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Brief Review on Carbohydrate Polymer

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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.

Keywords: Colon specific delivery, Colonic diseases, Enzymatically degradable polymers, Polysaccharides, Prodrug based approach, Coating with time or pH-dependent polymers

Introduction

Carbohydrates are sometimes known as "carbon hydrates." They are made up of simple sugars with the empirical formula CnH2nOn, where n is Z3 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 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 (Fig. 1). Different carbohydrate polymers are described in the book along with their source and structural unit. [4]

1) 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 pseudo plastic 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 cross linking densities (Fig. 1). By cross linking guar gum with tri sodium 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 Cyamopsistetragonoloba, 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. The Food and Drug Administration (FDA) sent Pro-Pharmaceuticals a letter about the new drug application (NDA) for DAVANAT®/5-FU on April 11, 2007. Pro-Pharmaceuticals announced the submission of the drug master file (DMF) for DAVANAT® to the FDA in December 2008 along with data for the DAVANAT® NDA to treat advanced colorectal cancer. [6]

Standard analytical methods were used to identify and characterize the material's structure, along with the following methods: 13C nuclear magnetic resonance (NMR); size exclusion chromatography with multi-angle laser light scattering (SEC- MALLS) for

determining the absolute molecular weight; and anion exchange liquid chromatography with pulsed amperometric detection (AELC-PAD) for determining the composition of the material's carbohydrates and confirming its uniformity and purity. In nude mice colon and breast cancer models, preclinical experiments using 5-fluorouracil, doxorubicin, irinotecan, and cisplatin shown considerable degrees of efficacy augmentation. [7]

Targeting particular receptors on cancer cells possibly galectins, but not necessarily DAVANAT® is being developed to improve the effectiveness of anti-neoplastic medications. The original plan was to use DAVANAT® as a type of chaperon along with 5-fluorouracil (5- FU) to facilitate its delivery into the cancer cell because it has a polymeric mannose backbone carrying galactose side chains and is therefore allegedly capable of interacting with some galectins, which are receptors specific for galactose residues (both - and -galactose, as it was recently shown). 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]

Roos et al. created the O-acetyl-galactoglucomannan (AcGGM) hydrogel of bovine serum albumin (BSA). AcGGM's degree of substitution (DS) was altered chemically by 2- hydroxy ethylmethacrylate (HEMA), an acrylate derivative, and enzymatically by -galactosidase. With a drop in DS, AcGGM is more hydrolyzed by -manganese. Whenmannanase was added, the BSA release from hydrogels with a DS of 0.36 was greatly improved, and reaching a maximum of 95% liberated BSA after 8 hours as opposed to 60% without enzyme [9].

2) 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 methoxypectins 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 of [29].the pectin molecules and the calcium ions establish an ionic connection to form calcium pectinateestablish. The structure that results resembles an "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]

As a model drug, predsinolone was investigated. Is composed of (1→4)-linked -d-mannopyranosyl units to which Single -d-They looked into the. (a) Chemical structure of the repeat unit in Davanat. Davanat is a galactomannan, whose backbone galactopyranosyl residues are periodically attached via a (1→6)-linkage, with an average repeatin unit of 17 -d-Man residues and 10 -d-Gal residues, and an Average polymeric

molecule containing approximately 12 such repeating units. Dopted 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 rreferre. To the web version of the article.) Adopted with permission from. The -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 Rele. Low water-soluble drug release kinetics from pectin micro-capsules. Microcapsule from highly methoxylated apple had the highest drug dissolution/diffusion number. [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 ion of colon-specific drugs using a variety of different drug delivery systems Delivery. [12]

3) 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 Carboxylate derivatives) can also be found, the majority of them are acid-soluble. Commercial chitosan production involves deacetylatingchitinin. It is a hydrophilic, cationic, and crystalline polymer with the capacity to gel and form films. [13]

Chitosan 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. esveratrol 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.(larrosa et. 2010). [14]

4) 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 blocks of guluronic acid residues interact ionically with divalent cations (often calcium ions), alginate gelation occurs, creating a three-dimensional network that is typically modeled using a "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]

5) 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-glucosidaseby 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 dextrin'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]

Dextrin'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 can be distinguished into two categories, no 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) orhydroxypropylmethyl cellulose phthalate (HPMCP) which are insoluble in acidic solutions but soluble in mildly acidic to slightly alkaline solutions. (Bassi & Kaur, 2010; Kosaraju 2005). [18]

6) Cellulose Acetate Phthalate

CAP is utilized in oral controlled release formulations and as an enteric polymer. It is a cellulose polymer in which half of the hydroxyl groups are esterified with acetyls, a quarter is esterified with one to two carboxyls of phthalic acid, and the rest are left unaltered. 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]

7) Cellulose Derivatives

The major cell wall of oomycetes, various types of algae, and green plants is structurally made up of 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 90% cellulose content. 40- 50%), and that of wood. A linear strand of molecules called cellulose is a few hundred to over ten thousand 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. In six healthy male volunteers, three were placed in the ascending colon (AC) and three were placed in the transverse colon (TC), the authors investigated the in vivo behavior of tablets. The hydrogel coating encasing the core tablet was thought to have become more hydrated after extended stay at the ileo caecal junction (ICJ). Tablet breakdown and radiolabel diffusion may have been delayed by inadequate previous hydration of the hydrogel layer impeding access of pectinolytic enzymes and decreased fluid availability in the TC. [21]

8) HPMC

Hypromellose (INN), also known as HPMC, is a solid that resembles an of white to beige powder and can be made into granules. Unlike methylcellulose, hypromellose does not exhibit heat gelation in and 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]

9) HPMCP

HPMCP was introduced into the market in 1971 as an enteric Coating polymer. Shin Estuchemical 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 loser pH 5–5.5 than CAP or acrylic polymers. [23]

10) Hpmc- Nacmc

Diclofenac potassium and dicyclomine hydrochloride were produced as a micro porous belayed osmotic tablet for distribution to the colon. As osmogens, HPMC and NACMC were employed. The quantity of the pore forming in the semi permeable membrane determined how many pores there would be. Results from in vitro dissolution tests demonstrated that the systemic

resistance, timed release, and could distribute the medication at a roughly zero order for up to 24 hours. [24]

11) Chitosan-HPMC

HPMC and chitosan acetate (CSA) can be used as compression coat additives. Nunthanidetal. 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 -glycosidase-mediated CSA degradation in the While adding a disintegrate 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 Priscileilaet.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 rich the colonic environment can be created. [26]

12) Pectin-HPMC

Ugurlu et.al.created compression coated nisin tablets using various pectin/HPMC mixtures. The nisincontaining 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 HPMCa 5% increase is necessary to manage the solubility o pectin.A2 hour lag period for the change in HPMC ratio in the pectin/HPM C 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 labelled with 4MBq (99m) Tc-DTPA. In six healthy male volunteers, three were placed in the ascending colon (AC) and three were placed in the transverse colon (TC), the authors investigated the in vivo behaviour of tablets. The hydrogel coating encasing the core tablet was thought to have become more hydrated after extended stay at the ileo caecal junction (ICJ). Tablet breakdown and radiolabel diffusion may have been delayed by inadequate previous hydration of the hydrogel layer impeding access of pectinolytic enzymes and decreased fluid availability in the TC. [27]

13) Alginate- Chitosan

Created a multiparticulates method for the delivery of celecoxib to the colon specifically for both systemic (in the chronotherapeutic treatment of arthritis) and local (in the prevention of colon carcinogenesis) therapy. Chitosan-Ca-alginate microspheres' solubility and vectorization, to make use of thesepolymers'colon-specific carrier characteristics an experimental 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. Both systemic and local uses of celecoxib were successful in achieving their desired outcomes. These findings demonstrated the viability of the combined use of the medication Cyclodextrin complexation and the chitosan-Ca-alginate microsphere [29].

14) Ethyl Cellulose–Starch Combination

Dispersion of high Amylose starch (Hylon VII) and ethylcellulose (Sure lease) (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 ethylcellulose (EC). Upon exposure to media that simulated the contents of the stomach, small intestine, and colon (including fresh fecal samples from Crohn's disease and Ulcerative Colitis patients), the water uptake and dry mass loss kinetics of the systems were observed. Furthermore, EC: Nutriose FB 06 and EC: Peas starch N-735 films demonstrated highly encouraging water uptake and dry mass loss kinetics in all the investigated media, indicating their potential to reduce premature drug release in the upper gastro-intestinal tract and enable controlled release once the colon is reached [31].Inflammatory bowel illnesses were researched by Karrout et al. using film-coated pellets of Eurylon 6 HPPG (hydroxypropylated and pre-gelatinized high amylase starch). In 0.1 N HCl and phosphate buffer, 5-ASA release could be successfully controlled pH 6.8, with or without pancreatic 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 breakdown, byproduct 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. However, the release rate dramatically increased and the medicine was released in a time-controlled manner as soon as the pellets came into contact with fecal samples from patients with inflammatory bowel disease [33].

15) Ethyl Cellulose–Carbopol Combination

Indomethacin matrix tablets for colon cancer were made by Ali et al. using various combinations of ethyl cellulose and Carbopol. A hydrophilic polymer matrix containing ethyl cellulose led to a sigmoidal in vitro drug release pattern with negligible to very low drug release in the initial phase (0-6 h) and regulated release for 14–16 h. Ethyl cellulose, which regulates the swelling of hydrophilic polymer(s), may be the cause of the reduced initial release. However, in the later phase, improved Indomethacin release was achieved through polymer relaxation at alkaline pH as a result of the ionization of acrylic acid units on 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].

16) 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-glycosidase, 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].

17) Amidated Pectin–Chitosan–Enteric Polymers

Chitosan and amidated pectin were used to construct the multiparticulates 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].

18) 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 insulin 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, insulin, and shellac as coating materials [39].

19) Guar Gum–Alginate

Tugcu created a matrix tablet out of guar gum and alginate for the delivery of ondasatron 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].

20) Chitosan–Alginate

Tugcu created a matrix tablet out of guar gum and alginate for the delivery of ondasatron 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-pareilcores. The distal small intestine, where a lumen pH of over 7 initiates the dissolving of the enteric polymer, is where the outer Eudragit's 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].

21) Dextran–Chitosan

A polyelectrolyte complex (PEC) was created by either wet phase-inversion or ionotropic crosslinking with 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. While the swelling kinetics for CS microspheres was non-Fickian, those for CS/TPP and CS/TPP/DS were near to Fickian diffusion. Ibuprofen from CS/TPP/DS microspheres released slowly over a period of three hours in simulated gastric fluid (SGF, pH 1.4), but within six hours after switching medium, nearly all of the initial ibuprofen content was released in simulated intestinal fluid (SIF, pH 6.8). 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].

22) 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 Tmax and Tlag 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's FS30D coating. The outcomes suggested that the system coated with guar gum and Eudragit's 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].

23) Pectin–Eudragit's

Microsponges containing dicyclomine for colonic administration were created using the Eudragit'sS-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].

24) CAP–Eudragit

Kotagale et al. created polymer-coated polysaccharide tablets to transport Azathioprine specifically to the colon. By using varied ratios of avicel micro-Crystalline Cellulose (MCC), insulin, 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 insulin 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].

25) 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 pHresponsive 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-succinyl-prednisolone 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]. Dubey et al. created the Eudragit-S-100 coated chitosan microspheres for 5-ASA and camylo fine dihydro chloride to treat ulcerative colitis. According to in vivo research, microspheres targeted the colon well since they transported the majority of their drug load (76.55 2.13%) to the colon after 9 hours. According to the study, oral microspheres of both medications could be combined to specifically deliver medication to the colon and lessen ulcerative colitis symptoms [50].

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 gastro intestinal transit time.

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