J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 48(2): 696-713, 2024
Doi: 10.33483/jfpau.1400920

REVIEW ARTICLE / DERLEME MAKALE

MUCOADHESIVE POLYMERS IN COLON TARGETED DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

MUKOADEZİF POLİMERLERİN KOLON HEDEFLİ İLAÇ TAŞIYICI SİSTEMLERDE KULLANIMI: DETAYLI BİR İNCELEME

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ABSTRACT

Objective: *Mucoadhesive polymers have emerged as crucial components in the realm of drug delivery systems, particularly in the context of targeted treatments within the colon. These polymers possess adhesive properties that enable them to form temporary bonds with mucosal surfaces, extending the contact time of drugs with the colonic mucosa. This review provides a comprehensive overview of mucoadhesive polymers for colon drug delivery systems. Natural polymers such as chitosan and alginate, along with synthetic counterparts like polyacrylic acid derivatives, find application in these systems. The advantages of mucoadhesive polymers lie in their ability to facilitate site-specific drug delivery, thereby minimizing systemic side effects, and in enabling controlled and sustained release of drugs for improved bioavailability. Despite these benefits, challenges including variability in mucosal conditions and the imperative need for biocompatibility must be addressed. The applications of mucoadhesive polymers span diverse medical conditions, including targeted delivery of anti-inflammatory drugs for inflammatory bowel diseases, localized administration of chemotherapeutic agents for colon cancer treatment, and precise delivery of antibiotics for colonic infections.*
Result and Discussion: *As a promising avenue for optimizing colon drug delivery, mucoadhesive polymers offer great potential for the development of effective and well-tolerated treatments for various colonic disorders.*
Keywords: *Colon, colon drug delivery systems, mucosa, mucoadhesion, mucoadhesive polymers*

ÖZ

Amaç: *Mukoadezif polimerler, özellikle kolon bölgesinde hedefe yönelik tedaviler bağlamında, ilaç taşıyıcı sistemler alanında çok önemli bileşenler olarak ortaya çıkmıştır. Bu polimerler, mukozal yüzeylerle geçici bağlar oluşturmalarını sağlayan ve ilaçların kolon mukozası ile temas süresini uzatan yapışkan özelliklere sahiptir. Bu derleme, kolon ilaç taşıyıcı sistemleri için mukoadezif polimerlere kapsamlı bir genel bakış sunmaktadır. Kitosan ve aljinat gibi doğal polimerlerin yanı sıra poliakrilik asit türevleri gibi sentetik muadilleri de bu sistemlerde uygulama alanı bulmaktadır. Mukoadhezif polimerlerin avantajları, bölgeye özgü ilaç dağıtımını kolaylaştırma, böylece sistemik yan etkileri en aza indirme ve gelişmiş biyoyararlanım için ilaçların kontrollü ve sürekli salınımını sağlama yeteneklerinde yatmaktadır. Bu avantajlara rağmen, mukozal koşullardaki değişkenlik ve biyouyumluluk için zorunlu ihtiyaç gibi zorluklar ele alınmalıdır. Mukoadezif polimerlerin uygulamaları, enflamatuar bağırsak hastalıkları için anti-enflamatuar ilaçların hedefe yönelik*

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Submitted / Gönderilme : 06.12.2023
Accepted / Kabul : 24.01.2024
Published / Yayınlanma : 20.05.2024

olarak verilmesi, kolon kanseri tedavisi için kemoterapötik ajanların lokalize olarak verilmesi ve kolon enfeksiyonları için antibiyotiklerin hassas bir şekilde verilmesi dahil olmak üzere çeşitli tıbbi koşulları kapsamaktadır.

Sonuç ve Tartışma: *Kolon ilaç dağıtımını optimize etmek için umut verici bir yol olan mukoadezif polimerler, çeşitli kolonik hastalıklar için etkili ve iyi tolere edilen tedavilerin geliştirilmesi için büyük bir potansiyel sunmaktadır.*

Anahtar Kelimeler: *Kolon, kolon ilaç taşıyıcı sistemler, mukoza, mukoadhezyon, mukoadhezif polimerler*

INTRODUCTION

The field of colon-specific pharmaceutical delivery systems is constantly evolving. Colonic drug administration has grown in significance for the systemic distribution of anti-asthmatic, anti-hypertensive, and anti-diabetic agents as well as for the delivery of pharmaceuticals for the local treatment of colon disorders including Crohn's illness and other similar conditions. To handle the limitations of the prior method and target the colon, new technologies and systems have been created.

Solid dosage forms for oral administration have historically been created to release their drug content in the upper gastrointestinal tract (GIT), where the environment is typically more favorable for drug absorption and dissolution. Managing the rate and position of the drug's release from drugs taken orally has recently received more attention in order to improve the patient's compliance and therapeutic effectiveness [1,2].

The term "targeted drug delivery system" refers to a method of introducing a therapeutic dose of pharmaceutical to a specific location in the body to achieve the required concentration of drug. Several factors, including unstable situation, a weak solubility, limited half-life, wide volume of the dissemination, weak absorption, weak specificity, and therapeutic index, can cause a pharmaceutical to be targeted toward an area of interest. The benefits of aimed drug delivery include raising the drug's therapeutic potency, limiting drug degradation, minimizing unwanted effects, and lowering the drug's unsafe dose [3].

For localized therapy of a number of colonic diseases, the colon was used as an aim for delivery of pharmaceuticals into the lower gastrointestinal system. The colon-specific system for drug delivery must be able to preserve the drug while it is being transported to the colon, which means that neither drug release nor absorption should take place in the stomach as well as small bowel, nor should the bioactive ingredient degrade during either of the the dissolution tests, but only once the system has arrived at the colon [4].

A higher concentration of the pharmaceuticals can reach the colon with less systemic absorption when it is delivered particularly to the colon rather than initially being absorbed in the upper digestive tract. The colon is the primary location for drug delivery, as the colonic mucosa is known to aid in the absorption of various medications and colonic contents have a longer retention time (up to five days). An oral or rectal route might be used to deliver a medication to the colon. Due to their simplicity, oral dosage forms are an extremely popular method of delivery for colon-specific administration [5,6].

Additionally, oral dose forms don't require sterile preparation, provide more design and manufacturing flexibility, improve patient compliance, and are generally safe to administer [7]. Targeting a medicine to particular areas in the colon is difficult with direct rectal delivery of pharmaceuticals [8]. The rectum provides the quickest route for administering medications to the colon, although it is challenging to reach the proximal region of the colon by the rectal route. The rectal route is challenging and uncomfortable for the patient, which reduces adherence among patients [9].

Colon drug delivery systems (CDDS) protect peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum and eventually release the drug into ileum or colon which results in greater systemic bioavailability. The colon is believed to be a suitable absorption site for peptides and protein drugs such as insulin and vasopressin for the following reasons: a lower variety and quantity of digestive enzymes; comparative proteolytic activity of colon mucosa is much lower than that detected in the small intestin [4].

Colonic Anatomy

The length of the large intestine is approximately 1.5 meters. It starts at the cecum in the right iliac fossa and ends at the rectum and anal canal, which are located deep within the pelvis. The average human large intestine is 1.5 meters long. The colon is made up of a series of tubes that are connected by mucosa, a moist, delicate pink lining [10,11]. The stomach, small intestine, and large intestine make up the GIT. There are three primary sections that make up the large intestine, which runs from the ileocecal connection to the anus. These are the rectum, the anal canal, and the colon [1,12]. The cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, and sigmoid colon make up the actual anatomy of the colon. Before the anus, the rectum is the final anatomical section [3,4]. Colonic anatomy is also depicted in Figure 1 [11].

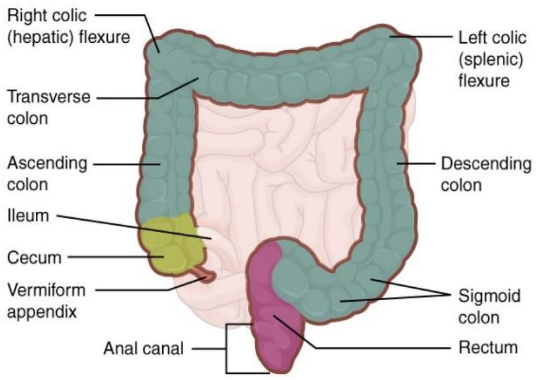

Figure 1. Colonic anatomy [11]

Colonic pH

Both within- and between subject changes can affect the GIT's pH. The pH of the GIT is influenced by disease severity, eating habits, and what is eaten. The creation of colon tailored medication delivery systems is based on the variations in pH in various GIT sections. To direct the medicine to the region, encapsulation is used with various polymers [13]. A diet high in carbohydrates may affect the pH level inside of the colon. This results from the colonic bacteria's fermentation of polysaccharides and subsequent synthesis of short fatty acid chains. Because it influences the medications' solubility in colonic fluid, the pH of the colon has an influence on the pharmacokinetics and pharmacodynamic action of a CDDS. For instance, the influence of colonic pH on drug release is significantly more pronounced if the CDDS formulation has a pH-sensitive coated membrane [14]. Length and pH of different parts of GIT were shown in Table 1 [8].

Table 1. Length and pH of different parts of gastrointestinal tract (GIT) [8]

Part of GIT	Length (cm)	pH
Stomach		1.5-2
Small intestine	550-700	6.6-7.5
Colon Ascending colon	20-25	6.4
Transverse colon	40-45	6.6
Descending colon	10-15	7.6

Colonic Transit Time

The colorectal bioavailability of medicines is significantly influenced by the passage through the colon time. The passage of dose forms is typically influenced by the administration timing, the presence

or lack of nutrition, and the kind of dosage form. The physical state, the size of the dosage form, or the presence of nutrition in the stomach have no effect on small intestinal transit. The dose form takes a consistent 3 to 4 hours to get from its source to the ileocecal tunction. Colon passage time greatly affects the bioavailability of pharmaceuticals released from dosage forms. Gender, dose form size, physiological variables like stress, the presence of nutrition, and sick status are the factors that affect colonic transit time. Small particles and solution move slowly in the proximal colon. In comparison to men, women exhibit a shorter colonic passage time [4,14]. Transit time of different parts of GIT was shown in Table 2 [8].

Table 2. Transit time of different parts of gastrointestinal tract (GIT) [8]

Organ	Transit time
Stomach	1-2 hr
Small intestine	3-4 hr
Colon	20-30 hr

Microflora and Colonic Enzymes

More than 400 different kinds of aerobic and anaerobic microorganisms, including *Escherichia coli* and *Clostridium species*, are found in the human colon. Numerous hydrolytic and reductive metabolizing enzymes are produced by these bacteria. These enzymes catalyze a variety of processes, such as the metabolism of pharmaceuticals and biomolecules such as bile acid, the inactivation of potentially toxic metabolites, as well as the fermentation of carbohydrates and proteins. Polysaccharides like chitosan, guargum, pectin and others are frequently used as release rate-controlling ingredients in dosage forms that target the colon. These polysaccharides can withstand intestinal and stomach enzymes. Nevertheless, are broken down by anaerobic bacteria found in the colon [14].

In different areas of the GIT, medication release is triggered by gut enzymes. These enzymes are typically produced by gut bacteria that is abundant in the colon. These enzymes are employed to break bindings between an active agent and an inert carrier (it means release of a drug from a prodrug) as well as to breakdown coatings or matrices [15]. The many metabolic reactions that occur in the GIT are caused by the enzymes secreted by various microorganisms, including *Clostridia, E. Coli, Lactobacilli, Streptococci* and *Eubacteria.* At least 10^{11}-10^{12} colony forming units of bacteria are present in the colon [13,16].

Advantages of CDDS

CDDS offer numerous advantages in the field of medication administration. The colon, being an ideal site for addressing local colonic illnesses, allows for targeted treatment with lower doses of medication, minimizing the potential for side effects and drug interactions. This, in turn, reduces dosing frequency, leading to cost savings, especially with expensive drugs. The extended retention period in the colon, lasting up to five days, enhances the bioavailability of therapeutic molecules that may not be well absorbed elsewhere. CDDS also facilitates the delivery of peptides, insulin, oral vaccinations, and growth hormones due to the colon's lower peptidase activity compared to other organs.

Moreover, administering medications through the colon mitigates stomach irritation, particularly for drugs like nonsteroidal anti-inflammatory drugs (NSAIDs), by bypassing upper gastrointestinal absorption. The avoidance of first-pass metabolism further contributes to the efficacy of treatment. The prolonged activity in the colon, whether during the day or night, enhances patient adherence to medication regimens. Importantly, CDDS ensures that the treatment directly targets the affected area, preventing medication breakdown and extending the effects and duration of therapy.

The colon’s capacity for both local and systemic treatment enables versatile applications, with local delivery allowing for effective topical therapy. Additionally, the colon's high water absorption and the viscous nature of its contents restrict access to the absorbent membrane for many drugs. Furthermore, the colon serves as a crucial site for various drug metabolism processes, including azo reduction and

enzymatic cleavage. In summary, CDDS offer a comprehensive approach to medication delivery, optimizing therapeutic outcomes across a spectrum of medical conditions [3,17-19].

Disadvantages of CDDS

While CDDS offer notable advantages, they also present certain challenges and limitations. The colon's small luminal surface area and tight connections contribute to delayed systemic absorption, leading to a sluggish onset of action for medications. Developing medications specifically targeted for the colon proves challenging due to various biological barriers. In the colonic mucosa, drug-metabolizing enzymes of the cytochrome (p450) class exhibit lowered affinity, affecting the metabolism of certain drugs.

The prolonged residence period of 3-5 days in the colon may lead to increased plasma levels of pharmaceuticals and enhanced bioavailability, particularly for medications that are substrates for these enzymes. However, the colon's lower and more viscous fluid levels compared to the upper gastrointestinal tract pose challenges in drug formulation. Additionally, multiple production steps are often required, further complicating the manufacturing process.

Issues such as non-specific drug binding to food residue, feces, mucus, and digestive secretions can limit a medicine's bioavailability. The metabolic degradation of medications by local microflora in the colon may also influence colonic function, adding another layer of complexity. Moreover, the requirement for drugs to be in a solution form prior to absorption can be a rate-limiting step for poorly soluble medicines. Finally, the distal location of the colon in the alimentary canal makes it challenging to access. In conclusion, while CDDS offer targeted therapeutic benefits, overcoming these inherent disadvantages is essential for optimizing their effectiveness in clinical applications [4,19-21].

Colon Absorption

In comparison to the small intestine, the colon has a substantially smaller surface area. The slower pace of transit in the colon allows the medicine to remain in contact with the mucosa for a longer amount of time than in the small intestine, compensating up for the much smaller surface area. Drugs are passively absorbed either through the paracellular or transcellular pathway. Paracellular absorption includes the transfer of pharmaceuticals through the tight connection between cells and is the route most hydrophilic drugs take, whereas transcellular absorption involves the transit of drugs through cells, which is the route most lipophilic drugs use.

The movement of water, electrolytes, and ammonia across the mucosa affects the absorption. The usage of absorption enhancers increases the drug's absorption in the colon, and it exhibits efficient absorption via various membranes. The absorption enhancers alter epithelial permeability by denaturing membrane proteins, open the paracellular route, change lipid-protein interactions, and disrupt the integrity of the lipid barrier by colonic electrolytes. They also cause disruption of the intracellular occluding junction complex. The release and adsorption characteristics of colon-specific drug delivery systems may be impacted by gastrointestinal disorders such as crohn's disease, constipation, diarrhea and so on [1,4,22].

Drug Criteria for CDDS

Drug Candidates: The most suitable medications for CDDS are those that exhibit low absorption from the stomach or intestine, including peptides, as well as those that exhibit stability at an alkaline pH of the gastrointestinal system. The medications used to treat intestinal disorders like inflammatory bowel syndrome (IBS), diarrhea, and colon cancer are perfect candidates for local colon administration. Because of the colon's long retention time, more poorly absorbed substances are absorbed, which increases overall absorption.

Drug Carrier: The decision of which drug carrier to use for a specific drug candidate is based on both the physiochemical character of the drug and the illness for which the system is intended to be used. The choice of drug carrier is also influenced by the chemical structure of the drug, its stability, partition coefficient, and the kind of absorption enhancers used. Finally, the choice of drug carrier is also influenced by the functional groups of the drug molecule. The carriers, which contain additives such polymers, may affect the systems' efficacy and release properties [3,17,23,24].

Mucoadhesion

Bioadhesion, which is defined as the formation of an attachment between a biological substance and an artificial substrate, is important for the development of drug delivery systems. Biopolymers often exhibit bioadhesive characteristics and are utilized for a variety of therapeutic goals [25,26]. Pharmaceutical formulations that are bioadhesive are often created to increase medication bioavailability through localizing the impact at the desired place and lengthening the residence duration of therapeutic agents. They also aid in the formulation design of local drug delivery systems, increasing bioavailability by avoiding metabolic pathways [27,28].

The natural defenses of the body against the deposition of impurities onto the mucous membrane might compromise the mucoadhesion of a system, although mucoadhesive compounds can increase contact with a particular site or tissue. Therefore, it is necessary to have the right properties in order to maintain an effective drug concentration at the action site, manage drug release, enable a reduction in the frequency of drug administration, and improve patient compliance with the therapy [29].

In drug delivery applications, mucoadhesion has rekindled interest in extending the residence period of mucoadhesive dosage forms via different mocusal routes. The bioavailability of topical and local systems based on mucoadhesives has increased. Due to its significant surface area and high blood flow, mucoadhesive drug administration provides quick absorption and good bioavailability. Drug delivery through the mucosa avoids the first-pass hepatic metabolism and gastrointestinal enzyme degradation [30].

Mechanism of Mucoadhesion

One way to characterize mucoadhesion is as an interfacial phenomenon where two materials are kept together by interfacial forces of attraction. One of the materials may be an artificial substance like a mucoadhesive polymer, while the other could be the mucin layer of the mucosal tissue. An artificial material that interacts with mucous membranes to be retained on them or hold them together for a long time is called a "mucoadhesive." Typically, there are two steps to the adhesion process, which are listed below. These mucoadhesion stages are also depicted in Figure 2. [31].

Contact stage: In this phase, an intimate wetting takes place between the mucoadhesive substance and the mucosal membrane as a result of contact. The mucosal membrane's mucus is responsible for wetting the mucoadhesive.

Consolidation stage: The mucoadhesive substance attaches itself to the mucus membrane through a variety of physicochemical factors of attraction, creating a mucoadhesion that is long-lasting. We refer to this phase as the consolidation stage. The process of mucoadhesion ends after these two phases [31].

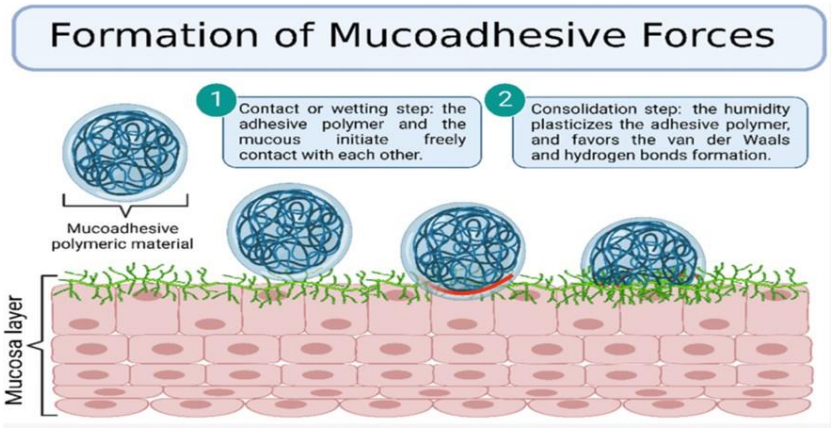

Figure 2. Mucoadhesion mechanism: There are two steps to mucoadhesion. (1) Contact stage: A bioadhesive and a membrane come into close contact (wetting or swelling phenomena). (2) Interactive stage: Interpenetration, or the bioadhesive's entry into the tissue or mucous membrane surface [31]

Challenges in Colon Drug Delivery

A colon-targeted drug delivery system's design must take into account the variations in the GI tract's segments' anatomy, physiology, and absorption properties, in addition to the dosage form's transit kinetics and the GI tract's site of drug release. Additionally, one should take into account the notable distinctions between each individual's healthy and sick GI tract. Understanding the GI tract environment is essential for developing effective dosage forms with enhanced in vitro and pre-clinical in vivo testing when it comes to colon-targeted drug delivery [32]. Consequently, in order to guarantee optimal efficacy following administration, we address here a few of the physiological and pathological aspects of the GI tract that are important in the design of colon-targeted drug delivery.

pH

The pH of the GIT varies depending on its segments. The small intestine has a pH range of 5.9-7.8, which is slightly acidic to neutral, while the stomach has an acidic pH range of 1-3. The pH of the colon varies from 5 to 8 [33]. Since the pH gradient makes it possible to create colon-targeted drug delivery systems that are specifically activated by colonic pH, pH-dependent drug delivery is a crucial tactic from the perspective of drug delivery. One way to prevent medication and carrier degradation in the stomach's acidic environment is to coat the complexes with Eudragit® S100 (polymethacrylate) polymers, which exhibit stability in an acidic pH [34].

However, the intrinsic inter-individual differences and intra-individual variability in GI tract pH values are the key issues with pH-dependent drug delivery devices. Furthermore, it has been observed that individuals with both Ulcerative Colitis and Crohn disease had decreased colonic pH values, which raises questions about the effectiveness of pH-dependent colon-targeted drug delivery regimens [35].

Mucus Barrier

Mucus is a hydrogel layer primarily made up of mucin and other big glycoproteins. When oral dosage forms are used, it is the initial physical barrier to drug absorption in the GI tract [34]. Human intestinal mucus is composed of two layers: a thicker, more adherent basal layer and a looser, luminal layer. The mucosal layer's total thickness varies between 10 and 200 μm (jejunum to colon). The GI mucus has several purposes, such as lubricating chyme, shielding the epithelium from mechanical damage, and adhering to and preventing pathogens from penetrating the epithelial cells. Poor therapeutic outcomes may arise from the majority of foreign particles, including conventional particulate-based drug delivery methods, being effectively retained in human GI mucosal layers by adhesion and eliminated in feces. This effectively limits the period of sustained local drug administration [36].

Transit Time

GI transit times are used by time-dependent release systems to deliver drugs to the colon. In the small intestine, a transit time of 4 hours is commonly acknowledged, with slight inter-individual variations ranging from 2 to 6 hours. On the other hand, colon transit times can differ greatly, ranging from 6 to 70 hours. Furthermore, it has been noted that individuals with colon illnesses such active Ulcerative Colitis have noticeably quicker intestinal transit. In patients with inflammatory bowel disease (IBD), diarrhea and bowel resection may lead to a shorter transit time for traditional oral formulations. Since diseased colon segments may be less exposed to topically active oral medicines as a result of this shortened transit time, therapeutic efficacy against active disease may be significantly diminished [37].

Colonic Microbiota

The human colon is home to around 400 distinct types of both aerobic and anaerobic bacteria. The majority of the anaerobic bacteria in the colon produce a variety of reductive and hydrolytic enzymes to break down polysaccharides in order to meet their energy needs. The large concentration of bacteria in the colon creates a unique environment that can be used to influence the behavior of drugs and dosage forms. Therefore, pro-drugs and polysaccharides that are broken down by colonic microbiota enzymes to release a medication are frequently used in colon-targeted drug delivery systems, such as guar gum, pectin, and chitosan. Nonetheless, a drug's bacterial metabolism may result in toxicity,

activity, or inactivity. Additionally, dietary changes, medication therapy, and illness can all cause variations in the colonic microbiota. These results highlight the ways in which these circumstances might alter the release of drugs from bacterial-enzyme dependent formulations, and they should be taken into account when developing a drug delivery system tailored to the colon [38,39].

Role of Mucoadhesive Polymers in Overcoming Challenges

Formulations with mucoadhesion characteristics can lengthen transit times by adhering to the GI tract's mucosal layers [40]. The mucus binds drug delivery systems by hydrophobic interactions. Alternatively, charged regions of mucin proteins may engage with charged carrier particles and hold them within the mucosal barrier. Drug delivery systems surface chemistry can be changed to boost or decrease adhesion to target-specific cells or biological membranes. Numerous studies showed that cationic drug delivery systems can stick to mucus in the colon and may therefore improve systemic medication absorption to a greater extent [41]. On the basis of this idea, current research has suggested that cationic drug delivery systems may improve mucoadhesion in the colon's surrounding tissues that contain ulcers, and that inflammatory cells' subsequent absorption of the substance may boost treatment outcomes. However, the benefits of cationic particulars in an effective colon delivery may be compromised by non-specific mucoadhesion in the proximal GI tract. It uses a clever strategy that involves shielding the cationic surface of the nano-drug delivery system before the formulation enters the colon and then pH-triggered de-shielding in the colon to get around this issue in oral colon-targeted formulations [42].

If loaded medicinal compounds could be adequately supplied in a sustained manner to the underlying mucosal tissues, colon-specific disorders may be treated more effectively and with fewer adverse effects. It has been highlighted that the GI tract mucosal layers that shield epithelial surfaces are important obstacles to drug delivery systems penetration. In this context, it has been reported on the creation of a mucus-penetrating drug delivery system through the coating of particulate surfaces with a thick layer of polyethylene glycol (PEG) [43].

Mucoadhesive Drug Delivery Systems

Different types of particles with surface modification (cationic or thiolated particulate system) and chemical or physical entrapment of drugs (system made of hydrogels and nanoparticles) are examples of mucoadhesive drug delivery systems. Non-floating in situ gelations (non-floating composite systems of polymeric nanoparticles and hydrogels) can still be achieved in a system made up of hydrogels and nanoparticles [44]. A system's mucoadhesion depends on how the hydrogel and mucosa structure interact. When the hydrogel comes into touch with the mucosa, it swells, which aids in cellular absorption and bioadhesion through chemical or physical interactions. Features like the polymer's molecular weight, hydration, hydrogen bonding ability, chain flexibility, charge, and biological environmental parameters all influence how the hydrogel and mucosa interact [45].

The gastrointestinal system has long been seen as a viable location for the creation of formulations based on mucoadhesives. The use of mucoadhesive polymers to modify the transit duration of delivery systems in a specific area of the gastrointestinal system has piqued the interest of researchers worldwide [46,47].

Mucoadhesive drug delivery system has some advantages and disadvantages and these are;

- Extend the duration of the drug's residency at the tumor site and raise its bioavailability,
- Lower the frequency of dosing,
- Enhance the permeability of drugs,
- Lower the medication dosage that is given,
- Swift onset of action,

But;

- It's possible for the formulation to come loose,
- Overhydration could cause the structure of the formulation to break down [48,49].

Mucoadhesive Polymers

Some mucoadhesive polymers used in colon drug delivery systems are listed below along with some information on how they are used.

Chitosan

A carbohydrate derived from natural sources; chitin is present in many organisms that live. It is present in the cell walls of fungus and yeast as well as being a component of the structure of the exoskeleton of crustaceans. On the chemical basis, it is a poly-β-(1➔4)-N-acetyl-D-glucosamine linear chain. Chitin's unique physicochemical characteristics make it challenging to employ, although it may be treated in an alkaline environment to produce chitosan, a deacetylate derivative [50]. Chitosan is a cationic polymer made up of a linear co-polymer of β-(1➔4)-N-acetyl-D-glucosamine with branches of β-(1➔4)-D-glucosamine that may be randomly distributed. The beneficial biological characteristics of chitosan, including its nontoxicity, biocompatibility, non-immunogenicity, and biodegradability, are widely acknowledged [51]. Chemical structure of chitin and chitosan are represented in Figure 3. [52].

Because free amino groups in its backbone chain are protonated, chitosan can dissolve into a non-Newtonian, shear-thinning fluid in aqueous solutions with pH values lower than its pKa (around 6.5). pH values above 7.5–8 are conducive to regeneration. Chitosan becomes insoluble under these circumstances, causing films, sponges, powders, and fibers to develop [53,54]. Since more amine groups become protonable as deacetylation rises, chitosan solubility is directly correlated with the degree of deacetylation, because chitosan turns unstable at low pH values in the upper gastrointestinal system, it must be coated with a protective layer to stop from solubilizing [55].

Applying various chemical or physical modifications to chitosan is another tactic used to stop it from quickly solubilizing. Crosslinking procedures like grafting, thiolation, carboxymethylation, succinylation, radiation, enzymatic modification, or copolymerization are the main examples of these procedures [56]. To try to increase its structural integrity and stability under various situations, chitosan can be successfully coupled with other natural polymers such alginate, pectin, gums, gelatin, carrageenan, or hyaluronic acid [57].

Because of its hydroxyl groups capacity to create hydrogen bonds, chitosan also possesses mucoadhesive qualities. Through electrostatic interactions, positively charged amino groups from chitosan bind to negatively charged sialic acid that is present on the mucus surface. Mucoadhesion is enhanced by high molecular weight chitosan as well as other elements with an elevated viscosity and degree of deacetylation. Since the sialic acid in mucus is negatively charged at colonic pH, positively charged chitosan/carboxymethyl chitosan nanogels demonstrated superior mucin adsorption and mucoadhesive characteristics. Numerous colonic drug delivery formulations have been tested to examine the mucoadhesive characteristics of chitosan [58].

The mucoadhesive polymer-drug conjugate system is investigated by Shen et al. for the treatment of inflammatory bowel disease (IBD). The quercetin conjugated glycol chitosan product micelles have been produced. They conjugated the medication to the polymer using a ROS responsive linker. Reactive oxygen species, or ROS, can be employed as a stimulus for targeted delivery since they are overexpressed near the site of inflammation in the colon. Less than 20% at physiological pH and with H_2O_2 present means that the entire medication is discharged. Micelle accumulation was seen in the colitis mouse model by biodistribution analysis. In the model of DSS mice, micellar suspension effectively reduced YNF-α, IL-6, and iNOS. This work showed quercetin's inflammatory focused administration for a better IBD therapeutic impact. This work supports the development of sophisticated drug delivery systems for IBD [59].

In order to treat inflammatory bowel disease (IBD), Nalinbenjapun et al. investigated the conjugation of 5-aminosalicylic acid with *N*-(4-aminobenzoyl)-chitosan for colon focused administration. 4-amino benzoyl serves as a divider. In simulated gastric fluid, simulated intestinal fluid, and simulated colon fluid, the medication sulfasalazine has not been released. However, 70% of the medication was released in a 24-hour period in all of the mediums above that contained rat stomach contents. But in just 24 hours, the chitosan-5-ASA conjugate releases only 25% of the medication. This study demonstrated the efficacy of the mucoadhesive polymer-drug conjugate approach in colon

targeted delivery of IBD patients [60].

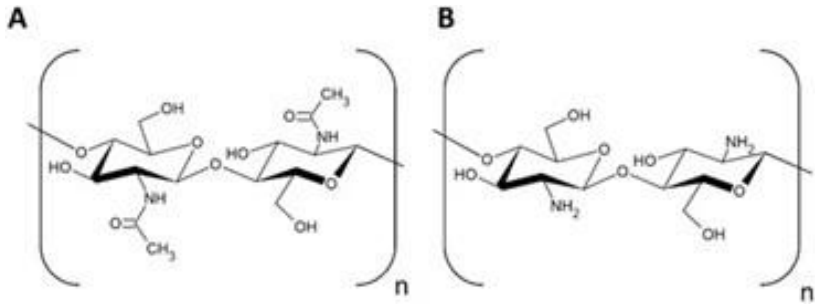

Figure 3. Chemical structure of A: Chitin and B: Chitosan [52]

Alginates

Alginates are naturally occurring linear anionic polysaccharides composed of β-D-mannuronic acid (M) and its C-5 epimer α-L-guluronic acid (G). They are mostly found in the cell walls of brown seaweed. Alginates are mixtures of MG structures (MG-blocks) and M (M-blocks) and G (G-blocks) residues arranged in groups. The ratio of the two monomers can vary depending on the initial natural source [61]. Because alginates are non-toxic, biodegradable, and gel properly, they are widely utilized in biomedicine for a wide range of applications. Traditionally, they have been used in the food business as well as the medicinal, cosmetic, and agricultural sectors [62].

Alginate backbones with carboxyl and hydroxyl groups above them make them ideal mucoadhesive polymers. Through hydrogen bonding, the positive charges of mucin sialic acid and sulfate residues interact with the anionic charges of these groups. Alginates have a lot of hydrophilic groups in their structure, which allows for a lot of hydrogen bonding locations both inside and across polymers, which promotes mucus adherence. A modified PEG containing a functional maleimide end-group was covalently bonded to the alginate backbone. The two reactive carbons in maleimide groups allow them to establish covalent connections with the thiols in mucin. The hydroxyl or amine groups of mucins can also establish hydrogen bonds with maleimide carbonyl groups, greatly enhancing the alginate's mucoadhesive capabilities [63]. Chemical structure of alginate depicted in Figure 4 [64].

In order to effectively transport medication to mice with ulcerative colitis caused by dextran sulfate sodium, Zhang et al. synthesized astaxanthin-enriched colon targeted alginate microsphere. They developed astaxanthin-rich alginate microspheres using high-pressure spraying and the ionic gelation process; the majority of the particles have a diameter between 0.5 and 3.2 μm. Microspheres that are well-tolerated in the mouth, stomach, and small intestine release xanthin in the colon as a result of the gut microbiota fermenting. The administration of microspheres via oral gavage to DSS colitis model mice resulted in significant improvements in weight loss, oxidative damage, inflammation, colon mucosal integrity, and disease activity index. Additional confirmation of the treatment group’s lower histological score comes from H&E staining analysis [65].

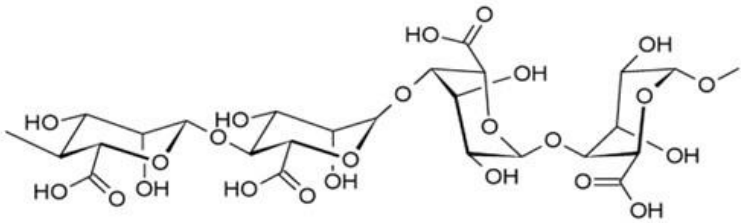

Figure 4. Chemical structure of Alginate [64]

Pectin

Pectins are linear, non-starch, negatively charged polysaccharides that dissolve in water and are

derived from the cell walls of plants. They have α-1,4 D-galacturonic acid and 1,2 D-rhamnose with D-galactose and D-arabinose chains as their backbone. Typically, they have high weights in the 50,000–150,000Da range. The presence or absence of methyl ester substituents in a molecule can vary depending on the plant origin and extraction technique. They are weak acids with a pKa of about 3.5 in aqueous environments. Pectins are inexpensive and non-toxic, which makes them ideal for use in the creation of medicinal formulations [66]. Chemical structure of pectin represented in Figure 5 [67].

Pectins may be broken down by the colonic microorganism pectinase, which makes them ideal for use in CDDS formulations. Pectins are insensitive to upper GIT enzymes found in the stomach and small intestine, such as protease and amylase [68].

Pectin indicate mucoadhesion by an electrostatic connection between the mucin molecule and pectin's carboxylic group, which forms a hydrogen bond with mucin [69].

It's interesting to note that Jorgensen et al.'s study on the impact of pectin's molecular weight on mucin layer penetration efficiency revealed that low molecular weight pectin penetrates the mucin layer more readily. Pectin with a low degree of esterification also exhibits stronger mucoadhesion activity than highly esterified pectin. Researchers looked at combining pectin with different polymers, like pectin-gellan gum beads, modified pectin-acrylate mixed carrier, and pectin-jackfruit seed starch beads, to increase the mucoadhesion activity of pectin [70].

Prezotti et al. developed gellan gum/pectin nanoparticles for the precise delivery of resveratrol to the colonic region via oral administration. They synthesized 330 nm-sized, spherically shaped nanoparticles with over 80% drug loading using the nebulization/ionotropic gelation process. Studies on drug release and permeability use triple co-culture models that secrete mucus and the caco-2 cell model. In stomach acid conditions, the mucoadhesive polymeric nanoparticles released 3% of their resveratrol in two hours, while in pH 6.8, they released 85% in thirty hours. 5.5% permeability was attained. According to this study, mucoadhesive pectin-based nanoparticles are a safe and effective delivery system for resveratrol that can be precisely delivered to the colon [71].

Wang et al. innovatively devised an oral colon-selective drug delivery system by utilizing a pectin/modified nano-carbon sphere nanocomposite gel film. To increase the targeted distribution of pectin-based oral colon products that contain 4-fluorouracil, 3-aminopropyltriethoxysilane modified nano-carbon sphere is inserted into the pectin Ca2+film. Their drug encapsulation efficiency (EE) ranged from 30 to 52%. In simulated gastric fluid (SGF), small intestinal fluid (SIF), and colon fluid (SCF), the composite fluids all displayed superior release rates, with values of 32, 22, and 635, respectively. The biocompatibility of the nanocomposite is confirmed by the in vitro cytotoxicity experiments. Thus, further research must be done before starting clinical trials [72].

Microparticles of amidated pectin were created by Deshmukh et al. to distribute sulfasalazine for inflammatory bowel disease (IBD) in a regulated manner. They created amidated pectin microparticles using the ionic gelation technique. In order to treat IBD, the microparticles placed in Eudragit S 100 coated hard gelatin capsules allow for pH- and time-dependent medication administration to the colon. The ideal formulation had a size of 463 nm, a zeta potential of -32, a yield of 91%, and an EE of 95%. At pH 6.8 and 7.4, the swelling index values are 0.88 and 0.98, respectively. During a 24-hour period, the drug releases 91% in simulated colonic fluid and 98% in rat cecal content. When given to the rabbit orally, the capsule crumbled at colonic pH 7.4 and released the medication from microparticles. The particles had a 3.3-year shelf life and demonstrated excellent stability. This study found that hard gelatin capsules coated with Eudragit S 100 and filled with amidated pectin microparticles may be a useful delivery strategy for the treatment of inflammatory bowel disease [73].

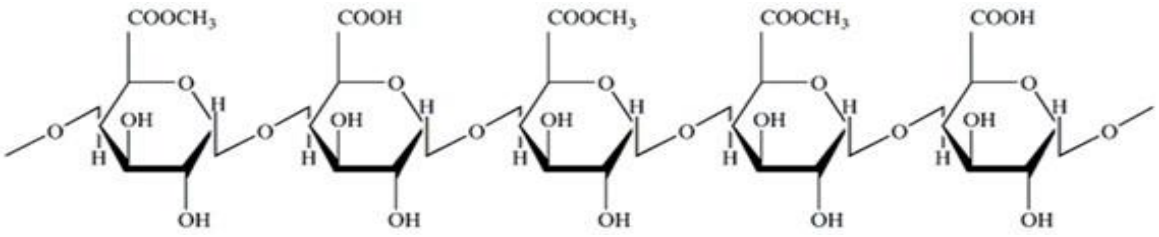

Figure 5. Chemical structure of Pectin [67]

Cellulose Derivatives

A cellulose derivative known as hydroxypropyl methylcellulose (HPMC) has hydroxypropyl and methoxyl group substituents joined to a cellulose backbone by ether bonds. The ether polymer HPMC is non-ionic, soluble in water, resistant to enzymes, and chemically stable at pH values between 3.0 and 11.0 [74].

Through hydrophobic/electrostatic interactions and hydrogen bonding, HPMC hydrophilic groups can form an association with the mucus layer. Mucin glycoproteins can interpenetrate the enlarged matrix to form a relaxed mesh and interact with the polymer, so swelling is essential for mucoadhesion to occur. The degree of crosslinking increases with an increase in HPMC content in a formulation, which limits the amount of HPMC chains available for the mucus layer to interpenetrate. A formulation's mucoadhesion is aided by the formation of additional pores in the enlarged matrix structure caused by a reduction in HPMC content. These pores allow mucin glycoproteins to interface with the matrix chains. Thus, it has been demonstrated that HPMC interacts with the mucosal layer but has inferior mucoadhesive qualities to other polymers [75,76].

Carboxymethyl cellulose (CMC) is a derivative of cellulose. It's a mucoadhesive polymer that dissolves in water. It is non-toxic, hydrophilic, bioadhesive, pH-sensitive, and gels readily. CMC is frequently utilized to deliver drugs. Because of their mucoadhesive responsive release properties, CMC hydrogels are more fascinating [77,78]. Chemical structure of CMC depicted in Figure 6 [79].

To deliver nucleolin specifically to colon adenocarcinomas, Nejabat et al. synthesized acetylated carboxymethylcellulose-coated mesoporous silica hydride nanoparticles. Hollow mesoporous silica nanoparticles (HMSNs) loaded with doxorubicin (DOX) and coated with acetylated carboxymethylcellulose (Ac-CMC) converted covalently with AS1411 aptamer. These nanoparticles improved blood circulation and released drugs in a regulated, sustained manner. The study conducted in vitro cytotoxicity and cellular uptake validates the targetability of AS1411 to nucleolin overexpressing MCF-7 and C26 cells. *In vivo* tumor inhibition demonstrated by the formulation was excellent [80].

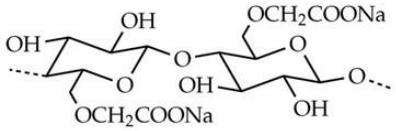

Figure 6. Chemical structure of Carboxymethyl Cellulose [79]

Poly (Acrylic Acid)

One of acrylic acid's derivatives is poly (acrylic acid), or PAA. As a homopolymer, PAA can generate a range of cross-linked and co-polymers. Being an anionic polymer, it could result in a negative charge if a proton is lost from the side chain of PAA. The deprotonated PAA exhibited the capacity to take in water and expand several times above its initial volume. Azobisisbutyronitrile (AIBN) and potassium persulfate can be used in free radical polymerization to create PAA. Because PAA is susceptible to mucoadhesion in its protonated form at colon pH, it is regarded as a mucoadhesive polymer. PAA's COOH and the sialic COOH of the mucin glycoprotein combine to form an H-bond. Viscosity was increased by this bond formation. Mucoadhesive colon drug delivery systems based on PAA have been fully investigated [81]. Chemical structure of PAA represented in Figure 7 [82].

Dey et al. used barley-grafted PAA to accomplish pH-sensitive delivery. In this investigation, 5-ASA was employed as a model medication for colon targeting. Given that barley is the fourth most widely grown food commodity in the world. Starch makes over 95% of the polysaccharides in barley. The most promising technique for changing polysaccharides is grafting. PAA grafted barley was created by Dey et al. with the use of a microwave. Anti-inflammatory medication 5-ASA is loaded, which is used to treat inflammatory bowel disease. Drug absorption rate is high in lower GIT; drug release follows the Fickian diffusion mechanism at both pH 1.2 and 7.2 [83].

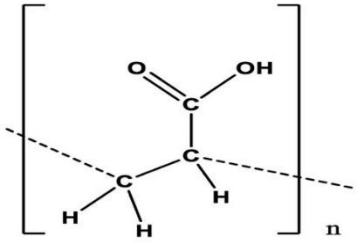

Figure 7. Chemical structure of Poly (Acrylic Acid) [82]

Current Chanllenges in Mucoadhesive Colon Drug Delivery

Mucoadhesive drug delivery systems encounter a number of difficulties, especially when it comes to colon-specific administration. Since last update, a few difficulties are as follows:

Variable Gastrointestinal Conditions: There are fluctuations in pH, enzyme activity, and transit time within the dynamic gastrointestinal environment. It can be difficult to design a mucoadhesive system that can tolerate these changes and release the medication in the colon efficiently.

Mucus Layer Variability: Individuals and various disease situations may have differences in the thickness and makeup of the mucus layer in the colon. The overall efficacy and mucoadhesive qualities of drug delivery systems may be impacted by this diversity.

Biodegradability and Biocompatibility: To prevent long-term negative effects, the materials employed in mucoadhesive systems must be both biocompatible and biodegradable. It is difficult to find materials that maintain excellent mucoadhesion while striking a compromise between these qualities.

Medication Stability: Some medications may degrade in the hostile gastrointestinal environment, which could have an impact on how effective they are. It is essential to guarantee the drug's stability during its passage through and release in the colon.

Optimal Release Kinetics: To optimize therapeutic efficacy, regulated and sustained medication release in the colon must be achieved. To guarantee the intended drug concentrations over an extended period of time, release kinetics must be carefully taken into account during the design of mucoadhesive systems.

Patient Compliance: Patients should find it convenient and agreeable to receive medication via mucoadhesive delivery methods. Patient compliance may be impacted by elements like dosage frequency, dosage form size, and simplicity of administration.

Regulatory Acceptance: For mucoadhesive drug delivery systems intended for colon-specific uses, regulatory approval necessitates proving safety, effectiveness, and uniformity. Complying with regulatory regulations makes the development process even more complex.

Scale-up Problems: Maintaining the uniformity and repeatability of mucoadhesive drug delivery systems can be difficult when moving from laboratory-scale production to large-scale manufacturing [78].

Through advances in materials science, formulation design, and targeted drug delivery systems, scientists and pharmaceutical companies are actively addressing these difficulties. Mucoadhesive colon medication delivery methods are becoming more dependable and successful as a result of developments in polymer chemistry, nanotechnology, and mucosal physiology.

RESULT AND DISCUSSION

Mucoadhesive polymers are essential for improving drug delivery methods, especially when it comes to administering drugs to the colon. These polymers have a number of benefits for colon-specific medication delivery because of their capacity to stick to mucosal surfaces. Mucoadhesive polymers enable focused and localized treatment by prolonging the duration of medication interaction with the intestinal mucosa due to their adhesive qualities. This is particularly important when treating disorders including colonic infections, colorectal cancer, and inflammatory bowel diseases. Both synthetic and natural polymers, such as alginate and chitosan, as well as derivatives of polyacrylic acid, are frequently

used in these systems.

Mucoadhesive polymers' capacity to deliver drugs to targeted sites while reducing systemic side effects is one of their main benefits. Moreover, the extended residence time promotes better bioavailability by enabling controlled and sustained medication release. Despite these advantages, there are also drawbacks, such as individual differences in mucosal conditions and the critical requirement to guarantee the biocompatibility of these polymers in order to avoid negative reactions. Mucoadhesive polymers are used in a wide range of medical applications, such as the precise delivery of antibiotics for colonic infections, the localized administration of chemotherapeutic agents for the treatment of colon cancer, and the targeted delivery of anti-inflammatory drugs for inflammatory bowel diseases.

In conclusion, mucoadhesive polymers present a viable approach to enhancing colon drug delivery, with enormous promise for the creation of efficient and well-tolerated treatments for a range of colonic illnesses.

AUTHOR CONTRIBUTIONS

Concept: A.D.G., T.C.; Design: A.D.G., T.C.; Control: A.D.G., T.C.; Sources: A.D.G., T.C.; Materials: A.D.G., T.C.; Data Collection and/or Processing: A.D.G., T.C.; Analysis and/or Interpretation: A.D.G., T.C.; Literature Review: A.D.G., T.C.; Manuscript Writing: A.D.G., T.C.; Critical Review: A.D.G., T.C.; Other: A.D.G., T.C.

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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