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Advancements in Mucoadhesive Delivery Systems for Gastroenterology

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Abstract: This review aimed to provide a comprehensive overview of recent advancements and applications of mucoadhesive delivery systems specifically designed for the treatment and diagnosis of gastrointestinal (GI) tract diseases. This review focuses on the potential of these systems to address the challenges associated with conventional dosage forms, offering insights for researchers, clinicians, and pharmaceutical professionals involved in the development of innovative GI therapies. The review examines various mucoadhesive delivery systems, including tablets, pellets, gels, and micro/nanoparticles, and details their formulations and mechanisms of action. Special attention is paid to the interaction between these delivery systems and the complex GI environment. The analysis included a comparative evaluation of different systems to highlight their respective

benefits and limitations in enhancing drug residence time and achieving targeted, sustained drug release. Our findings suggest that mucoadhesive properties significantly improve the performance of drug delivery systems in the GI tract by increasing residence time and ensuring more controlled, localized drug release. Each system presents unique attributes that make it a promising candidate for improving therapeutic outcomes in gastroenterology. This review highlights the enhanced efficacy of mucoadhesive systems compared with traditional methods. The review highlights the innovative potential of mucoadhesive delivery systems in overcoming the limitations of conventional dosage forms, particularly in the context of GI diseases. By improving drug delivery precision and retention in the GI tract, these systems represent significant advancements in pharmaceutical technology, offering new avenues for both diagnosis and treatment.

Keywords: gastrointestinal tract; gastroenterology; mucoadhesive delivery system; gastric mucosa

胃肠病学黏膜粘附递送系统的进展

摘要：本综述旨在全面概述专门用于治疗和诊断胃肠道(GI)疾病的黏膜粘附递送系统的最新进展和应用。本综述重点介绍这些系统应对传统剂型相关挑战的潜力，为参与开发创新GI疗法的研究人员、临床医生和药学专业人士提供见解。本综述研究了各种黏膜粘附递送系统，包括片剂、颗粒、凝胶和微/纳米颗粒，并详细介绍了它们的配方和作用机制。特别关注这些递送系统与复杂的GI环境之间的相互作用。分析包括对不同系统的比较评估，以突出它们在延长药物停留时间和实现有针对性的持续药物释放方面的各自优势和局限性。我们的研究结果表明，黏膜粘附特性通过增加停留时间和确保更受控制的局部药物释放，显著改善了胃肠道药物递送系统的性能。每个系统都具有独特的属性，使其成为改善胃肠病学治疗结果的有希望的候选者。本综述重点介绍了黏膜粘附系统与传统方法相比的增强功效。本综述重点介绍了黏膜粘附给药系统在克服传统剂型局限性方面的创新潜力，特别是在胃肠道疾病方面。通过提高药物输送精度和胃肠道保留时间，这些系统代表了制药技术的重大进步，为诊断和治疗提供了新的途径。

关键词：胃肠道；胃肠病学；粘膜粘附递送系统；胃粘膜

1. Introduction

The gastrointestinal (GI) tract has emerged as a marvel of intricate physiological design, charting a complex course within the human body with a remarkable length of 9 m and dynamic diameters [1]. It plays a central role in the intricate processes of nutrient digestion and absorption and in the elimination of solid waste from the body. Comprising the mouth, pharynx, esophagus, stomach, small intestine, and large intestine, the GI tract forms a dynamic and interconnected network of organs, each contributing to the seamless coordination of digestive functions. The liver, pancreas, and gallbladder are the solid organs of the digestive system [2, 3].

At its core, the major portion of the GI tract, spanning from the esophagus to the large intestine, functions as a collapsed muscular tube. This flexible tube expands or distends in response to the transport of liquids or food, showing its remarkable adaptability to the ever-changing contents it encounters. Our exploration initiates from the mouth and pharynx, guiding us through distinct segments, each characterized by unique anatomical and functional features [1–3].

Descending into the esophagus, a hollow muscular tube measuring 25–30 cm in length and 2–3 cm in diameter, we confront the widespread challenge of gastroesophageal reflux disease (GERD), which involves the irritation of the esophageal wall by stomach acids, resulting in the discomfort of painful heartburn. The diagnostic journey often involves gastroscopy, uncovering potential complications such as hiatus hernia, Barrett's esophagus, or cancer, all of which are confirmed through meticulous histological analysis and biopsy sampling [4].

Transitioning further down, the base of the esophagus introduces us to the stomach, a 25-cm-wide collapsed sac-like chamber with an impressive capacity to expand from 0.1 to 4 liters. The internal stomach wall, shielded by a protective layer of mucus, experiences robust peristaltic contractions, which contribute to the intricate interplay of mechanical and chemical digestion. Peptic ulcers, characterized by crater-like lesions exposing the stomach wall to caustic stomach contents, present a common challenge, often necessitating upper GI endoscopy for diagnosis and ruling out gastric malignancy [5].

Continuing our journey into the small intestine, a 6-meter-long tube with a diameter of approximately 3 cm, we encounter a complex interplay of smooth muscular contractions and digestive juices. Disorders such as lactose intolerance and celiac disease underscore the importance of comprehending the nuanced functionality of mucosal cells, calling for reliable diagnostic methods such as biopsy or, increasingly, antibody tests for identifying conditions such as celiac disease [6].

As the material exits the small intestine, the focus shifts to the large intestine, a 1.5-m-long muscular tube encompassing the cecum, colon, rectum, and anal canal. This segment crucially facilitates water absorption and hosts a diverse community of bacteria that is pivotal for digestion. Challenges persist with disorders such as diverticular disease, chronic inflammation, ileal disease, ulcerative colitis, and Crohn's disease, underscoring the need for a comprehensive understanding and advanced diagnostic and therapeutic interventions in the expansive domain of GI health [7]. Figure 1 depicts the anatomical structures of the GI system with a focus on highlighting the major diseases affecting each organ.

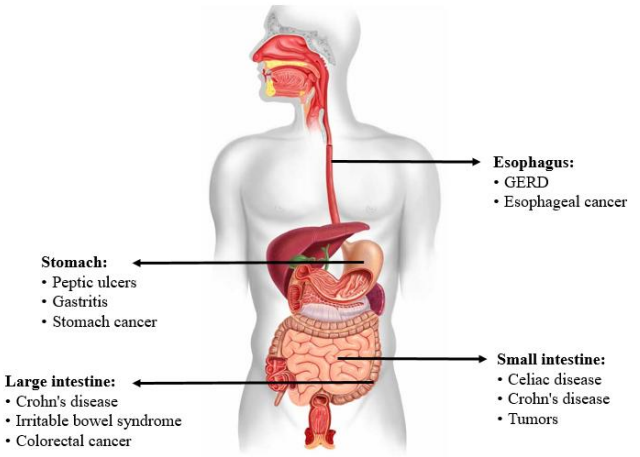

Figure 1. Anatomical overview of the GI system; major diseases in each organ [7]

Additionally, the intricacies in treating a spectrum of GI diseases stem from the intricate characteristics of the GI tract. With an extensive length of 9 m, achieving consistent drug distribution and absorption throughout the tract poses a considerable challenge [8]. The dynamic and flexible nature of the GI tract during digestion presents challenges in controlled drug release and maintaining optimal therapeutic concentrations. The pH variations from highly acidic in the stomach to a more neutral environment in the small intestine further complicate drug design for maximum efficacy. The ever-present and dynamic microbial flora within the GI tract adds an additional layer of complexity that influences drug interactions, metabolism, and absorption. Addressing selective absorption processes in the small intestine necessitates inventive drug design [9]. The segmented structure of the large intestine presents hurdles in delivering therapeutics to specific areas, requiring creative strategies for disorders that affect distinct segments. Individual variations in the GI anatomy, treatment responses, and continuous material movement through the tract amplify the challenges of effective therapy. Specific disease characteristics and the need for invasive diagnostic procedures contribute to the intricate management of GI diseases [6, 7]. Overcoming these challenges requires ongoing advancements in drug delivery technologies, a nuanced understanding of the GI microbiome, and the evolution of personalized treatment approaches to enhance the therapeutic effectiveness for a diverse array of GI disorders.

Furthermore, significant progress in the diagnosis and treatment of GI diseases has stemmed from technological advancements and evolving medical strategies. Techniques such as endoscopic ultrasound and virtual colonoscopy provide precise imaging, whereas molecular and genetic testing allows personalized treatment plans [10]. Noninvasive diagnostic methods, such as blood and stool tests, minimize the need for invasive procedures. Therapeutic endoscopy, including procedures such as endoscopic mucosal resection and dissection, has revolutionized both diagnosis and treatment [11]. Targeted pharmacological treatments, such as biologics and immunomodulators, address specific aspects of GI conditions [12]. Precision medicine, customized interventions based on individual profiles, and telemedicine for remote consultations further enhance patient care. Artificial Intelligence applications assist in accurate diagnosis through the analysis of medical images and patient data [13]. Additionally, the integration of advanced nanotechnology introduces groundbreaking possibilities, enabling targeted drug delivery and heightened diagnostic precision at the molecular level [14]. These multifaceted advancements collectively drive progress in GI care, fostering more efficient, personalized, and patient-centered approaches with ongoing breakthroughs in the comprehensive management of GI health.

In this review, we discuss the state-of-the-art drug delivery systems tailored to the intricate landscape of the GI tract. Focusing on mucoadhesive platforms, such as tablets, pellets, gels, and micro/nanoparticles, we aimed to provide a thorough overview of their roles in gastroenterology. Our exploration dissects each mucoadhesive method and examines formulations, mechanisms, and their transformative impact on the treatment and diagnosis of various GI tract conditions. By extending the drug residence time to enable targeted release, these advanced systems show great promise.

The focus of this review on mucoadhesive delivery

systems is driven by the complex physiological and pathological landscape of the GI tract, which presents significant challenges for effective drug delivery. With its intricate structure, variable pH environment, and dynamic motility, the GI tract poses barriers to achieving optimal drug absorption and retention. Conventional drug delivery methods often struggle with poor bioavailability and a lack of targeted release. Thus, mucoadhesive systems, known for their ability to adhere to mucosal surfaces and extend the residence time of therapeutic agents, were chosen as research objects. These systems, including tablets, pellets, gels, and micro/nanoparticles, have the potential to overcome the limitations of traditional formulations by ensuring localized and sustained drug release, which is critical for effectively addressing GI diseases.

2. Mucoadhesive Delivery Systems

Mucoadhesion refers to the ability of a material, typically a polymer, to adhere to mucosal surfaces found in different parts of the body, including the GI tract, respiratory system, and reproductive system. This interaction involves the binding of mucoadhesive polymers to mucins on the mucosal surface [15].

Mucins are glycoproteins produced by the mucous glands in the body and constitute a major component of mucus [16]. They are large, heavily glycosylated proteins that form a gel-like layer on mucosal surfaces and play essential roles in lubrication, protection, and immunity [17]. There are various types of mucins, each with unique structures and functions. Examples include MUC1, MUC2, MUC3, MUC4, MUC5AC, and MUC6 in the GI tract; MUC5B and MUC5AC in the respiratory tract, and MUC16 in the reproductive system [18]. Mucins significantly influence the interactions between drugs and mucosal surfaces. They can act as a barrier, impeding drug penetration, while also serving as drug reservoirs by binding to drugs and prolonging their presence on mucosal surfaces [19].

Diverse administration routes, including ocular, nasal, buccal, gingival, GI (oral), vaginal, and rectal routes, contribute to the appeal and adaptability of mucoadhesive drug delivery systems in dosage form development. Recent reports indicate a rapid expansion in the market for these systems [15, 20].

Mucoadhesive delivery systems present a range of advantages that significantly enhance their efficacy in drug administration. First, they prolong the duration for which the dosage form stays at the absorption site, fostering extended contact with the mucosal surface. This prolonged interaction contributes to increased drug absorption, ultimately amplifying the therapeutic effectiveness of the administered drug [21]. The mucoadhesive system ensures exceptional accessibility to the absorption site, facilitating swift absorption owing to the substantial blood supply and robust blood flow rates characteristic of mucosal tissues. Additionally, the mucoadhesive system plays a vital role in boosting drug bioavailability by overcoming the challenges associated with the first-pass metabolism. Furthermore, the drug is shielded from degradation in the acidic environment of the GI tract, thereby ensuring its stability and efficacy. The mucoadhesive delivery system promotes improved patient compliance, offering a user-friendly drug administration experience. Finally, the system enables a quicker onset of action, leveraging its interaction with the mucosal surface, thereby optimizing the overall therapeutic outcomes [22, 23].

3. Mucoadhesive Polymers

Mucoadhesive polymers are pivotal for the success of mucoadhesive drug delivery systems, ensuring effective retention at the mucous layer and sustained drug release. Polymers possessing carboxyl, amine, or hydroxyl groups with specific molecular weights demonstrate potential for prolonged system retention within the mucous layer. Commonly used mucoadhesive polymers include cellulose, chitosan, pectin, hyaluronic acids, alginates, and thiolated derivatives. Notably, specific mucoadhesive polymers such as chitosan, hyaluronic acid, alginate, polyacrylates, and cellulose derivatives not only extend residence time but also enhance drug permeability through the epithelium by modifying tight junctions between cells [24, 25].

The polymers utilized in mucoadhesive drug delivery systems include cationic, anionic, nonionic, and thiolated polymers. Prominent examples include acrylate polymers, cellulose derivatives, chitosan, and alginates. The system design incorporates various composite materials, chemically modified polymers, and combinations of polymers. The lack of standardized assay methods and diverse experimental evaluations poses challenges in categorizing polymers based on their mucoadhesion strength. Additionally, classifying polymers based on their mechanism of mucoadhesion is intricate because polymers often act through multiple mechanisms or mechanisms that are not fully understood [26].

Various theories have been formulated to elucidate the mechanisms underlying mucoadhesion, drawing inspiration from the classical metallic and polymer adhesion theories. The primary theories include the electronic, adsorption, wetting, and diffusion theories. The electronic theory posits electron transfer between mucus and mucoadhesive, resulting in the formation of a double layer of electrical charges and attractive forces. In the adsorption theory, molecular bonding and attractive forces, including hydrogen and van der Waals bonds, play a significant role. The wetting theory underscores the importance of interfacial energy

in mucoadhesion, correlating mucus and mucoadhesive surface tension. The diffusion theory encompasses the interpenetration and physical entanglement of protein and polymer chains in mucus and mucoadhesive substances, influenced by various factors. The essential requirements for effective mucoadhesive drug delivery and intestinal locomotion include adhesiveness, swelling for drug release, prolonged residence time, and biocompatibility [26, 27].

For further insight, Table 1 provides information on the classification, categories, and examples of mucoadhesive polymers.

Table 1. Classification and examples of mucoadhesive polymers [27]

Polymer	Source	Charge	Solubility	Mucoadhesive Interaction
Chitosan	Natural	Cationic	Water-insoluble	Electrostatic interaction
Agarose	Natural	Nonionic	Water-insoluble	-
Gelatin	Natural	Nonionic	Water-insoluble	-
Sodium alginate	Natural	Anionic	Partially soluble	-
Pectin	Natural	Anionic	Partially soluble	-
Carrageenan	Natural	Anionic	Water-insoluble	-
Poly(vinyl alcohol)	Synthetic	Nonionic	Water-soluble	Hydrogen bonding
Carboxymethyl cellulose	Synthetic	Anionic	Water-soluble	-
Carbopol	Synthetic	Anionic	Water-soluble	Hydrogen bonding
Polycarbophil	Synthetic	Anionic	Water-insoluble	Hydrogen bonding
Polyacrylates	Synthetic	Anionic	Water-insoluble	Covalent bonding

4. Mucoadhesive Systems for GI Applications

Oral administration of therapeutic agents is the primary and preferred method, but it faces challenges such as first-pass metabolism and stability issues in the GI environment. Factors such as gastric pH variation, irritation, and interaction with mucosal membranes further complicate oral delivery [23, 28]. To address these issues, it is crucial to explore alternative administration routes such as transmucosal delivery. Transmucosal delivery offers distinct advantages by leveraging the milder environment of the mucosal lining, reducing drug dosage, and minimizing systemic side effects compared with the hostile environment of oral delivery. The GI tract, which is essential for digestion, comprises layers such as the mucosa, which plays a crucial role in absorption and secretion. Despite facing challenges such as low pH in the stomach and specific absorption in the large intestine, the adaptive structure of the mucosa caters to organ-specific needs. The interdigestive myoelectric cycle regulates digestive functions in the GIT mucosa, creating an ideal environment for mucoadhesive delivery systems [24].

Mucoadhesive drug delivery systems, including tablets, lozenges, solid inserts, wafers, pessaries, films, gels, micro- and nano-particulate suspensions, in situ gelling systems, and sprays, address these challenges [15, 29]. By incorporating polymeric excipients that are crucial for mucoadhesivity, these formulations aim to adhere to mucosal surfaces, optimize bioavailability, and achieve targeted drug delivery in the GI tract [27, 30]. This review explores the applications and benefits of mucoadhesive delivery systems in gastroenterology, highlighting their pivotal role in overcoming barriers and enhancing drug delivery for the treatment and diagnosis of GI diseases.

4.1. Mucoadhesive Tablets

Tablet dosage forms are solid pharmaceutical formulations characterized by convenience, portability, and ease of administration. These compressed or molded units contain active pharmaceutical ingredients and various excipients. Tablets offer several advantages, including accurate dosing, stability, and ease of manufacture and storage. It provides a convenient and patient-friendly method for oral drug delivery, ensuring precise dosage administration. However, disadvantages include the potential for a slower onset of action compared to liquid forms, difficulty for patients with swallowing issues, and limitations in flexibility for dose adjustments. Additionally, certain individuals may experience difficulty in fragmenting or subdividing tablets for personalized dosage requirements [31]. Overall, tablets are widely used and versatile dosage forms in pharmaceutical practice [32].

Mucoadhesive tablets possess the potential for controlled-release drug delivery, and integrating mucoadhesive properties into tablets offers additional advantages. These tablets can be specifically designed to adhere to various mucosal tissues within the GI tract, providing opportunities for both localized and systemically controlled drug release. The mucoadhesive nature allows prolonged contact with the mucosa, enhancing drug absorption and bioavailability. Moreover, mucoadhesive tablets offer targeted delivery, minimize systemic side effects, and improve therapeutic outcomes. The ability to tailor these tablets to adhere to specific regions of the GI tract highlights their versatility in achieving optimal drug release profiles for various pharmaceutical formulations [24, 33].

Manivannan et al. [31] developed mucoadhesive tablets for once-daily esomeprazole controlled release using carbopol as the primary polymer and different hydroxypropyl methylcellulose grades as secondary polymers. Nine formulations were prepared, and formulation FB2 proved to be optimal for sustained drug release, adhering closely to the desired kinetics. Mucoadhesive strength, evaluated using goat intestines, showed that FB2 had high mucoadhesion. Stability studies over a month confirmed compliance, meeting the criteria for hardness, thickness, friability, and weight variation. Formulation FB2 (Carbopol 934p and HPMC K15M) demonstrated superior mucoadhesive properties among the tablet formulations, satisfying the in vitro drug release and assay criteria, exhibiting high mucoadhesive strength, and conforming to zero-order release kinetics with diffusion-controlled drug release. Further studies are recommended to include in vivo assessments and extended stability evaluations [31].

Reddy Donthi and Dudipala [34] aimed to address upper GI ulcers by developing a famotidine multi-unit tablet system. The matrix polymers POLYOXWSR 1105 and HPMC K4M controlled the drug release, and a direct compression technique was employed for tablet preparation. Physicochemical parameters, including weight variation, hardness, friability, buoyancy, drug content, in vitro dissolution, and mucoadhesive properties of porcine gastric mucosa, were evaluated, all meeting USP standards. The optimized formulation exhibited a floating lag time of 10 ± 2 s, total floating time of 12 h, and in vitro release of 99.14 ± 3.21% in 12 h. The mucoadhesion time surpassed 12 h in pH 6.8 phosphate buffer. In vivo radiographic imaging conducted on healthy human volunteers demonstrated a mean gastric residence time of 8 h for a single mini tablet [34].

Patil and Talele [35] suggested developing a mucoadhesive sustained-release system for lafutidine, a histamine H2-receptor antagonist, to enhance bioavailability. They created mucoadhesive tablets using natural polymers: sodium alginate, xanthan gum, and Karaya gum. Mucoadhesion, a complex process involving wetting and polymer chain interpenetration, was explored. Tablets containing xanthan gum exhibited favorable results, indicating the potential for prolonged drug release in the stomach, improved bioavailability, and reduced dosing frequency. Non-Fickian release was identified as a drug release mechanism. The optimized tablet (B3) had mucoadhesive strength of 435 g. In vivo studies on rabbits using X-ray imaging revealed effective adhesion in the stomach for 410 h. After 3 months of storage under specified conditions, the optimized lafutidine mucoadhesive tablets showed no significant changes in appearance, drug content, mucoadhesive properties, or dissolution pattern [35].

4.2. Mucoadhesive Pellets

Pellets, characterized by their spherical shape and size ranging from 0.5 to 2.0 mm, present various advantages in drug delivery. These include attributes such as free flow, mechanical stability, and enhanced properties of powdered substances, which foster stability. Pelletization transforms pharmaceutical ingredients and excipients into small spherical units suitable for oral administration. Despite being primarily intended for oral use, pellets have also been used in implants for subcutaneous and intramuscular drug delivery. Pharmaceutical pellets offer therapeutic advantages, including uniform drug absorption throughout the GI tract, customizable peak plasma drug concentrations, minimized adverse effects, and reduced irritation of the gastric mucosa. Challenges associated with pellet-based drug delivery include difficulties in tablet compression, specialized equipment requirements, and control complexities due to multiple process variables [36].

In parallel, mucoadhesive pellets, crafted by integrating suitable concentrations and types of mucoadhesive polymers, offer distinct advantages, particularly in GI treatment and diagnostics. These pellets can be tailored to precise drug delivery to gastric, colonic, and vaginal regions. Their enhanced adhesion to mucosal surfaces prolongs their residence time, thereby facilitating improved drug absorption. The mucoadhesive performance was evaluated through tests such as mucoadhesion wash-off or texture analyzer assessments. Comparative studies of mucoadhesive performance involve the assessment of biopolymers, synthetic polymers, and composite polymers. The appeal of mucoadhesive pellets lies in their easy development, evaluation, and scalability in industrial settings, making them attractive to pharmaceutical researchers and industry players seeking commercial applications in GI treatments and diagnostics.

In addition, Gattani et al. [37] explored the formulation of floating-mucoadhesive beads composed of alginate and hydroxypropyl methylcellulose, incorporating clarithromycin. The principal aim of this study was to prolong the antibiotic's contact duration, thereby enhancing its efficacy in the treatment of gastric ulcerations. The floating-mucoadhesive beads were meticulously prepared and characterized for their in vitro performance, followed by an exploration of ex vivo outcomes in albino Wistar rats. The beads were crafted using the ionic gelation technique, employing calcium chloride as the gelating agent, and incorporating liquid paraffin to facilitate the floating property. The comprehensive evaluation encompassed parameters such as particle size, drug entrapment, swelling, and surface morphology using scanning

electron microscopy. Further investigations involved X-ray radioimaging studies in rabbits, in vitro mucoadhesion assessments using rat stomach mucosal membranes, and in vitro drug release studies. The ex vivo performance of alginate-hydroxypropyl methylcellulose beads was scrutinized using albino rats and compared with that of simple alginate-calcium beads. The study concluded that alginate-hydroxypropyl methylcellulose beads exhibit potential as a floating-mucoadhesive drug delivery system for the effective delivery of clarithromycin in the treatment of stomach ulcers [37].

Furthermore, Rabisková et al. [38] developed coated pellets for the targeted delivery of rutin to the colon and assessed their effectiveness in experimental colitis in rats. Pellets were coated with three formulations by extrusion/spheronization. Dissolution studies simulated the GI conditions. Alginate/chitosan-coated pellets demonstrated low rutin release in the upper GI tract and rapid release in the colon, suggesting a favorable targeted delivery. In a colitis rat model, orally administered pellets and rectally administered rutin solutions were compared. Rutin (10 mg/kg) had positive effects on colonic healing. The best efficacy was observed with orally administered pellets coated with alginate/chitosan and rectally administered rutin solution, offering a promising approach for severe colitis therapy [38].

Additionally, Atyabi et al. [39] examined the mucoadhesive properties of pectinate beads for oral drug delivery to different parts of the GI tract. This study assessed the in vitro mucoadhesive features of pectinate bead formulations on everted rat GI sections, with and without trimethyl chitosan, a chitosan derivative known for absorption enhancement and moderate mucoadhesion. Comparisons were made between mucoadhesive Carbomer 934P granules and non-mucoadhesive ethyl cellulose-coated pellets. Water uptake studies were performed to understand the effects of hydration on mucoadhesion. Pectinate beads demonstrated mucoadhesive properties, similar to those of Carbomer 934P granules, across the GI tissues. Trimethyl chitosan-containing beads showed increased mucoadhesion in the dry state, whereas simple pectinate beads were more mucoadhesive in the moist state. This investigation indicates that the incorporation of trimethyl chitosan into beads may enhance mucoadhesive properties, particularly when prehydration can be circumvented, such as when beads are encapsulated in a specific oral delivery system prior to reaching the target tissue. Further research is necessary to confirm its in vivo feasibility [39].

Recently, Vaja and Detroja [40] optimized a rectal suppository with mucoadhesive mesalamine pellets for convenient once-daily treatment of inflammatory bowel disease. The process involved crafting mucoadhesive pellets through extrusion spheronization and loading them into rectally administered suppositories. The pellets were evaluated, and the optimized batch with Eudragit RLPO and carrageenan showed favorable mucoadhesion, swelling, and drug release characteristics. These pellets were incorporated into cocoa butter suppositories, which melted at 35–37°C, disintegrated in 8–9 min, and maintained drug release akin to that of standalone mucoadhesive pellets. The study suggested that this approach could offer a once-daily regimen, potentially reducing drug requirements and associated side effects [40].

4.3. Micro- and Nanoparticles

Micro- and nanoparticles have emerged as promising tools for GI treatment, characterized by their minute size and potential to revolutionize drug delivery. Their small dimensions, ranging from micrometers to nanometers, result in an increased surface area, which facilitates efficient interactions with mucosal surfaces within the GI tract. The advantages of these particles include enhanced bioavailability, controlled drug release, and the ability to tailor formulations to meet specific therapeutic requirements. However, challenges such as limited drug-loading capacity and complex formulation processes must be addressed [41]. Despite their restricted drug loading, mucoadhesive micro- and nanoparticles have been extensively explored for their ability to adhere to mucosal surfaces. This unique feature enables prolonged contact with the oral mucosa, potentially improving drug absorption. The very large specific surface area allows robust interactions, and the sustained-release characteristics contribute to prolonged therapeutic effects. In summary, the intricate design of micro- and nanoparticles, especially when engineered to be mucoadhesive, holds significant promise for advancing GI drug delivery and optimizing therapeutic outcomes [24].

Preisig et al. [42] explored the potential of mucoadhesive microparticles formulated in a capsule for local drug delivery to the GI tract. Despite their promise, challenges such as swelling and agglomeration of hydrophilic polymers in the GI milieu may impact particle retention. To address this, a dry coating with nano-sized hydrophilic fumed silica was examined for its effect on the dispersion and retention of mucoadhesive microparticles. This study focused on antibiotic therapy for Clostridium difficile infections using metronidazole as a model drug. The microparticles, prepared using a two-step fluidized-bed method, were coated with the mucoadhesive polymer chitosan. The optimal molecular weight and chitosan content were determined based on particle retention in porcine colonic mucosa under dynamic flow conditions. Microparticles coated with 5% of low

molecular weight chitosan showed good in vitro particle retention. The addition of silica improved dispersibility without impairing mucoadhesion, showcasing the potential of this advanced drug delivery concept, especially for the localized treatment of GI diseases [42].

Patel and Patel [43] aimed to develop and assess mucoadhesive amoxicillin microspheres for treating gastric and duodenal ulcers associated with *Helicobacter pylori*. The microspheres containing chitosan as a mucoadhesive polymer were prepared using the emulsification phase separation technique with glutaraldehyde as a cross-linking agent. Varied conditions, such as cross-linking parameters, polymer-to-drug ratio, and stirring speed, influenced the microsphere characteristics. The optimized batch demonstrated a high drug entrapment efficiency (70%), sustained drug release (>12 h), and strong mucoadhesion (79% after 1 h). A factorial design was used to analyze the impact of key parameters, revealing that the polymer-to-drug ratio was more influential. Scanning electron microscopy illustrated favorable morphological characteristics. In vitro release tests indicated a slightly faster release under acidic conditions. In vivo H. pylori clearance tests on infected rats showed better efficacy with amoxicillin mucoadhesive microspheres than with amoxicillin powder. These findings suggest that mucoadhesive microspheres may contribute to complete H. pylori eradication due to the prolonged GI residence time and enhanced stability of amoxicillin [43].

Umamaheshwari et al. [44] designed mucoadhesive gliadin nanoparticles with amoxicillin and evaluated their efficacy against Helicobacter pylori. They used the desolvation method to formulate these nanoparticles and studied the influence of factors, such as gliadin concentration and initial drug loading, on various nanoparticle characteristics. Rhodamine isothiocyanate–loaded formulations were used in in vivo gastric mucoadhesion studies on rats. Increased gliadin concentration enhanced mucoadhesive properties, with up to 82 ± 4% of the nanoparticles remaining, indicating strong mucoadhesion to the stomach. In vitro antimicrobial activity indicated slower eradication by amoxicillin-loaded nanoparticles owing to controlled drug delivery. In infected gerbils, both amoxicillin-loaded nanoparticles and amoxicillin showed anti–H pylori effects, with nanoparticles requiring a lower dose for complete eradication. In conclusion, amoxicillin-loaded gliadin nanoparticles were more effective against H pylori than amoxicillin owing to prolonged GI residence time from mucoadhesion. A dosage form of mucoadhesive nanoparticles and potential antibiotics holds promise for thorough H pylori eradication [44].

Raj et al. [42] aimed to prepare and characterize curcumin-loaded chitosan nanoparticles coated with Eudragit FS 30D for targeted drug delivery to the colon, specifically for treating ulcerative colitis. Chitosan nanoparticles were formulated by ionic gelation using tripolyphosphate. To achieve pH-sensitive delivery, curcumin-loaded chitosan nanoparticles were coated with Eudragit FS 30D using the solvent evaporation method. Various process parameters were assessed, and the optimized formulation was characterized for particle size, size distribution, zeta potential, and encapsulation efficiency before lyophilization. The lyophilized product was subjected to Fourier-transform infrared spectroscopy, and particle morphology and in vitro drug release in different media were investigated. The in vitro drug release kinetics of curcumin-loaded chitosan nanoparticles demonstrated sustained release behavior. Gamma scintigraphy for in vivo biodistribution revealed favorable accumulation of the developed nanocarriers in the colonic region. In conclusion, the successful achievement of sustained and pH-stimulated delivery of curcumin to the colon was accomplished by coating chitosan nanoparticles with Eudragit FS 30D, addressing issues related to the poor absorption and availability of curcumin.

4.4. Mucoadhesive Gel and Hydrogels

In the realm of drug delivery, in situ gelling mucoadhesive systems present a promising strategy to address the challenges associated with conventional dosage forms, particularly in addressing poor mucus permeation and limited drug bioavailability. Their unique advantage lies in their liquid form, which allows convenient application even via injection. Upon reaching the target site, the amalgamation of gelation and distinct mucoadhesive properties results in increased resistance to flow and extended residence time, making them versatile for both localized and systemic therapeutic applications. Specifically, in the context of gastric drug delivery, formulations designed to gel within the gastric environment are beneficial for sustained drug release, with the incorporation of mucoadhesive polymers enhancing the overall drug bioavailability. Ion-sensitive polymers, when co-administered with compounds such as calcium carbonate, induce gelation in acidic gastric conditions, showing potential advantages in therapies aimed at eradicating Helicobacter pylori [45].

For example, Xu et al. [46] explored mucoadhesive drug delivery systems designed to adhere to mucosal tissues, thereby prolonging the local retention time of the drugs. With specific reference to ulcerative colitis, a condition characterized by chronic inflammation of the colonic mucosa, the commonly prescribed medication sulfasalazine undergoes metabolism by intestinal flora, resulting in the production of the

therapeutic compound 5-aminosalicylic acid and a potentially toxic by-product, sulfapyridine. Although sulfasalazine can be administered orally or rectally, the latter approach aims to circumvent unintended absorption or degradation in the upper GI tract. However, rectal administration often faces challenges related to the limited retention time. To address this, the researchers proposed a mucoadhesive hydrogel composed of catechol-modified chitosan cross-linked with genipin. After loading the gel with sulfasalazine, its efficacy was evaluated in a mouse model of ulcerative colitis. Rectal sulfasalazine/catechol-modified chitosan delivery proved to be more effective than oral sulfasalazine treatment, demonstrating equivalent histological scores while inducing a lower plasma concentration of the potentially toxic sulfapyridine by-product. These findings suggest that sulfasalazine/catechol-modified chitosan rectal hydrogels are more effective and safer formulations for treating ulcerative colitis than oral sulfasalazine [46].

Maeng et al. [47] introduced a novel approach for GI endoscopy by developing a recombinant human epidermal growth factor (rhEGF)-containing ulcer-coating polymeric sol–gel designed for endoscopic applications. Utilizing chitosan and Pluronic F127 for their thermoresponsive and bioadhesive properties, the polymeric sol–gel remains in liquid form during endoscopic application at temperatures below 21°C and transforms into a gel at body temperature after application to ulcers. In vitro cellular wounding assays demonstrated that the rhEGF sol–gel significantly enhanced cell migration and reduced the wound area, outperforming non-treated solutions and sol–gels without rhEGF. In an in vivo ulcer-healing study using an acetic acid-induced gastric ulcer rat model, rhEGF endoscopic sol–gel facilitated the ulcer-healing process more efficiently than other treatments. Notably, the mucosal thickness in the rhEGF sol–gel group increased significantly compared to that in the non-treated group. Gastric retention studies further demonstrated that the rhEGF sol–gel adhered to the gastric mucosa for more than 2 h after application. This study suggests that rhEGF sol–gel holds promise as a prospective candidate for endoscopic treatment of gastric ulcers [47, 48].

5. Application of the Findings

The findings of this review underscore the transformative potential of mucoadhesive drug delivery systems in the field of gastroenterology. By enhancing drug residence time and improving targeted release, these systems offer significant improvements in the treatment of GI diseases such as inflammatory bowel disease, peptic ulcers, and GERD. Furthermore, these advanced delivery platforms pave the way for more personalized and effective therapies, reduced systemic side effects, and improved patient compliance. This review's insights can guide the future development of innovative formulations that cater to the specific physiological demands of the GI tract, ultimately improving therapeutic outcomes.

6. Innovations

In the existing literature, the innovative aspect lies in the exploration of the ability of mucoadhesive drug delivery systems to extend drug residence time and achieve localized, sustained release within the GI tract. These systems address key challenges such as the fluctuating pH environment, rapid GI transit, and poor bioavailability associated with conventional formulations. This review highlights how different delivery forms, such as tablets, gels, pellets, and micro/nanoparticles, leverage mucoadhesive properties to improve drug stability, enhance therapeutic effectiveness, and minimize side effects. The integration of nanotechnology and targeted delivery also sets this research apart, offering new avenues for personalized and more effective treatments for GI diseases.

7. Conclusion

In conclusion, the exploration of mucoadhesive delivery systems in gastroenterology has witnessed remarkable progress, showing their potential to revolutionize drug delivery for the GI tract diseases. Mucoadhesive tablets, pellets, gels, and micro/nanoparticles provide unique solutions to challenges such as limited drug absorption and poor bioavailability. These systems offer sustained release, targeted delivery, and improved therapeutic outcomes. As research continues to advance in this field, the future holds promise for personalized and effective treatment of a spectrum of GI disorders. As highlighted in this review, the versatility of mucoadhesive delivery systems underscores their significance in shaping the landscape of gastroenterology and heralding a new era in enhanced patient care.

Based on the findings of this review, several recommendations are proposed for advancing the development and application of mucoadhesive delivery systems for GI treatments.

Further research: Continued exploration of new and more effective mucoadhesive polymers is recommended to enhance drug retention and absorption in the GI tract. Developing polymers with stronger mucoadhesive properties and improved biocompatibility will be the key to future innovations.

In vivo studies: While in vitro studies have demonstrated the potential of mucoadhesive systems, there is a need for more comprehensive in vivo studies to evaluate their performance under physiological conditions. These studies should focus on drug release

profiles, bioavailability, and therapeutic outcomes.

Personalized treatment: The application of mucoadhesive systems should be further integrated into personalized medicine, tailoring drug delivery based on individual patient profiles, disease states, and specific GI conditions.

Nanotechnology integration: Expanding the use of nanotechnology in mucoadhesive delivery systems could improve targeted drug delivery, reduce systemic side effects, and allow for the development of more sophisticated GI therapies.

These recommendations highlight the need for innovative approaches to drug formulation and testing to optimize the use of mucoadhesive delivery systems in GI diseases.

Declarations

Author Contributions

Conceptualization, I.H.A.A.; methodology, A.A.D.; formal analysis, N.T.A.S.; investigation, M.T.A.S. and M.N.; resources, M.A.-Z. and W.A.D.; writing—original draft preparation, all authors contributed equally; writing—review and editing, H.A.; supervision, I.H.A.A.; project administration, I.H.A.A. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancies have been completely observed by the authors.

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