

Comprehensive Overview of Carbohydrate Polymers

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Abstract

Targeting drug delivery specifically to the colon has become increasingly crucial for treating various colonic diseases like colorectal cancer, amebiasis, ulcerative colitis, and Crohn's disease. Numerous strategies have been developed for this purpose, including using enzymatically degradable polymers, employing prodrug-based approaches, coating drugs with polymers sensitive to time or pH changes, utilizing osmotically and pressure-controlled delivery systems. Polysaccharides activated by the colon's physiological environment show significant potential as they offer enhanced site specificity and address therapeutic requirements effectively. However, delivery systems relying solely on a single polysaccharide often fail to ensure precise targeted release due to variations in pH and transit time among individuals and disease states. Traditional methods often result in premature drug release. To overcome these challenges, combining or chemically modifying polysaccharides has been explored, effectively mitigating the limitations associated with single polysaccharide use. This review explores emerging approaches in this field, reexamines current technologies, and outlines future developments.

Keywords: Colonic diseases, targeted drug delivery, enzymatically degradable polymers, polysaccharides, site specificity

INTRODUCTION

Carbohydrates are sometimes known as “carbon hydrates.” They are made up of simple sugars with the empirical formula $C_nH_{2n}O_n$, where n is ≥ 3 and denotes that water and carbon atoms have been joined in some way. There has been a substantial rise in the number of reviews that cover the broad topic of carbohydrate medicinal chemistry as a result of the extremely promising and exciting development of carbohydrate-based drugs in modern medicine and chemistry. This demonstrates the growing significance of these recent advances in carbohydrate-drug design, with a particular emphasis on novel synthetic pathways and their use in colon-specific delivery. The availability and low cost of carbohydrate polymers of monosaccharide have drawn a lot of interest for medications that target the

colon. Natural polymers are used for colon-targeted administration because anaerobic bacteria in the colon can recognize different substrates and break them down with enzymes. The unique property of natural polymers, which make them ideal for colon-targeted delivery due to their stability in the gastric environment of the upper GIT, has also garnered a lot of interest [1].

The single polysaccharide-based colon-specific delivery technologies do not effectively support focused release. Depending on the person and the specific disease state, the pH and transit time may change. In certain circumstances, drug release may be erratic or non-existent altogether. The disadvantages of using a single polysaccharide were removed by combining them or creating

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chemically modified forms of them. The usage of polysaccharide combinations and their structurally/chemically modified forms is being used in industrial research. In this review, a focus is placed on the use and characteristics of modified or combined carbohydrate polymers used for colon-specific administration [2].

CARBOHYDRATE POLYMER

The pharmaceutical industry and researches for creating colonic drug delivery systems/technology have paid close attention to carbohydrate polymers. Because they are readily available, affordable and adaptable to more sophisticated forms [3].

The effectiveness of a single carbohydrate is lower than that of its modified form or combination with another polymer. With the right cross-linking agent, carbohydrates polymer like guar gum, pectin, chitosan, etc. can be joined together. The desired drug release is controlled by the cross-linked polymers (Figure 1). Different carbohydrate polymers are described in the book along with their source and structural unit [4].

Guar Gum

Guar gum's large molecular weight results in a very viscous solution in cold water. Cold water makes guar gum soluble, and it hydrates quickly to form viscous pseudoplastic solutions that, despite generally having greater low-shear viscosity than other hydrocolloids, are shear thinning. Guar gum gelling delays medication release and makes it vulnerable to colonic area degradation. The enzymatic degradation and swelling properties of the changed products are superior. Guar gum and glutaraldehyde were combined in an acidic environment to produce a variety of compounds with varying crosslinking densities (Figure 1). By crosslinking guar gum with trisodium trimeta phosphate, glutaraldehyde, which was capable of transporting drug to the colon, it was possible to prevent premature drug release [5].

The creation of DAVANAT®, a modified galactomannan from guar gum or *Cyamopsis tetragonoloba*, uses the good manufacturing practice (GMP). Pro-Pharmaceuticals, Inc. is creating DAVANAT®. DAVANAT® is a galactomannan with a backbone made up of (14) linked d-mannopyranosyl units to which single d-galactopyranosyl residues are intermittently attached via a (16)-linkage. An average polymeric molecule of DAVANAT® contains about 12 of these repeating units on average. On April 11, 2007, the Food and Drug Administration (FDA) communicated with Pro-Pharmaceuticals regarding the new drug application (NDA) for DAVANAT®/5-FU. Subsequently, in December 2008, Pro-Pharmaceuticals submitted the drug master file (DMF) for DAVANAT® to the FDA, along with data supporting its NDA for treating advanced colorectal cancer [6].

To assess DAVANAT®'s properties, various analytical methods were employed, including ¹³C nuclear magnetic resonance (NMR), size exclusion chromatography with multi-angle laser light scattering (SEC-MALLS) for determining molecular weight, and anion exchange liquid chromatography with pulsed amperometric detection (AELC-PAD) for analyzing carbohydrate composition, confirming uniformity, and ensuring purity. In preclinical experiments using nude mice colon and breast cancer models, significant enhancements in efficacy were observed with 5-fluorouracil, doxorubicin, irinotecan, and cisplatin [7].

DAVANAT® is designed to target specific receptors on cancer cells, potentially including galectins, though not exclusively. It aims to enhance the effectiveness of anti-neoplastic medications. Originally, DAVANAT® was intended to act as a facilitator alongside 5-fluorouracil (5-FU) by utilizing its polymeric mannose backbone with galactose side chains, enabling interaction with

galectins, receptors specific for galactose residues (both α and β -galactose, as recently demonstrated). Because 5-FU has been the traditional first-line treatment for metastatic colorectal cancer for more than 40 years, it was chosen as the chemotherapeutic medication in the DAVANAT® combination [8].

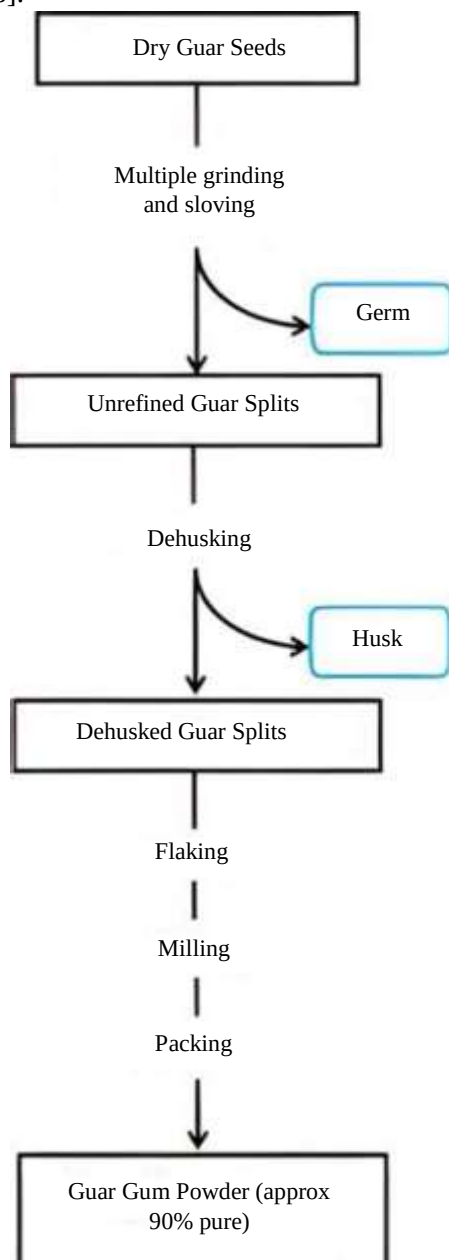


Figure 1. Schematic flow chart for guar gum extraction [9].

Roos and colleagues developed a hydrogel comprising O-acetyl-galactoglucomannan (AcGGM) and bovine serum albumin (BSA). AcGGM's degree of substitution (DS) was altered chemically by 2-hydroxyethyl methacrylate (HEMA), an acrylate derivative, and enzymatically by α -galactosidase. With a drop in DS, AcGGM is more hydrolyzed by α -mannanase. The inclusion of mannanase significantly enhanced the release of BSA from hydrogels with a DS of 0.36, with up to 95% of BSA liberated after 8 hours, compared to only 60% released in the absence of the enzyme.

Pectin

The fact that pectin can be broken down by colonic bacteria and is resistant to gastric acid is its most desired quality. The amount of methyl ester substituents in pectin varies depending on the plant source and processing. By producing calcium pectinate, the solubility of pectin can be reduced for a more dramatic shielding effect. The methyl groups also have an impact on pectin's solubility and gelation. Higher methoxy pectins need a pH of about 3 and fewer soluble particles in order to gel. While low methoxy pectin's do not require either sugar or acid to gel, they do require a controlled amount of calcium ions. Pectins react with calcium salts or multivalent cations to generate stiff gels when the esterification level is less than 50%, which crosslinks the pectin's. the primary polymer chains' galacturonic acids, which are the most desirable. The carboxylic acid groups present in pectin molecules interact with calcium ions, forming an ionic bond to create calcium pectinate. The structure that results resembles a "eggbox" Methoxy pectin content has an impact on how drugs are released from polymer matrixes. Pectin from various sources, with varying molecular weights and degrees of esterification, were used by Muhidinov et al. to create a new microcapsular system delivery for colon delivery [10].

The investigation focused on prednisolone as a model drug. It consists of (1→4)-linked α -d-mannopyranosyl units, with single α -d-glucopyranosyl units attached. The chemical structure of Davanat's repeat unit was examined, revealing it as a galactomannan with periodic attachment of galactopyranosyl residues via a (1→6)-linkage. On average, each repeating unit contains 17 α -d-Man residues and 10 α -d-Gal residues, with approximately 12 such repeating units in the polymeric molecule. The binding domain of Davanat on gal-1 was explored, revealing residues on the folded structure of gal-1 that are most influenced by Davanat binding. This interaction occurs at a site distinct from the conventional galectin carbohydrate binding domain. Additionally, the release kinetics of low water-soluble drugs from pectin microcapsules were investigated, with microcapsules derived from highly methoxylated apple demonstrating the highest drug dissolution/diffusion rate [11].

When anionic surfactants and calcium ions are present with pectin instead of for the highly charged citrus pectin systems. Capsule made with ethyl acetate also displayed retarded drug release, although there was substantially less medication enclosed compared to those made by other emulsion techniques. The study concluded that using biodegradable pectin polysaccharides in manufacturing of colon-specific drugs using a variety of different drug delivery systems Delivery [12].

Chitosan

The percentage of GlcNAc residues in the polymer chain is determined by the level of acetylation which has a substantial impact on the physico-chemical characteristics of chitosan, including solubility, reactivity, biodegradability, and cell responsiveness. Although water-soluble derivatives (such carboxylated derivatives) can also be found, the majority of them are acid-soluble. Commercial chitosan production involves deacetylating chitin. It is a hydrophilic, cationic, and crystalline polymer with the capacity to gel and form films [13].

Chitosan's capacity to extend the gas's period in residence Mucoadhesion in the gastrointestinal system, as well as its capacity to increase permeability and increase absorption, have all been significant considerations influencing its broad assessment as a part of oral dosage styles. Despite the remarkable scientific advancement no progress has been made in the use of chitosan in medication delivery systems Drug delivery methods based on chitosan have been introduced to a market yet. However, given that there are current clinical trials for a variety of chitosan-based products can be used in a variety of medicinal formulations.be anticipated soon, and it has already been suggested that In drug delivery systems, chitosan might be the carrier material of the twenty-first century In the

mouse dextran sulfate sodium (DSS) model al. investigated the efficiency of several resveratrol prodrugs and pro-prodrugs to reduce colon inflammation. A very low dose of either resveratrol-3-O-(6'-O-butanoyl)-D-glucopyranoside (6) or resveratrol-3-O-(6'-O-octanoyl)-D-glucopyranoside (7) was given to mice, and it prevented the development of colitis symptoms and improved the disease activity index (DAI) six times over resveratrol. According to the study, these pro-prodrugs had two effects: (1) they prevented resveratrol from being rapidly metabolized and increased the amount of resveratrol delivered to the colon; and (2) they reduced mucosal barrier imbalance and stopped diarrhea, which in turn made it easier for the delivered resveratrol to act on the colon mucosa (Iarrosa et. 2010) [14].

Structural formula of a carbohydrate polymer, showing linked monosaccharide units and protein model with lactose binding site and dimer interface are shown in figure 2.

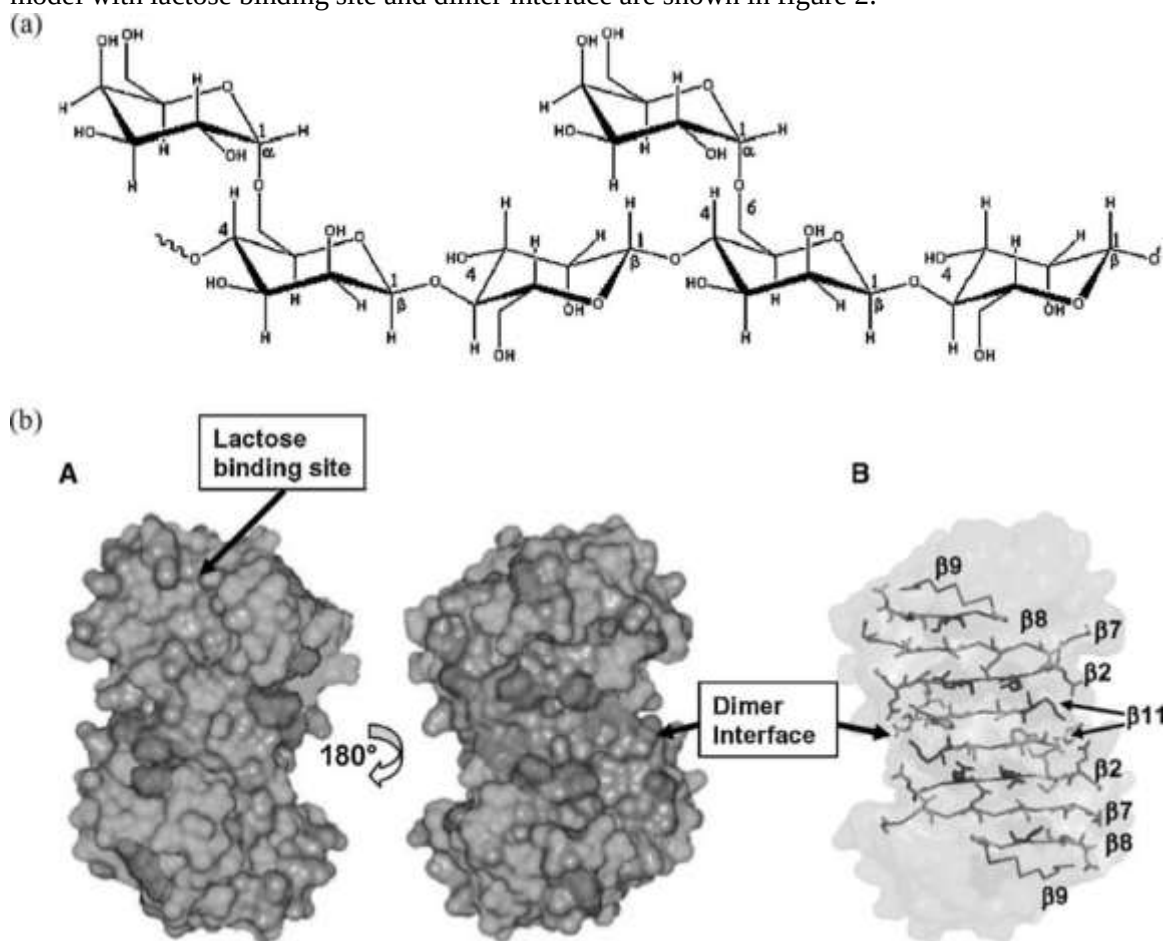


Figure 2.(a) Structural formula of a carbohydrate polymer, showing linked monosaccharide units. (b) Protein model with (A) lactose binding site and (B) dimer interface.

Alginate

Drug release from the core is delayed by the gastric medium's polysaccharide gel formation. Alginates do not gel because they include stiff poly (l-guluronic acids), which gel in the presence of calcium ions, hence the presence of calcium ions is required. When clusters of guluronic acid residues interact with divalent cations, commonly calcium ions, gelation of alginate takes place, forming a three-dimensional network often represented by an "egg-box" model. The colonic swelling and subsequent degradation of sodium alginate are thought to be caused by the ion exchange mechanism between sodium and calcium ions. Ionic characteristics affect the swelling and mechanical characteristics of alginate, which is created via ionic crosslinking with cations (shah et. al. 2011) [15].

Dextran

Water soluble dextran is easily functionalized by its hydroxyl-reactive chemical processes. The spontaneous enzymatic breakdown of polysaccharide bonds is how biodegradation takes place by the liver, spleen, lungs, brain, and other organs' dextran-1,6-glucosidase by dextranases produced in the colon by bacteria. A dextran Lacking non-specific cell binding, resists protein, and expanded its application as a biomaterial. The hydroxyl properties due to dextran's chemical alteration and affordable price availability has enhanced the field of medicine's use of conjugates of polysaccharide polymers for biomaterials ((Hu & Jing, 2009; Lee, Jeong, Kang, Lee, & Park, 2009) [16].

Dextran's methacrylated and succinic derivative, Dex-MA-SA, and a methacrylated and succinic derivative were used to create a novel pH-sensitive and biodegradable composite hydrogel. OF PHEA, short for poly(N-2-hydroxyethyl)-dl-aspartamide. The PHM-SA was ready. The was to acquire a colon-specific medication Utilizing a delivery mechanism that takes advantage of both pH-sensitive behavior and Degradability specific to the colon. A was used to prepare the hydrogel. Appropriate polysaccharide to polyamino acid ratio. It Cellulose is commonly utilized as a tablet excipient because it exhibits swelling behavior under gastrointestinal simulation circumstances and is chemically and enzymatically degradable. (Liu et al., 2003; Raymond, Paul, & Sian, 2006; Sarfaraz, 2004) [17].

Cellulose esters are divided into two main categories: non-enteric and enteric. Non-enteric esters, including cellulose acetate, cellulose acetate butyrate (CAB), and cellulose acetate propionate, lack pH-dependent solubility and are generally insoluble in water, with rare exceptions in commercial products. These non-enteric cellulose esters can be employed to sustain drug release from oral delivery systems by forming either a matrix or an impermeable yet soluble film. On the other hand, enteric esters, such as cellulose acetate phthalate (CAP) or hydroxypropyl methylcellulose phthalate (HPMCP), are insoluble in acidic environments but exhibit solubility in mildly acidic to slightly alkaline solutions. (Bassi & Kaur, 2010; Kosaraju 2005) [18].

Cellulose Acetate Phthalate

CAP is utilized in oral controlled release formulations and as an enteric polymer. This cellulose polymer undergoes esterification where half of its hydroxyl groups are acetylated, a quarter are esterified with one to two carboxyl groups from phthalic acid, while the remaining hydroxyl groups remain unmodified. CAP has been utilized as a medicinal excipient for many years and possesses pH-dependent solubility. While CAP coated formulations are easily soluble in mildly alkaline medium (intestine), they are resistant to acidic pH (gastric fluids). The degree of substitution mostly determines the pH dependent solubility of CAP [19].

Cellulose Derivatives

The primary structural component of the cell wall in oomycetes, diverse algae, and green plants is cellulose. Some bacterial species secrete material to create biofilms. The most prevalent material is cellulose. Earth's chemical compounds (Mandal et al., 2010). roughly 33% of Cellulose makes up all plant stuff; cotton has a 90% cellulose content. 40- 50%), and that of wood. A linear strand of molecules called cellulose is a few hundred to over ten to us and 1,4 connected d-glucose units, as opposed to 1,3 linked starch. Cellulose is made of these 1, 4 connections. Human indigestible, very crystalline, and linear [20].

Because it has a limited potential for toxicity and is not systemically absorbed after oral administration, cellulose is a generally acknowledged as safe (GRAS) listed substance. Cellulose is a kind of the most significant food and medicinal excipients. created the pectin-HPMC compression coated tablet labeled with 4MBq (99m) Tc-DTPA. The authors examined the in vivo behavior of tablets by placing three of six healthy male volunteers in the ascending colon (AC) and the remaining three in the transverse colon (TC).The hydrogel coating encasing the core tablet was thought to have

become more hydrated after extended stay at the ileocaecal junction (ICJ). Insufficient hydration of the hydrogel layer prior to tablet breakdown may have hindered the access of pectinolytic enzymes and reduced fluid availability in the transverse colon, potentially delaying tablet breakdown and radiolabel diffusion [21].

HPMC

Hypromellose (INN), also known as HPMC, is a solid that resembles an off-white to beige powder and can be made into granules. Unlike methyl cellulose, hypromellose does not exhibit heat gelation in an aqueous solution. The amount of methoxy determines how rigid/viscous the HPMC solution is. The solution will be more viscous or less flexible the higher the methoxy content [22].

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 HPMCP 50, 55 and HP-55-S. HPMCP is the Trade name for hydroxyl propyl methyl cellulose phthalate. These Polymers dissolve at lower pH 5–5.5 than CAP or acrylic polymers [23].

HPMC- NACMC

Diclofenac potassium and dicyclomine hydrochloride were produced as a microporous bilayer osmotic tablet for distribution to the colon. As osmogens, HPMC and NACMC were employed. The quantity of the pore forming in the semipermeable membrane determined how many pores there would be. Results from in vitro dissolution tests demonstrated that the system added resistance, timed release, and could distribute the medication at a roughly zero order for up to 24 hours [24].

Chitosan-HPMC

HPMC and chitosan acetate (CSA) can be used as compression coat additives. Nunthanid et al. used spray drying CSA and novel compression-coats on HPMC to manufacture the 5-ASA tablet. They investigated the tablet's applicability by looking at the impact of pH and enzymatic

Breakdown. When delivering colon. The α -glucosidase-mediated CSA degradation in the While adding a disintegrant or an osmotic agent to the core tablets would alter the medicine colonic fluid improved drug release [25].

Human electric coated chitosan based drug delivery method for metronidazole distribution to the colon as created by Priscileila et al. Because enteric polymers, such as CAP and HPMCP, are insoluble in conditions with low pH levels, they were included. Since their swelling capacity can be adjusted by changing the composition the results showed that relatively simple drug carrier systems that can reach the colonic environment can be created [26].

Pectin-HPMC

Ugurlu et al. created compression coated nisin tablets using various pectin/HPMC mixtures. The nisin containing core tablets could not be sufficiently protected by pectin on its own. The conclusion of the for 100% pectin tablets, 6 hours later, 40% deterioration was seen. HPMC a 5% increase is necessary to manage the solubility of pectin. A 2 hour lag period for the change in HPMC ratio in the pectin/HPMC combination release of nisin. 80% pectin and 20% HPMC appeared to be an best combination for additional analysis. Hodges et al. created the pectin-HPMC compression coated tablet labeled with 4MBq (99m) Tc-DTPA. The in vivo behavior of tablets was examined in six healthy male volunteers, with three individuals positioned in the ascending colon (AC) and the remaining three in the transverse colon (TC). The hydrogel coating encasing the core tablet was thought to have become more hydrated after extended stay at the ileocaecal junction (ICJ). Insufficient pre-hydration of the hydrogel layer might have hindered access to pectinolytic enzymes, thereby potentially

delaying both tablet breakdown and radiolabel diffusion. Additionally, reduced fluid availability in the transverse colon could have contributed to this delay [27].

Alginate- Chitosan

A multi-particulate approach was developed to deliver celecoxib specifically to the colon, aiming to address both systemic needs, such as in the chronotherapeutic management of arthritis, and local requirements, like in the prevention of colon carcinogenesis. The A ternary complexation system with hydroxypropyl-PVP (polyvinyl pyrrolidone) with cyclodextrin, to enhance drug.Chitosan-Ca-alginate microspheres' solubility and vectorization,To make use of these polymers' colon-specific carrier characteristics. Anexperimental statistical design was used to demonstrate [28]. Alginate, CaCl₂, chitosan, and time of cross-linking all have an impact on how well microspheres entrap drugs that are released after 4 hours in colonic medium. In the framework of Quality by Design (QBD), which necessitates a multivariate approach to comprehend the multifactorial interactions among formulation parameters, design of experiment was applied. The desired outcomes for both systemic and local applications of celecoxib were effectively achieved. These findings demonstrated the viability of the combined use of the medication cyclodextrin complexation and the chitosan-Ca-alginate microsphere [29].

Ethyl Cellulose–Starch Combination

Dispersion of high amylose starch (Hylon VII) and ethyl cellulose (Surelease) (1:2, w/w) of (5-aminosalicylic acid; 5-ASA) was used to coat the colon targeted pellets that Freire et al. manufactured. Developed In vivo testing of the formulation was done on rabbits. The pills with coatin Were able to withstand the release of the medication in the stomach and small intestine And were able to provide the colon with the maximal load [30].

A unique polymeric film was created for the site-specific administration of medications to the colon of patients with inflammatory bowel disorders. Different kinds of derivatives of bacteria-sensitive starch were combined with ethyl cellulose (EC). The systems' water uptake and dry mass loss kinetics were observed when exposed to simulated stomach, small intestine, and colon contents, including fresh fecal samples from patients with Crohn's disease and Ulcerative Colitis. Among them, EC: Nutriose FB 06 and EC: Pea starch N-735 films displayed promising water uptake and dry mass loss kinetics across all tested media, suggesting their potential to mitigate premature drug release in the upper gastrointestinal tract and facilitate controlled release upon reaching the colon [31]. Additionally, Karrou et al. investigated inflammatory bowel diseases using film-coated pellets of Eurylon 6 HPPG, a hydroxypropylated and pregelatinized high amylose starch.In 0.1 N HCl and phosphate buffer, 5-ASA release could be successfully controlled.pH 6.8, with or without pancreatin or pepsin, but occurring . The moment the pellets made contact with culture medium that had been injected with feces from patients with inflammatory bowel disease. This is caused by the starch's partial break down. By product produced by bacterially produced enzymes in the colon of Patients. The created formulation is adaptable to the pathophysiological circumstances individuals with inflammatory bowel disease. In addition, medication release was unaffected after a year [32].

The 5-ASA-loaded beads made by extrusion-spheronization and coated with various Nutriose: EC blends were also examined by this group. It's interesting to note that, regardless of the level of agitation and the presence or absence of enzymes, the release of 5-ASA could be successfully controlled when exposed to release media replicating the conditions in the upper GIT. Nevertheless, once the pellets came into contact with fecal samples from patients with inflammatory bowel disease, there was a significant surge in the release rate, leading to the immediate release of the medication in a time-controlled manner [33].

Ethyl Cellulose–Carbopol Combination

Ali et al. developed indomethacin matrix tablets for colon cancer treatment, employing various combinations of ethyl cellulose and Carbopol. Utilizing a hydrophilic polymer matrix containing ethyl cellulose resulted in a sigmoidal in vitro drug release profile, characterized by minimal to very low

drug release during the initial phase (0-6 hours), followed by controlled release for 14–16 hours. The presence of ethyl cellulose, which controls the swelling of hydrophilic polymers, likely contributed to the reduced initial release. However, improved indomethacin release during the later phase was facilitated by polymer relaxation under alkaline pH conditions, induced by the ionization of acrylic acid units in Carbopol and polycarbophil. It was possible to obtain a sigmoidal release pattern that would be suitable for indomethacin colonic administration in the prospective treatment of colon cancer [34].

Pectin–Chitosan

Bigucci et al. investigated the vancomycin release characteristics from the poly electrolyte complex of pectin-chitosan. According to release studies carried out in the presence of beta-glucosidase, the specific composition of these complexes enhanced vancomycin availability at alkaline pH on the basis of an enzyme-dependent degradation [35].

This group went one step farther and created vancomycin hydrogels systems using pectin and chitosan. According to their research, vancomycin release from pectin/chitosan microspheres was restricted under acidic conditions while it was released under alkaline conditions. Confirmed their potential as a colon-specific medication delivery method under simulated colonic circumstances [36].

Amidated Pectin–Chitosan–Enteric Polymers

Chitosan and amidated pectin were used to construct the multi particulate triamcinolone colon-specific delivery system by Giselle et al. The method successfully included HPMCP and CAP, which helped the carbs perform their intended function. The in vitro drug release tests revealed that the PC:CS:TC particles had better control over drug release in all media when both enteric polymers, CAP and HPMCP, were added. In a replica colonic media, particles from all charges likewise demonstrated enzyme-controlled drug release characteristics. The greatest control over the drug release across all media was achieved with the inclusion of CAP and HPMCP. Only 1.33% of the medication was released by the CAP:TC formulation after two hours in an acidic medium, compared to 45.52% by the control formulation [37].

Guar Gum–Chitosan

For local adjuvant or neoadjuvant treatment of colorectal cancer, guar gum and chitosan polysaccharide films coated with celecoxib were created. A recurrent low-dosage regimen and a single large dose were compared in terms of their effects. Dosing in vivo. The perfused intestine of a rat was used for tests with Cx. The rat that was sedated. The research recommended maximizing therapy effectiveness while exposing healthy tissue as little as possible. For exploiting biodegradable polysaccharide composites as a local delivery system, such as the suggested adhesive [38].

Using diltiazem hydrochloride as the reference medicine and natural polysaccharides such chitosan and guar gum as the carriers, Ravi et al. created a unique colon targeted tablet formulation. Studies conducted in vitro showed that the inulin and shellac-coated tablets restricted drug release in the stomach and small intestine while releasing the greatest amount of medication into the colon. The study showed that colon medication targeting for both local and systemic illnesses may be successfully accomplished using polysaccharides as carriers, inulin, and shellac as coating materials [39].

Guar Gum–Alginate

Tugcu created a matrix tablet out of guar gum and alginate for the delivery of ondasetron to the colon specifically for the treatment of IBD. Irritable bowel syndrome (IBS) patients' visceral sensitivity and motor activity inhibition were systemically reduced by the proposed formulation [40].

Chitosan–Alginate

Tugcu created a matrix tablet out of guar gum and alginate for the delivery of on dasatron to the colon specifically for the treatment of IBD. With the created formulation for chronotherapeutic delivery, it was possible to diminish visceral sensitivity and inhibit motor activity in patients with irritable bowel syndrome (IBS). Delay in release is shown to be caused by guar gum's gelling capabilities and Eudragit's pH-dependent solubility behaviour. Colon-specific guar gum-based multi-unit pellets were created by Jietal. In a fluid-bed coater, the pH-sensitive polymer Eudragit FS30D was successively applied to the guar gum to coat the drug-loaded non-pareil cores. The distal small intestine, where a lumen pH of over 7 initiates the dissolving of the enteric polymer, is where the outer Eudragit FS layer, which shields the system from the gastrointestinal environment, dissolves quickly. The pellets are further protected by the inner guar gum coating, which functions as a time-controlled retardant until it is broken down by microbial enzymes in the proximal colon. Guar gum is a workable coating material to accomplish timed and enzyme-triggered fluorouracil release, according to in vitro studies. A study on the pharmacokinetics of beagle dogs reveals a delayed absorption of roughly 5 hours and a small absorption fraction [41].

Dextran–Chitosan

A polyelectrolyte complex (PEC) was formed through either wet phase-inversion or ionotropic crosslinking methods involving sodium tripolyphosphate (Na^+ -TPP) and dextran sulfate (DS). The PEC was made up of porous chitosan hydrogel microspheres of ibuprofen. The CS/TPP/DS microspheres withstood biodegradation in enzymatic conditions as well as hydrolysis in high acid. The swelling kinetics of CS microspheres exhibited non-Fickian behavior, while those of CS/TPP and CS/TPP/DS approached Fickian diffusion. Ibuprofen released slowly from CS/TPP/DS microspheres over three hours in simulated gastric fluid (SGF, pH 1.4), but upon switching to simulated intestinal fluid (SIF, pH 6.8), nearly all initial ibuprofen content was released within six hours. Overall, the findings showed that hydrophobic drugs may be successfully delivered to the intestine using CS/TPP/DS microspheres without experiencing drug degradation in the stomach, and might therefore be candidates for use as an oral colon medication delivery method [42].

Guar gum–Eudragit

Ji et al. created an indomethacin multi-unit delivery system that is pH and enzyme dependent and targets the colon by sequentially coating drug-loaded pellets with guar gum and Eudragit FS30D. A pharmacokinetic investigation in beagle dogs revealed that uncoated pellets had the quickest absorption and the smallest T_{max} and T_{lag} values. The T_{max} and T_{lag} of pellets coated with Eudragit FS30D were delayed to approximately 2.5 and 1 hours, respectively. T_{lag} was further delayed to approximately 2.8 h after another guar gum coating, adding an additional 2 h of lag time based on the Eudragit FS30D coating. The outcomes suggested that the system coated with guar gum and Eudragit FS30D may be employed to deliver medications to the colon. [43]. Theophylline (THEO), a colon-targeted drug delivery system that uses pH-enzyme sensitivity to avoid asthma episodes in the morning, was developed using a chronotherapeutic approach. Theophylline-containing guar gum microspheres were created using the emulsification method. Utilizing pH-sensitive Eudragit® polymers and the solvent evaporation process, microspheres were coated. The new formulation for chronotherapeutic delivery enabled the controlled release of THEO after a lag time. Delay in release is shown to be caused by guar gum's gelling capabilities and Eudragit's pH-dependent solubility behavior [44].

Pectin–Eudragit

Microsponges containing dicyclomine for colonic administration were created using the Eudragit S-100 platform. The microsponges were compressed, then coated with a pectin: HPMC mixture to create the colon-specific tablets. Compression-coated colon-specific formulations began releasing the medication at the sixth hour, which corresponds to the time the drug arrived at the colon, according to in vitro release experiments. An innovative method for colon-specific medication administration was revealed in the study [45].

CAP–Eudragit

Kotagale et al. created polymer-coated polysaccharide tablets to transport azathioprine specifically to the colon. By using varied ratios of avicelMicro Crystalline Cellulose (MCC), inulin, and triacetin, tablets were made using the direct compression method. The coating materials employed were cellulose acetate phthalate (CAP), eudragit-S, and eudragit-L. The concentration of the plasticizer (triacetin) caused an increase in drug release. The drug release is increased when inulin and citric acid concentrations rise over 5% (w/w). In the presence of rat cecal content, the addition of inulin to the formulation with a coating level of 28% (w/w) showed enhanced drug release. The findings showed that a formulation system with an inulin-containing ES, EL, and CAP (1:1:1) polymer coating may be employed to deliver azathioprine to specific locations with a desired release pattern [46].

Chitosan–Eudragit

To effectively distribute oxaliplatin (L-OHP) to colon cancers, hyaluronic acid-coupled chitosan nanoparticles enclosed in Eudragit S100-coated pellets were produced. With prolonged exposure period and relatively high local drug concentration in colonic cancers in mouse models, the drug delivery method offers the possibility of increased antitumor efficacy with less systemic damage [47].

In contrast to the pH responsive methods now employed for ulcerative colitis, Ibekwe and colleagues presented a unique dual-triggered colonic delivery system with better site-specificity. The system was made up of a single layer matrix film made of pH-responsive Eudragit S and resistant starch. Eight healthy participants participated in a three-way crossover research and received tablets. Gamma scintigraphy was used to determine the location of intestinal breakdown. The coated pills could withstand stomach and small intestine disintegration. The two bacterially and pH-triggered processes In healthy volunteers, coating was put to tablets and dosed a total of 23 times while they were fed under three distinct conditions: without meal, with breakfast, or 30 minutes before breakfast. During the study period, the tablet did not empty from the stomach, but of the 22 that did, breakdown took place at the ileo-caecal junction or in the large intestine, indicating that this approach was successful in targeting. Within a pH-responsive polymer, the separate triggers of a bacterially-triggered component are efficient, complimentary, and serve as failsafe mechanisms for one another [48].

The chitosan-succinylprednisolone conjugate microspheres (Ch-SP-MS/EuL) with a Eudragit L100 (EuL) coating were created for IBD. The most effective dose-dependent order for these microspheres' effectiveness was Ch-SP-MS/EuL > ChSP-MS > prednisolone (PD) alone, and Ch-SP-MS/EuL demonstrated good colitis state recovery. The toxicity increased in the following order: PD > >Ch-SP-MS > Ch-SP-MS/EuL. Thymic atrophy brought on by PD was greatly lessened by Ch-SP-MS and Ch-SPMS/EuL. It was proven that Ch-SP-MS/EuL significantly reduced the hazardous side effects of PD while increasing its effectiveness. Additionally, the prediction made by earlier in vitro and in vivo research was confirmed by these data [49].

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 show greater promise due to the sudden rise in bacterial population and enzyme activity in the colon, which occurs independently of the gastrointestinal transit time and presents a non-continuous event.

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