REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Impact of Mucoadhesive Membrane Formulations on Bioavailability

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Abstract

Mucoadhesive polymers have crucial roles in drug delivery systems that facilitate targeted therapies in the colonic area. The polymers facilitate drug transport across mucosal tissue, so circumventing hepatic first-pass metabolism and providing protection against gastrointestinal enzyme breakdown. The prolonged retention of mucoadhesive dosage forms at the site of action allows for sustained drug release, which boosts bioavailability levels and improves therapeutic impact. The adhesive capabilities of these polymers enable them to create transient attachments to mucosal surfaces, thus prolonging drug exposure on the colonic mucosa. Considerable benefits exist, but challenges remain because mucosal conditions differ between patients and because products must be biocompatible. Medical applications of mucoadhesive polymers cover diverse uses that include delivering anti-inflammatory drugs to specific sites of irritable bowel syndrome and enabling drug administration through localized routes to activate systemic therapeutic mechanisms successfully. The review starts with an overview of mucosal membrane structure, followed by explanations about mucoadhesion mechanisms, as well as theories, and then concludes with a summary of mucoadhesive systems advantages against conventional delivery systems. The review discusses recent developments in research regarding mucoadhesive properties and polymers.

Keywords: Mucoadhesive Polymer, Colon, IBS, pharmaceutical application.

1. Introduction

A targeted drug delivery system functions as a specialized approach that introduces pharmaceutical medications directly to precise areas inside the body to establish required drug concentrations. Several factors, including an unstable situation, combined with weak solubility, a limited half-life, a wide volume of dissemination, weak absorption and weak specificity, and a therapeutic index, can lead pharmaceutical drugs to target specific areas of interest. Through targeted drug delivery, medical professionals gain higher drug therapeutic

effectiveness while protecting drugs from degradation and reducing adverse reactions (Anita et al., 2019).

Pharmaceutical products delivered to the lower gastrointestinal tract serve to treat various digestive system diseases through colonic delivery mechanisms. A drug delivery system targeting the colon must first guarantee drug stability while ensuring complete protection of the drug until it arrives at its target site within the colon (Sangeetha et al., 2011).

The pharmaceutical concentration in the colon increases while systemic absorption decreases when medications reach the colon through direct delivery instead of first passing through upper digestive regions. The colon functions as the main drug delivery area because its mucosal membrane actively supports medication absorption while containing contents for five days. Oral delivery methods conjugate with rectal administration serve to transport medicines into the colon compartment. The attractiveness of oral dosage forms for delivering drugs specifically to the colon is immense, primarily because of their straightforward design (Kumar et al., 2010) & (Philip et al., 2010)

Colonic drug administration has gained significance for the systemic distribution of anti-asthmatic, antihypertensive, and anti-diabetic medications, in addition to local therapy of colonic illnesses such as Ulcerative colitis and Crohn's disease. New technologies and techniques have been created to overcome the limitations of previous treatments and specifically target the colon. Historically, solid dosage forms for oral administration have been designed to release their drug content in the upper gastrointestinal tract (GIT), where conditions generally benefit drug absorption and dissolution. Recently, regulating the rate and location of drug release from oral formulations has gained increased attention to enhance patient compliance and therapeutic efficacy (Anil et al., 2010) & (Gazzaniga et al., 2022).

Colon drug delivery systems (CDDS) establish protection for peptide drugs through the duodenum and jejunum while controlled drug release happens in the ileum or colon to achieve superior systemic bioavailability. The colon is a suitable site for peptide and protein drug absorption because it contains reduced enzyme variety and activity levels compared to the small intestines (Leuva et al., 2012).

Colonic pharmaceutical delivery systems continue to advance in their current development state. The significance of colonic drug administration of pharmaceuticals for treating local colon disorders, including IBS, Ulcerative colitis, and similar conditions. The development of innovative technologies and systems emerged to address former method weaknesses and properly deliver drugs to the colon (Choudhary et al., 2020).

Colonic Anatomy

The colon extends from the ileocecal valve to the rectum, spanning approximately 1.5 meters, and is segmented into the cecum, ascending, transverse, descending, and sigmoid colon, followed by the rectum. Its wall comprises four layers: mucosa, submucosa, muscularis externa, and serosa. The mucosa, lined with absorptive cells and goblet cells, has a limited surface area (about 0.3 m^2) due to the absence of villi, reducing passive drug diffusion compared to the small intestine's 200 m^2. The submucosa contains blood and lymphatic vessels critical for systemic drug uptake, while the muscularis externa, with its taeniae coli and circular muscle, drives slow motility **(Tortora & Derrickson, 2017).** The colon's prolonged transit time (12-24 hours) benefits sustained-release formulations, though its thick mucus layer can impede drug penetration, especially for hydrophilic compounds. This anatomy supports absorption of drugs with appropriate solubility and stability but poses challenges for rapid-onset formulations **(Washington et al., 2001).** Colonic anatomy is also depicted in Figure 1 **(Herp et al., 2021).**

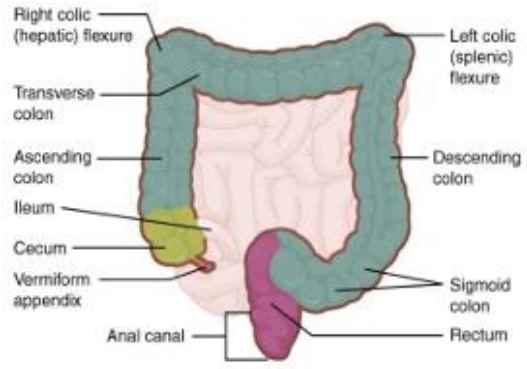


Figure I: Colonic anatomy (Herp et al., 2021).

Colonic transient time

The colorectal bioavailability of medicines is significantly influenced by the passage through the colon time. Factors such as administration timing, nutrition, and dosage form type affect the passage of dose forms. Small intestinal transit does not affect physical state, size, or stomach nutrition. The dose form takes 3 to 4 hours to reach the ileocecal function. Factors affecting colon passage time include gender, dose form size, physiological variables like stress, nutrition, and sick status. Women exhibit shorter colonic passage time compared to men. **(Amidon et al., 2015)** The transit time of different parts of the digestive tract is shown in Table 1. **(Choudhary et al., 2020)**

Table 1: Transit time of different parts of gastrointestinal tract (GIT)

Organ	Transient time
Stomach	1-2 hrs
Small Intestine	3-4 hrs
Colon	20-30 hrs

Colonic pH and Microflora

The colonic luminal pH ranges from 6.4 in the proximal colon to 7.6 in the distal colon, influenced by microbial fermentation of carbohydrates into short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate **(Cummings & Macfarlane, 1997).** This neutral-to-alkaline environment enhances the solubility of weakly basic drugs, improving their absorption potential compared to the acidic small intestine **(Friend, 1991).** However, pH variability—due to diet, disease, or microbial activity—can affect drug dissolution and stability **(Fallingborg, 1999).** The colon hosts a dense microflora, with up to 10^{11}-10^{12} bacteria per gram of content, predominantly anaerobes like *Bacteroides*, *Clostridium*, and *Bifidobacterium* **(Sender et al., 2016).** This microbiome metabolizes certain drugs, activating prodrugs (e.g., sulfasalazine into 5-ASA for ulcerative colitis) or degrading others (e.g., glycosides), altering bioavailability **(Sousa et al., 2008).** SCFAs may also modulate epithelial transporters, such as monocarboxylate transporters, influencing drug uptake **(Gill et al., 2006).** The interplay of pH and microflora thus offers opportunities and challenges for drug design.

Colonic Enzymes

Colonic enzymes, primarily of microbial origin, significantly affect drug absorption. Unlike the small intestine, where pancreatic and brush-border enzymes dominate, the colon has minimal host-derived enzymatic activity but abundant bacterial enzymes, including β-glucuronidases, azoreductases, and glycosidases **(Sousa et al., 2008).** Azoreductases, for example, cleave azo bonds in prodrugs like olsalazine, releasing active moieties locally **(Chourasia & Jain, 2003).** β-glucuronidases hydrolyze glucuronide conjugates, potentially reactivating drugs excreted via bile, enhancing reabsorption **(Hawksworth et al., 1971).** However, these enzymes can also degrade drugs, reducing bioavailability, as seen with certain glycosylated compounds **(Rubinstein, 1995).** The colon's low proteolytic activity compared to the small intestine favors peptide and protein delivery, though efflux transporters like P-glycoprotein may counteract this advantage **(Lennernäs, 2014).** Enzymatic activity varies with microbial composition, diet, and disease states (e.g., dysbiosis in IBD), introducing unpredictability in drug metabolism **(Quigley, 2013).**

Implications for Drug Absorption

The colon's anatomy, pH, microflora, and enzymes collectively create a niche for targeted drug delivery. Its prolonged transit and neutral pH suit sustained-release systems, while microbial enzymes enable prodrug activation, as exploited in treatments for inflammatory bowel disease **(Friend, 1991).** However, limited surface area, variable pH, and enzymatic degradation challenge consistent absorption. Advances in pharmaceutical technology—pH-dependent coatings, microbial-triggered systems, and enzyme-resistant formulations—leverage these properties to optimize local and systemic delivery **(Chourasia & Jain, 2003).** For instance, the colon's stability supports peptide absorption, though inter-individual differences in transit and microbial profiles necessitate tailored approaches **(Davis et al., 1986).**

Advantages of Colon Drug Delivery System

The colon drug delivery system (CDDS) offers

several advantages, particularly for targeted therapy. One of its primary benefits is the ability to deliver drugs directly to the colon, making it highly effective for treating localized conditions such as ulcerative colitis, Crohn's disease, and colorectal cancer **(Maroni et al., 2013).** By bypassing the stomach and small intestine, CDDS protects drugs from degradation in acidic or enzymatic environments, enhancing their bioavailability **(Friend, 2005).** Additionally, the system allows for sustained or controlled drug release, which reduces the frequency of dosing and improves patient compliance **(Philip & Philip, 2010).** Another significant advantage is the avoidance of first-pass metabolism, as drugs absorbed in the colon bypass the liver, leading to increased therapeutic efficacy **(Sinha & Kumria, 2001).** The colon's lower proteolytic enzyme activity also makes CDDS suitable for delivering protein and peptide-based drugs, which are often unstable in the upper gastrointestinal tract **(Yang et al., 2002).** Furthermore, the system minimizes systemic side effects by localizing drug delivery, reducing systemic absorption and associated adverse effects (Friend, 2005).

Disadvantages of Colon Drug Delivery System

Despite its advantages, the colon drug delivery system (CDDS) has several limitations. One major challenge is the complexity of formulating a system that reliably targets the colon, as variations in gastrointestinal physiology such as pH, transit time, and microbial flora can affect its performance **(Maroni et al., 2013).** The colonic environment itself is highly variable, with factors like pH, motility, and microbial activity differing between individuals, which can lead to inconsistent drug release and absorption **(Philip & Philip, 2010).** Some systems rely on colonic bacteria to trigger drug release, which may not be consistent in all patients (e.g., those with altered gut microbiota) **(Gazzaniga et al., 2006).** Additionally, the colon has a smaller surface area and lower permeability compared to the small intestine, which can limit the absorption of certain drugs **(Sinha & Kumria, 2001).** There is also a risk of premature drug release in the stomach or small intestine, which can reduce the system's effectiveness **(Lautenschläger et al., 2014).** The development and manufacturing of CDDS are often expensive due to the complexity of the technology, and the system's reliance on colonic microflora for drug release may not be consistent in patients with altered gut microbiota **(Yang et al., 2002).** Furthermore, not all drugs are suitable for colonic delivery, particularly those requiring rapid systemic absorption, and patient-specific factors such as diet, disease state, and gastrointestinal motility can further affect the system's performance **(Friend, 2005).** Scaling up lab-scale formulations to large-scale production also poses significant challenges, affecting consistency and quality **(Maroni et al., 2013).**

Colon Absorption

The colon is a unique site for drug absorption, offering several advantages for targeted drug delivery. It's relatively neutral pH (6.8–7.8) and lower enzymatic activity compared to the stomach and small intestine make it suitable for delivering drugs that are sensitive to acidic or proteolytic degradation **(Friend, 2005).** Additionally, the colon's slower transit time (up to 48 hours) allows for prolonged drug release, which is beneficial for sustained or controlled-release formulations **(Philip & Philip, 2010).** The colon also plays a critical role in systemic drug absorption, particularly for drugs that are poorly absorbed in the upper gastrointestinal tract. This is because the colon bypasses first-pass metabolism, allowing for higher bioavailability of certain drugs **(Sinha & Kumria, 2001).** Furthermore, the colon's unique microbial environment can be leveraged for site-specific drug delivery, as colonic bacteria can degrade polysaccharides and other polymers to trigger drug release **(Yang et al., 2002).** These characteristics make the colon an attractive target for drug delivery, especially for treating localized diseases such as ulcerative colitis, Crohn's disease, and colorectal cancer **(Maroni et al., 2013).**

Absorption is impacted by the passage of ammonia, water, and electrolytes across the mucosa. When absorption enhancers are used, the drug's absorption in the colon is increased and shows effective absorption via different membranes. By denaturing membrane proteins, the absorption enhancers modify epithelial permeability, expand the paracellular pathway, alter lipid-protein interactions, and cause colonic electrolytes to compromise the integrity of the lipid barrier. They also disrupt the intracellular occluding junction complex. Gastrointestinal conditions like Crohn's disease, constipation, diarrhea, and others might affect the release and adsorption properties of colon-specific drug delivery systems **(Wang et al., 2022).**

CDDS challenges

Despite its potential, colon drug delivery faces several challenges. One major issue is the variability in colonic physiology, including differences in pH, transit time, and microbial activity among individuals, which can affect drug release and absorption **(Philip & Philip, 2010).** The colon's smaller surface area and lower permeability compared to the small intestine also limit the absorption of many drugs, particularly those with poor solubility or low permeability **(Sinha & Kumria, 2001).** Another challenge is the risk of premature drug release in the stomach or small intestine, which can occur due to the unpredictable nature of gastrointestinal transit and pH changes **(Lautenschläger et al., 2014).** Additionally, the reliance on colonic microflora for drug release can be problematic in patients with altered gut microbiota, such as those with inflammatory bowel disease or those taking antibiotics **(Yang et al., 2002).** Formulating a reliable colon-targeted drug delivery system is also complex and costly, as it requires precise control over drug release mechanisms and stability **(Maroni et al., 2013).** These challenges highlight the need for continued research and innovation to optimize colon drug delivery systems for clinical use.

Drug Criteria for Colon Drug Delivery System

The selection of appropriate drug candidates is critical for the success of colon-targeted drug delivery systems (CDDS). Ideal drug candidates for CDDS are those that are either intended for local action in the colon or have poor absorption in the upper gastrointestinal (GI) tract. Drugs used for treating localized colonic diseases, such as ulcerative colitis, Crohn's disease, and colorectal cancer, are prime candidates for CDDS **(Friend, 2005).** Examples include 5-aminosalicylic acid (5-ASA), corticosteroids, and immune-suppressants, which require direct delivery to the colon to maximize therapeutic efficacy and minimize systemic side effects **(Maroni et al., 2013).** Additionally, drugs that are unstable in the acidic environment of the stomach or susceptible to enzymatic degradation in the small intestine, such as peptides and proteins, are suitable for colonic delivery due to the colon's relatively neutral pH and lower proteolytic activity **(Yang et al., 2002).**

Drugs with low solubility or permeability in the upper GI tract but better absorption in the colon, such as certain anti-diabetic and anti-inflammatory agents, are also ideal candidates for CDDS **(Philip & Philip, 2010).**

Drug carriers play a pivotal role in ensuring the effective delivery of drugs to the colon. These carriers must be designed to protect the drug from premature release in the stomach and small intestine while ensuring controlled or sustained release in the colon. Common drug carriers include pH-sensitive polymers, time-dependent systems, and microbially triggered delivery systems **(Sinha & Kumria, 2001).** pH-sensitive polymers, such as Eudragit® coatings, dissolve at the neutral pH of the colon, ensuring site-specific release **(Lautenschläger et al., 2014).** Time-dependent systems rely on the relatively consistent transit time through the small intestine to achieve colonic delivery, while microbially triggered systems use colonic bacteria to degrade polysaccharides like pectin, chitosan, or guar gum, releasing the drug in the colon **(Maroni et al., 2013).** Nanoparticles, microparticles, and hydrogels are also being explored as advanced carriers for colon-specific drug delivery, offering improved drug stability and controlled release profiles **(Yang et al., 2002).**

In addition to drug candidates and carriers, other factors must be considered for successful colon drug delivery. These include the physicochemical properties of the drug, such as solubility, stability, and molecular weight, as well as the physiological conditions of the colon, such as pH, transit time, and microbial activity **(Philip & Philip, 2010).** The drug's absorption characteristics in the colon, which depend on the colonic mucosa's permeability and surface area, also play a crucial role in determining its suitability for CDDS **(Sinha & Kumria, 2001).** Furthermore, patient-specific factors, such as diet, disease state, and gut microbiota composition, can influence the performance of CDDS, necessitating personalized approaches to drug delivery **(Friend, 2005).** Advances in formulation technology, such as the use of prodrugs and nanotechnology-based carriers, are addressing some of these challenges, offering new opportunities for optimizing colon-targeted drug delivery **(Maroni et al., 2013).**

Mucoadhesion

Mucoadhesion refers to the ability of a material to adhere to mucosal surfaces, such as those found in the gastrointestinal tract, nasal cavity, or oral cavity. This phenomenon has gained significant attention in drug delivery systems due to its potential to enhance the residence time of formulations at the site of action, thereby improving drug bioavailability and therapeutic efficacy **(Smart, 2005).** Mucoadhesive drug delivery systems are particularly advantageous for localized treatment, sustained release, and targeted delivery, as they can prolong contact between the drug and the mucosal membrane, facilitating better absorption **(Andrews et al., 2009).** The mucosal layer, composed of glycoproteins, lipids, and water, provides a sticky and viscous surface that interacts with mucoadhesive polymers, enabling adhesion **(Peppas & Buri, 1985).** This review explores the mechanisms and theories underlying mucoadhesion, which are critical for designing effective mucoadhesive drug delivery systems.

Mechanism of Mucoadhesion

Mucoadhesion is a complex process that involves several stages: contact, consolidation, and prolonged adhesion. Initially, the mucoadhesive material comes into intimate contact with the mucosal surface, facilitated by wetting or swelling of the polymer **(Peppas & Buri, 1985).** During the consolidation stage, interpenetration and entanglement of polymer chains with the mucin glycoproteins occur, forming secondary chemical bonds such as hydrogen bonds, van der Waals forces, and electrostatic interactions **(Smart, 2005).** Finally, prolonged adhesion is maintained through the continuous interaction between the polymer and mucin, which can be influenced by factors such as polymer flexibility, molecular weight, and the presence of functional groups **(Andrews et al., 2009).** The mucoadhesion process is also affected by environmental conditions, including pH, hydration, and the presence of ions, which can alter the viscosity and adhesion strength of the polymer-mucin complex **(Peppas & Buri, 1985).**

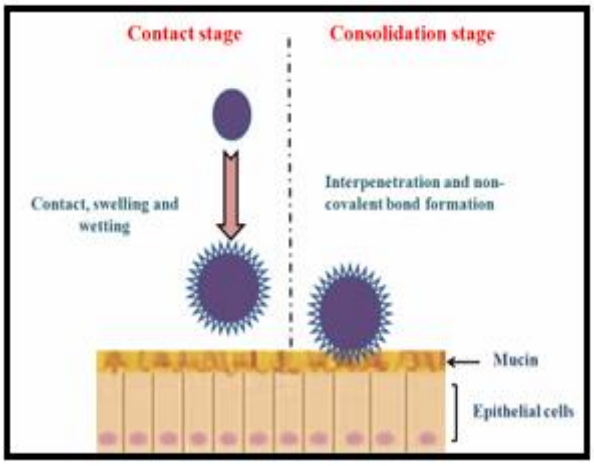


Fig. 2: Steps of mucoadhesion.

Theories of Mucoadhesion

Several theories have been proposed to explain the mechanisms of mucoadhesion, each focusing on different aspects of the interaction between mucoadhesive polymers and mucosal surfaces. The **adsorption theory** suggests that mucoadhesion occurs due to the formation of secondary chemical bonds, such as hydrogen bonds and van der Waals forces, between the polymer and mucin **(Smart, 2005)**. The **diffusion theory** proposes that interpenetration and entanglement of polymer chains with mucin glycoproteins are responsible for adhesion, with the depth of interpenetration depending on the molecular weight and flexibility of the polymer **(Peppas & Buri, 1985).** The **electronic theory** attributes mucoadhesion to the transfer of electrons between the polymer and mucin, resulting in the formation of an electrostatic double layer that enhances adhesion **(Andrews et al., 2009).** The **wetting theory** emphasizes the importance of surface energy and spreading coefficient, suggesting that mucoadhesion is influenced by the ability of the polymer to spread and wet the mucosal surface **(Smart, 2005).** Lastly, the **fracture theory** focuses on the mechanical strength of the adhesive bond, analyzing the force required to separate the polymer from the mucosal surface **(Peppas & Buri, 1985).** These theories collectively provide a comprehensive understanding of mucoadhesion, guiding the design and optimization of mucoadhesive drug delivery systems.

Mucoadhesive Polymers

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

1- Alginates

Alginates are naturally occurring polysaccharides derived from brown seaweed, primarily composed of β-D-mannuronic acid (M) and α-L-guluronic acid (G) units. These biopolymers are widely used in pharmaceutical and biomedical applications due to their biocompatibility, biodegradability, and ability to form hydrogels in the presence of divalent cations such as calcium **(Lee & Mooney, 2012).** Alginates have gained significant attention as mucoadhesive polymers because of their ability to interact with mucosal surfaces, making them ideal for drug delivery systems targeting the gastrointestinal tract, nasal cavity, and oral mucosa **(Pawar et al., 2011).** Their unique properties, such as high water absorption capacity and mild gelation conditions, further enhance their suitability for mucoadhesive applications **(George & Abraham, 2006).**

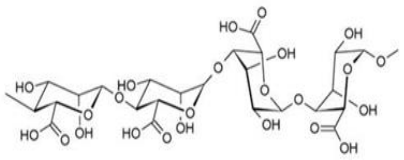


Figure 3: Chemical structure of Alginates (Rosiak, 2021)

Mucoadhesive Properties of Alginates

The mucoadhesive properties of alginates are primarily attributed to their ability to form hydrogen bonds and electrostatic interactions with mucin glycoproteins present on mucosal surfaces (Pawar et al., 2011). The carboxyl groups in the guluronic acid units of alginates play a crucial role in mucoadhesion by interacting with the sialic acid residues of mucin, creating a strong adhesive bond (George & Abraham, 2006). Additionally, the high water absorption capacity of alginates allows them to swell and form a gel-like layer, which enhances their contact with the mucosal surface and prolongs adhesion (Lee & Mooney, 2012). The mucoadhesive strength of alginates can be further modulated by adjusting their molecular weight, guluronic acid content, and crosslinking density, making them versatile polymers for designing mucoadhesive drug delivery systems (Pawar et al., 2011).

Applications of Alginates in Mucoadhesive Drug Delivery

Alginates have been extensively explored for mucoadhesive drug delivery systems due to their ability to provide sustained and localized drug release. In oral drug delivery, alginate-based mucoadhesive tablets and microspheres have been developed to enhance the residence time of drugs in the gastrointestinal tract, improving bioavailability and therapeutic efficacy (George & Abraham, 2006). For nasal and buccal drug delivery, alginate hydrogels have been used to create mucoadhesive films and gels that adhere to the mucosal surfaces, ensuring prolonged drug release and reduced systemic side effects (Pawar et al., 2011). Alginates have also been combined with other mucoadhesive polymers, such as chitosan and carbopol, to create hybrid systems with enhanced adhesive properties and controlled release profiles (Lee & Mooney, 2012). These applications highlight the versatility of alginates as mucoadhesive polymers in drug delivery.

Challenges and Future Perspectives

Despite their advantages, the use of alginates as mucoadhesive polymers faces several challenges. One limitation is their relatively weak mechanical strength, which can lead to premature detachment from mucosal surfaces under physiological conditions **(George & Abraham, 2006).** Additionally, the variability in the composition and molecular weight of natural alginates can affect their mucoadhesive performance, necessitating careful characterization and standardization **(Pawar et al., 2011).** To address these challenges, researchers are exploring chemical modifications of alginates, such as grafting with synthetic polymers or crosslinking with other biopolymers, to enhance their mucoadhesive properties and mechanical stability **(Lee & Mooney, 2012).** Future research is also focused on developing alginate-based nanocomposites and stimuli-responsive systems for advanced mucoadhesive drug delivery applications **(George & Abraham, 2006).**

1- Methocel K15M

Methocel K15M, a high-viscosity grade of hydroxypropyl methylcellulose (HPMC), is a

widely used polymer in pharmaceutical formulations due to its excellent mucoadhesive and controlled-release properties **(Nokhodchi et al., 2012).** Its ability to form a gel layer upon hydration makes it particularly suitable for colon-targeted drug delivery systems (CDDS), where prolonged residence time and controlled drug release are essential **(Tiwari et al., 2010).** Colon-targeted delivery using Methocel K15M is advantageous for treating localized colonic diseases such as ulcerative colitis, Crohn's disease, and colorectal cancer, as well as for systemic delivery of drugs that are poorly absorbed in the upper gastrointestinal tract **(Boateng et al., 2013).** The polymer's biocompatibility, non-toxicity, and ability to withstand the harsh conditions of the stomach and small intestine further enhance its suitability for colon-specific drug delivery **(Nokhodchi et al., 2012).**

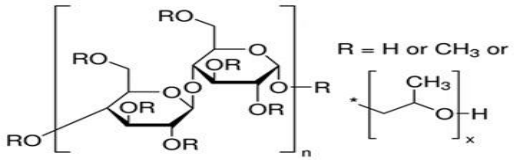


Figure no.4: Chemical structure of Methocel **(Tho, 2002)**

Mucoadhesive Properties of Methocel K15M in Colon Targeting

The mucoadhesive properties of Methocel K15M play a critical role in its effectiveness for colon-targeted drug delivery. When Methocel K15M comes into contact with the colonic mucosa, it swells and forms a gel layer that adheres to the mucosal surface, prolonging the residence time of the drug at the target site (Tiwari et al., 2010). This adhesion is facilitated by hydrogen bonding between the hydroxyl groups of Methocel K15M and the glycoproteins in the mucosal layer **(Nokhodchi et al., 2012).** The high viscosity and molecular weight of Methocel K15M contribute to its strong mucoadhesive strength, ensuring sustained drug release in the colon **(Boateng et al., 2013).** Additionally, the polymer's ability to maintain its gel structure in the colonic environment enhances its performance in colon-targeted delivery systems **(Tiwari et al., 2010).**

Applications of Methocel K15M in Colon-Targeted Drug Delivery

Methocel K15M has been extensively used in the development of colon-targeted drug delivery systems. It is commonly incorporated into matrix tablets, multiparticulate systems, and hydrogels designed to release drugs specifically in the colon **(Nokhodchi et al., 2012).** For example, Methocel K15M-based matrix tablets have been developed to deliver 5-aminosalicylic acid (5-ASA) for the treatment of ulcerative colitis, providing sustained drug release and improved therapeutic efficacy **(Tiwari et al., 2010).** The polymer has also been used in combination with other colon-specific polymers, such as Eudragit® and pectin, to create hybrid systems that enhance targeting efficiency and mucoadhesion **(Boateng et al., 2013).** Furthermore, Methocel K15M has been explored in the formulation of microspheres and nanoparticles for colon-targeted delivery, offering controlled release and improved drug stability **(Nokhodchi et al., 2012).**

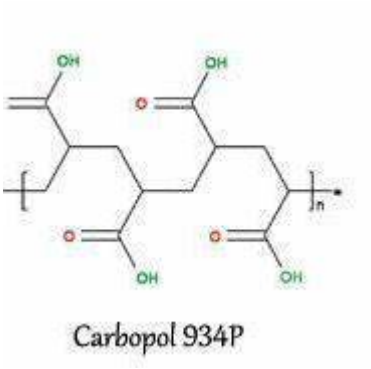
Challenges and Future Perspectives

Despite its advantages, the use of Methocel K15M in colon-targeted drug delivery systems faces several challenges. One limitation is its sensitivity to environmental conditions, such as pH and hydration, which can affect its swelling and gelation properties **(Tiwari et al., 2010).** Additionally, the high viscosity of Methocel K15M can make it difficult to process and formulate into certain dosage forms, requiring optimization of formulation parameters **(Boateng et al., 2013).** To address these challenges, researchers are exploring chemical modifications of Methocel K15M and its combination with other polymers to enhance its mucoadhesive properties and mechanical stability **(Nokhodchi et al., 2012).** Future research is also focused on developing Methocel K15M-based stimuli-responsive systems and nanocomposites for advanced colon-targeted drug delivery applications **(Tiwari et al., 2010).**

3. Carbopol 934

Carbopol 934 is a high-molecular-weight polymer of acrylic acid, crosslinked with allyl sucrose or allyl pentaerythritol, and is widely used in pharmaceutical formulations due to its excellent mucoadhesive and gel-forming properties

(Laffleur & Michalek, 2017). Its ability to swell in aqueous environments and form a viscous gel makes it particularly suitable for colon-targeted drug delivery systems (CDDS), where prolonged residence time and controlled drug release are essential **(Liu et al., 2005).** Carbopol 934is highly effective in adhering to mucosal surfaces, making it ideal for treating localized colonic diseases such as ulcerative colitis, Crohn's disease, and colorectal cancer **(Chaudhary et al., 2013).** Its biocompatibility, non-toxicity, and ability to withstand the harsh conditions of the gastrointestinal tract further enhance its suitability for colon-specific drug delivery **(Laffleur & Michalek, 2017).**



Carbopol 934P

Mucoadhesive Properties of Carbopol 934in Colon Targeting

The mucoadhesive properties of Carbopol 934 are attributed to its ability to form hydrogen bonds with mucin glycoproteins present on mucosal surfaces **(Liu et al., 2005).** When hydrated, Carbopol 934swells and forms a gel-like layer that adheres to the colonic mucosa, prolonging the residence time of the drug at the target site **(Chaudhary et al., 2013).** The polymer's high viscosity and molecular weight contribute to its strong adhesive strength, ensuring sustained drug release in the colon **(Laffleur & Michalek, 2017).** Additionally, Carbomer 934's ability to maintain its gel structure in the colonic environment enhances its performance in colon-targeted delivery systems **(Liu et al., 2005).** Its mucoadhesive properties can be further modulated by adjusting the pH and concentration of the polymer, making it a versatile material for colon-specific drug delivery **(Chaudhary et al., 2013).**

Applications of Carbopol 934in Colon-Targeted Drug Delivery

Carbopol 934has been extensively used in the development of colon-targeted drug delivery systems. It is commonly incorporated into matrix tablets, hydrogels, and multiparticulate systems designed to release drugs specifically in the colon **(Liu et al., 2005).** For example, Carbomer 934-based matrix tablets have been developed to deliver 5-aminosalicylic acid (5-ASA) for the treatment of ulcerative colitis, providing sustained drug release and improved therapeutic efficacy **(Chaudhary et al., 2013).** The polymer has also been used in combination with other colon-specific polymers, such as Eudragit® and chitosan, to create hybrid systems that enhance targeting efficiency and mucoadhesion **(Laffleur & Michalek, 2017).** Furthermore, Carbopol 934has been explored in the formulation of nanoparticles and microspheres for colon-targeted delivery, offering controlled release and improved drug stability **(Liu et al., 2005).**

Challenges and Future Perspectives

Despite its advantages, using Carbopol 934in colon-targeted drug delivery systems faces several challenges. One limitation is its pH and ionic strength sensitivity, which can affect its swelling and gelation properties **(Liu et al., 2005).** Additionally, the high viscosity of Carbopol 934 can make it difficult to process and formulate into certain dosage forms, requiring optimization of formulation parameters **(Chaudhary et al., 2013).** To address these challenges, researchers are exploring chemical modifications of Carbopol 934 and its combination with other polymers to enhance its mucoadhesive properties and mechanical stability **(Laffleur & Michalek, 2017).** Future research is also focused on developing Carbomer 934-based stimuli-responsive systems and nanocomposites for advanced colon-targeted drug delivery applications **(Liu et al., 2005).**

Challenges in Colon-Targeted Drug Delivery

1. Variable Gastrointestinal Conditions

The gastrointestinal (GI) environment is highly dynamic, with fluctuations in pH, enzyme activity, and transit time. These variations make it challenging to design mucoadhesive systems that can consistently release drugs in the colon **(Friend, 2005).** For example, the pH of the stomach (1.5–3.5) and small intestine (6.0–7.5) differs

significantly from that of the colon (6.8–7.8), which can affect the performance of pH-sensitive polymers **(Liu et al., 2005).** Additionally, variations in transit time can lead to premature drug release or incomplete drug delivery to the colon **(Chaudhary et al., 2013).** Advanced strategies, such as dual-responsive systems that combine pH and enzyme sensitivity, are being explored to address these challenges **(Laffleur & Michalek, 2017).**

2. Mucus Layer Variability

The thickness and composition of the mucus layer in the colon can vary significantly between individuals and in different disease states, such as inflammatory bowel disease (IBD) **(Liu et al., 2005).** This variability can impact the mucoadhesive properties and overall efficacy of drug delivery systems **(Friend, 2005).** For instance, a thicker mucus layer may hinder drug penetration, while changes in mucus composition can affect the adhesion of mucoadhesive polymers **(Laffleur & Michalek, 2017).** Researchers are investigating the use of mucolytic agents and mucus-penetrating nanoparticles to overcome these challenges **(Chaudhary et al., 2013).**

3. Biodegradability and Biocompatibility

Mucoadhesive systems must be both biodegradable and biocompatible to avoid long-term adverse effects **(Liu et al., 2005).** However, finding materials that balance these properties while maintaining strong mucoadhesion is challenging **(Friend, 2005).** Natural polymers, such as chitosan and alginate, are often used due to their biocompatibility, but their mechanical properties and degradation rates may not always meet the requirements for colon-specific delivery **(Laffleur & Michalek, 2017).** Synthetic polymers, such as Carbomer, offer better control over properties but may raise concerns about biocompatibility **(Chaudhary et al., 2013).**

4. Drug Stability

The harsh GI environment, characterized by acidic pH and enzymatic activity, can degrade drugs before they reach the colon **(Friend, 2005).** Ensuring drug stability during transit and release in the colon is critical for maintaining therapeutic efficacy **(Liu et al., 2005).** Strategies to protect drugs include encapsulation in pH-sensitive polymers or the use of prodrugs that are activated by colonic enzymes **(Laffleur & Michalek, 2017).** However, these approaches require careful optimization to ensure consistent performance **(Chaudhary et al., 2013).**

5. Optimal Release Kinetics

Achieving controlled and sustained drug release in the colon is essential for maximizing therapeutic efficacy **(Friend, 2005).** The design of mucoadhesive systems must carefully consider release kinetics to ensure that the drug is delivered at the desired concentrations over an extended period **(Liu et al., 2005).** Challenges include balancing the rate of polymer swelling, drug diffusion, and mucoadhesive strength **(Laffleur & Michalek, 2017).** Advanced systems, such as nanoparticles and hydrogels, are being developed to achieve optimal release profiles **(Chaudhary et al., 2013).**

6. Patient Compliance

Mucoadhesive drug delivery systems must be convenient and acceptable to patients to ensure compliance **(Friend, 2005).** Factors such as dosage frequency, size of the dosage form, and ease of administration can influence patient adherence **(Liu et al., 2005).** For example, large or complex dosage forms may be difficult for some patients to swallow, while frequent dosing can be inconvenient **(Laffleur & Michalek, 2017).** Designing user-friendly systems, such as mucoadhesive films or gels, can improve patient compliance **(Chaudhary et al., 2013).**

7. Regulatory Acceptance

Regulatory approval for mucoadhesive drug delivery systems requires demonstrating safety, efficacy, and consistency **(Friend, 2005).** Meeting these requirements adds complexity to the development process, particularly for novel systems that combine multiple polymers or advanced technologies **(Liu et al., 2005).** Regulatory agencies also require extensive preclinical and clinical testing to ensure that the systems perform as intended in diverse patient populations **(Laffleur & Michalek, 2017).** These requirements can increase the time and cost of development **(Chaudhary et al., 2013).**

8. Scale-up Challenges

Scaling up mucoadhesive drug delivery systems from laboratory-scale production to large-scale manufacturing can be challenging **(Friend, 2005).** Maintaining the uniformity and reproducibility of the systems during scale-up is critical for ensuring consistent performance **(Liu et al., 2005).** Factors such as polymer blending, crosslinking, and drug loading must be carefully controlled to avoid batch-to-batch variability **(Laffleur & Michalek, 2017).** Advanced manufacturing techniques, such as 3D printing and continuous processing, are being explored to address these challenges **(Chaudhary et al., 2013).**

Pharmaceutical Applications

Plecanatide:

A peptide drug used to treat chronic idiopathic constipation and IBS, plecanatide is susceptible to degradation in the upper GIT. Mucoadhesive polymers such as sodium alginate, Methocel K15M and Carbopol 934 have been used to develop colon-targeted formulations of plecanatide, enhancing its stability and bioavailability **(Gupta et al., 2020).**

Curcumin:

A natural polyphenol with anti-inflammatory and anticancer properties, curcumin has poor solubility and bioavailability. Mucoadhesive polymers like sodium alginate, Methocel K15M and Carbopol 934 have been employed to develop colon-targeted curcumin formulations, improving its therapeutic efficacy for colonic diseases **(Zhang et al., 2021).**

The kneading technique is a widely used method for preparing inclusion complexes of curcumin with Hydroxypropyl-β-cyclodextrin (HP-β-CD). This technique involves the physical mixing of curcumin and HP-β-CD in the presence of a small amount of solvent (e.g., water or ethanol) to form a paste, which is then kneaded until a homogeneous mixture is obtained. The mixture is dried and ground into a fine powder, resulting in an inclusion complex with improved solubility and bioavailability of curcumin. **(Tonnesen et al., 2002)**

Hydroxypropyl-β-cyclodextrin (HP-β-CD) is the most preferred cyclodextrin for increasing the bioavailability of curcumin. This preference is due to its favorable properties, such as high water solubility, low toxicity, and excellent complexation efficiency with curcumin (**Yallapu et al., 2012).** Below are the reasons why HP-β-CD is widely used for curcumin:

1. Enhanced Solubility

Curcumin is highly lipophilic and has extremely low water solubility, which limits its bioavailability. HP-β-CD forms inclusion complexes with curcumin, significantly improving its aqueous solubility **(Tonnesen et al., 2002).** This enhanced solubility facilitates better absorption in the gastrointestinal tract (GIT).

2. Improved Stability

Curcumin is prone to degradation in alkaline pH and under light exposure. HP-β-CD protects curcumin from degradation by encapsulating it within its hydrophobic cavity, thereby enhancing its chemical stability **(Yallapu et al., 2012).**

3. Increased Bioavailability

The formation of an inclusion complex with HP-β-CD improves the dissolution rate and permeability of curcumin, leading to higher plasma concentrations and improved bioavailability **(Tonnesen et al., 2002).** Studies have shown that HP-β-CD-curcumin complexes exhibit significantly higher bioavailability compared to free curcumin **(Yallapu et al., 2012).**

4. Low Toxicity

HP-β-CD is considered safe for pharmaceutical use, with low toxicity and good biocompatibility. It is approved by regulatory agencies such as the FDA for use in drug formulations **(Stella & He, 2008).**

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.

Conclusion

Mucoadhesive polymers have emerged as a promising strategy for colon-targeted drug delivery, addressing challenges such as premature drug release, low solubility, and poor mucosal adhesion. Sodium alginate, Carbopol 934, and Methocel K15M are widely used mucoadhesive polymers that enhance drug residence time and absorption in the colon. Despite their advantages, challenges such as variability in mucoadhesion and mucus turnover remain. Future research should focus on developing novel mucoadhesive polymers and formulations to overcome these limitations and improve the therapeutic efficacy of colon-targeted drug delivery systems.

CONFLICT OF INTEREST

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

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