The bioavailability requirements for controlled release products are covered in the U.S. Code of Federal Regulations under 21 CFR.320.25 (FDA Guidance, 2009b, 2009c).

In post FDA approval stage factors that can render the drug substance abuse-ready should be considered so that appropriate risk management strategies can be applied after approval of drug product (Mc Cormick, 2006; FDA guidance 2009a; Spagnolo & Daloiso, 2009).

Many pharma industries are working on advanced oral colon specific drug delivery. They have novel patented technology, most

Table 3
Carbohydrate based colon targeted industrial development/technology.

Trade name	Drug	Carbohydrate polymer/s	Company/organisation	References
COLAL-PRED®	Prednisolone metasulfobenzoate sodium ('PMSBS')	Ethylcellulose and a specific form of amylose (derived from starch).	Alizyme Therapeutics Limited (UK)	alizyme (2011)
ENCODE-Phloral™	[a]	Starch, Eudragit S	ENCAP drug delivery (UK)	Glavas Dodov et al. (2009) and encapdrugdelivery (2011)
Clipper®	Beclometasone dipropionate	Hypromellose (E.464) MCC Maize starch, Eudragit	Chiesi Limited (UK)	medicines (2011)
GLARS	Simvastatin, Lovastatin, Fluvastatin, Acetaminophen	HPMC, HPC, CMC	GL Pharm Tech, (Korea)	Sang et al. (2010)
TIME R_x and Syncro Dose™	[a]	Xanthan gum, locust bean gum	Patterson, NY, US	Penwest (2011)
TARGIT™ Technology	[a]	Starch CAP, HPMCP	West Pharmaceutical London, UK	Watts and Smith (2005)
Chrono Cap	[a]	HEC, HPMC, PVP, HPC	Universita degli Studi di Milano–IT	Andrea et al. (2010) and Gazzaniga et al. (2008, 2009)
Chronotopic®	[a]	HPMC	–	Sangalli et al. (2004)

[a] Non drug specific.

of them are in clinical trials. Some important developments are described below.

7.1. COLAL-PRED® technology

COLAL-PRED® technology was developed by Alizyme Therapeutics Limited. COLAL-PRED® comprises small pellets containing prednisolone metasulfobenzoate sodium (PMSBS) with a coating of ethyl cellulose and a specific form of amylose (derived from starch) that is broken down only in the colon by enzymes from locally occurring bacteria. This enables PMSBS to be taken orally and delivered topically to the colon, rather than systemic delivery, since release in the stomach and small intestine is prevented. This makes possible the effective treatment of ulcerative colitis without the usual debilitating side effects typically associated with such steroids. It has been shown in a Phase III clinical trial to provide a significantly improved risk-benefit profile to that of conventional oral prednisolone (alizyme, 2011).

7.2. ENCODE-Phloral™

ENCODE technology was developed by ENCAP drug delivery, includes the Phloral™ system licensed from the School of Pharmacy in London. This is a unique coating technology that is designed to target the release of drugs to the colon region. It consists of a blend of bacteria-activated (starch) and pH-activated (Eudragit S) component. The dual pH- and bacterially-triggered coating was applied to tablets and dosed a total of 23 times in healthy volunteers under three different feeding conditions. On one occasion, the tablet did not empty from the stomach during the study period, but of those 22 tablets that emptied, disintegration occurred at the ileo-caecal junction or in the large intestine confirming successful targeting with this system.

The independent triggers of a bacterially-triggered component within a pH-responsive polymer are effective, complementary and act as failsafe mechanisms for each other. This platform technology could theoretically be adapted to any drug and used for a variety of disease states. The clinical potential for inflammatory bowel disease is obvious with a low risk of dose dumping and low risk of the tablets passing intact and for new systemic applications for colonic delivery (Glavas Dodov et al., 2009; encapdrugdelivery, 2011).

7.3. Clipper®

Clipper® is gastro-resistant prolonged-release tablet of beclometasone dipropionate. This technology was developed by Chiesi Limited, UK. The tablet core consist of hypromellose (E. 464), microcrystalline cellulose maize starch, etc., while the tablet coating was made up of Eudragit L100-55. The tablets are indicated for the treatment of mild or moderate ulcerative colitis in active phase, as add-on therapy to 5-ASA containing drugs in patients who are non-responders to 5-ASA therapy in active phase (medicines, 2011).

7.4. GLARS (geometrically long absorption regulated system)

The focus of GL Pharm Tech over the past ten years has been on developing a technology named GLARS. The system entraps more gastro-intestinal fluid into the dosage form at early dissolution time to give further extended absorption in the colon. GLARS technology developed by GL Pharm Tech (Korea) consists of oral sustained-release triple layer tablet containing (1) an inner immediate-release layer comprising a therapeutically active ingredient and (2) two outer layers having swellable polymers, wherein, upon exposure to aqueous media, the exposed lateral side of the inner immediate-release layer is surrounded by the two swollen outer layers to control the release of active ingredient. The swellable polymers are selected from cellulose derivative. The technology was evaluated for its proof of concept on tianeptine and tamsulosin (Fig. 4) (Sang et al., 2010).

7.5. Chrono Cap

Chrono Cap is patented technology of Universita degli Studi di Milano-IT. The Chrono Cap technology relates to an oral capsular device intended for pulsatile (time-controlled) release of drugs to colonic region. The Chrono Cap can optionally be coated with gastric-resistant polymers (HEC, HPMC, PVP, HPC, etc.) thus being adapted to a time-dependent colon delivery system. Such capsules are prepared from hydrophilic polymeric materials that undergo a glassy–rubbery transition when exposed to aqueous fluids, thereby delaying the release of the contents for a programmable period of time following administration. The lag time that precedes the onset of release can be modulated as a function of the thickness and composition of the capsule shell. Chrono Cap devices can be filled just like hard gelatin capsules and may convey solid (powders, capsules, tablets, granulates, pellets, micro- or nano-particles), semi-solid or liquid drug formulations. Colonic release is of high interest not only for the therapy and prevention of pathologies that affect the large intestine (ulcerative colitis, Crohn's disease, colorectal adenocarcinoma, microflora disorders), but also for pharmacological treatments that require a systemic absorption of the drug

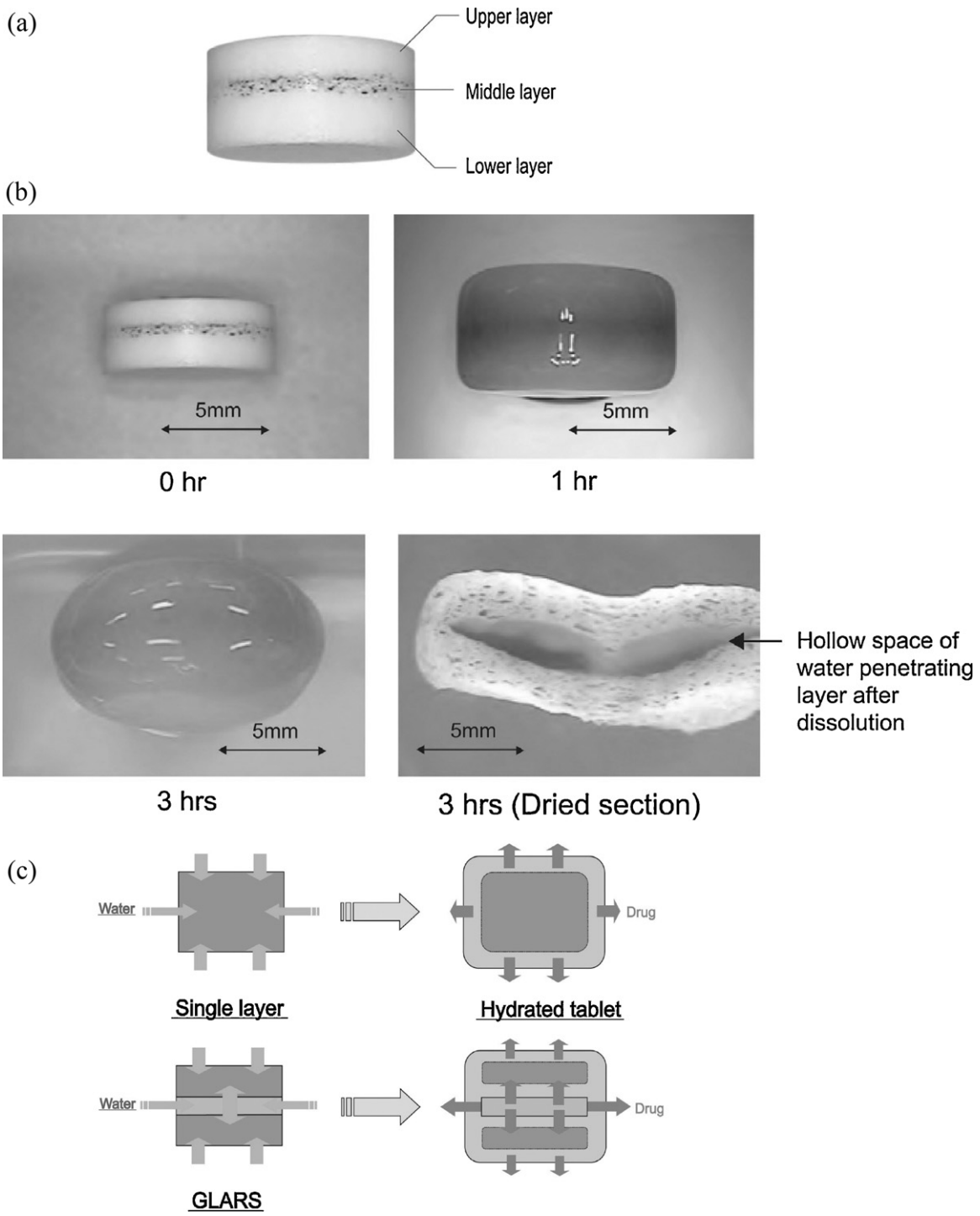


Fig. 4. (a) Triple-layered structure of GLARS. (b) Morphological changes in GLARS upon water contact. (c) GLARS Technology: Schematic representation of rapid water penetration through middle layer as well as swelling and enclosing of upper and lower layers.

(Andrea et al., 2010; Gazzaniga, Palugan, Foppoli, & Sangalli, 2008; Gazzaniga et al., 2009).

7.6. *Chronotopic*®

The Chronotopic® comprises a drug-loaded core coated with HPMC, a swellable hydrophilic polymer. The HPMC coating undergoes a glassy–rubbery transition when in contact with aqueous fluid. The drug is then released across the gel-layer either by diffusion and/or erosion. The onset of drug release and lag-time are controlled by the thickness and viscosity grade of the HPMC coat employed during formulation. The film allows the system to stay intact until reaching the intestine where it eventually erodes and exposes the HPMC layer to the intestinal fluid thus allowing the system to be pH-responsive. The tablet matrix is prepared by firstly granulating the drug with a range of excipients which is then compressed. A mixture of HPMC and PEG solutions is then spray coated onto the core and allowed to dry. Thereafter a coating of Eudragit® is applied onto the outer surface of the tablet matrix (Sangalli et al., 2004).

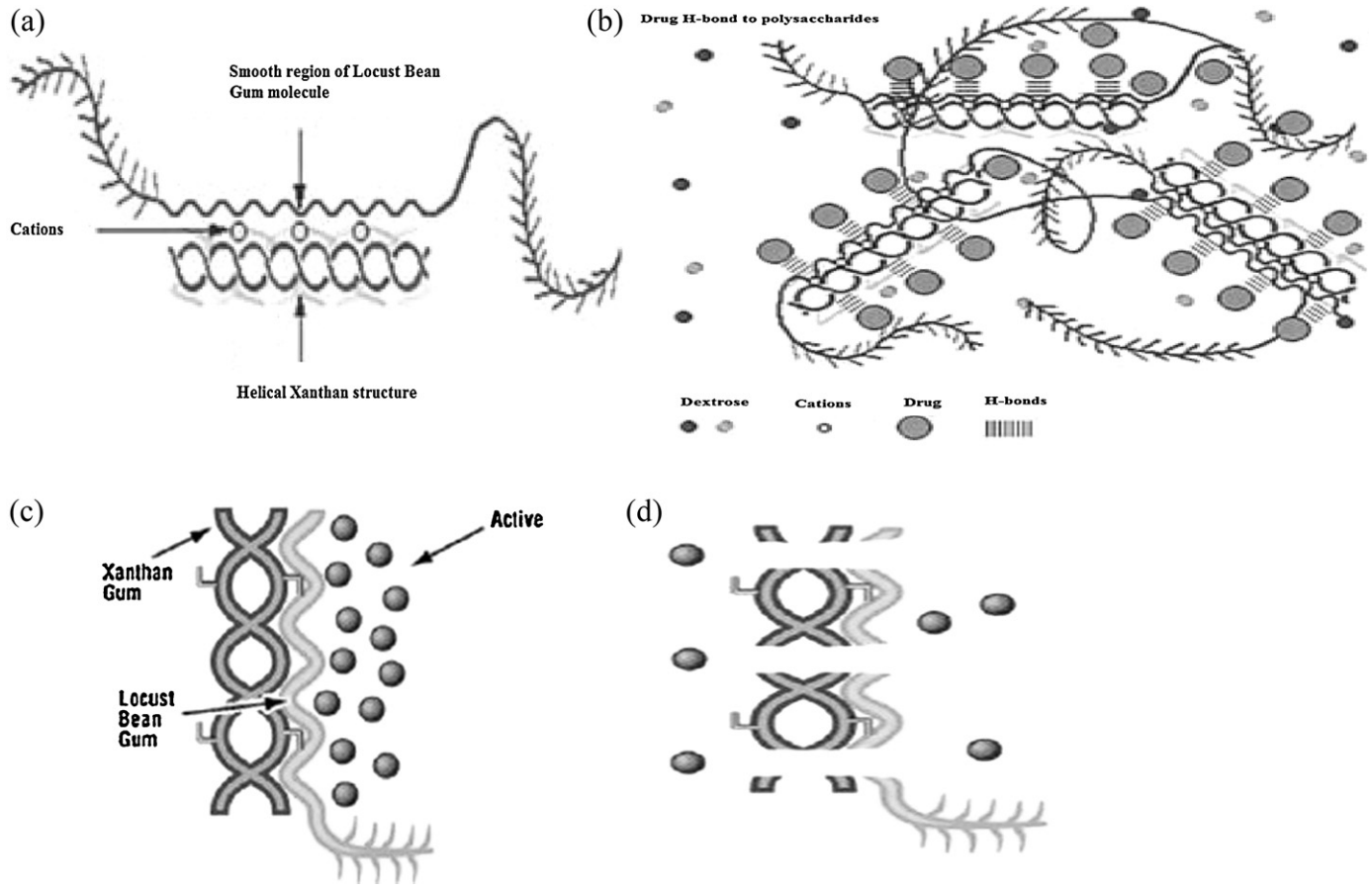


Fig. 5. (a) When xanthan and locust bean gum are mixed together, the smooth unsubstituted regions of the locust bean gum molecules associate with the helical xanthan structures to produce a matrix that is both stronger than high viscosity xanthan and less ribbery than cross-linked locust bean gum. This process is stimulated by the presence of cations (o). (b) Molecular structure of xanthan gum and Locust bean in Time Rx drug delivery technology. (c) At initial stage the water starts hydrating the xanthan and locust bean gum. (d) The interface has continued to progress through the tablet allowing for more matrix to become wetted and gelled. The unwetted core reduces to only a very small percentage of the tablet.

7.7. *TIME R_x and Syncro Dose*™

TIME R_x and Syncro Dose™ were developed by Penwest. It is designed to release the drug after a preprogrammed period of time. The novel oral controlled-release drug delivery system TIMERx is a pregranulated blend composed of synergistic heterodisperse polysaccharides (usually xanthan gum and locust bean gum) together with a saccharide component (generally dextrose). It can be used for the treatment of diseases of the large intestine, such as ulcerative colitis and Crohn's disease. It consists of drug containing core part and bio degradable coating layer of xanthan gum and locust bean gum (Fig. 5). Xanthan gum consists of two β-D-glucose units linked through the 1 and 4 positions, with side chains consisting of two mannose and one glucuronic acid units. Interaction between two of these chains give a double helix like structure to the xanthan gum, which swells in the presence of water. The locust bean gum works synergistically with the xanthan gum and forms a tight gel structure, which retards water penetration into the dosage form, and as a result, controls the release of the active ingredient (Baichwal, Woodcock, & Labudzinski, 2005; Penwest, 2011; Staniforth & Baichwal, 2005).

7.8. *TARGIT*™ *technology*

TARGIT™ technology is developed by West Pharmaceutical London, UK. It comprises of an enteric-coated injection-moulded starch capsule system that is designed for targeting specific delivery to the colonic region. The starch capsules are coated with gastric resist polymers like CAP, HPMCP, Polyvinyl acetate phthalate and mostly mixture of Eudragit L, Eudragit S (Watts & Smith, 2005).

8. Conclusion

There has been tremendous interest in developing colon targeted drug delivery systems over the last decade, but only enteric-coated colonic tablets have been able to hit the market so far. The vagaries in pH of different organs of the GIT pose problems for those systems that take into consideration specific values of pH for their activation. Microflora-activated systems appear to be more promising because the abrupt increase of the bacteria population and associated enzyme activity in the colon represent a non-continuous event independent of gastrointestinal transit time.

Chemical modifications made to polysaccharides make it possible to reduce release of the drugs in the gut. However, the kinetics of degradation and of solute release from hydrogels depends on numerous parameters and on the nature of the drugs. For these reasons, the formulation of a hydrogel designed to permit specific drug delivery to the colon, is dependent on the physicochemical characteristics of the drugs incorporated into the dosage forms. Combinations of polysaccharides and polymers that are either insoluble or soluble at colonic pH have been tested. These combinations are based on the erosion and swelling of film coatings all along

the gastrointestinal tract and degradation of polysaccharides in the colon. While some in vitro studies with Eudragit® would appear to be promising, more in-depth investigation is still required. Moreover, in vivo studies must be carried out to confirm the interesting results obtained in vitro with these combined polymers.

Prodrugs seem to be promising therapeutic agents for the management of diseases of the lower bowel due to their ability to show the required action with lower doses as they release the entire dose at the site of action. Additionally, they reduce the side effects compared to the parent drug. Such systems can be formulated in a much easier manner and many technical difficulties faced in preparation of other types of colon specific delivery systems, like coated, multiple coated, systems, etc., can be avoided. These agents, however, are new chemical entities and require more detailed toxicologic studies before they can be used as colon carriers. Also the biologic effects of the various carrier molecules need to be investigated further.

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