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Challenges and Future Perspective of Gastroretentive Mucoadhesive Dosage Forms

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ABSTRACT

Gastroretentive Mucoadhesive Dosage Form (GMDF) is one type of Gastroretentive Drug Delivery System (GRDDS) technology designed to exploit the adhesiveness of dosage forms in the gastric mucosa. This aims to increase drug residence time, enhance drug solubility and absorption, and ultimately improve drug bioavailability and therapeutic effect. Various studies have explored the use of different polymers to develop GMDF systems and dosage forms. However, despite extensive research in this field, there are still limited GMDF products approved by the US FDA and INA FDA. Therefore, this review addresses the challenges in developing GMDF, its current state, and potential future opportunities. This literature review is performed by searching Google Scholar, PubMed, and ScienceDirect and Google Patents using the terms "gastroretentive", "mucoadhesive", "challenge", "strategy", and "patent." Additionally, searches were conducted in the US FDA and INA FDA Drug Approval Databases. Based on our study, we identified numerous challenges in developing GMDF, including patient physiological challenges, drug formulas, production processes, product analysis, and clinical trials. To address these challenges, multiple strategies should be developed to optimize the formulation, production process, and product analysis of GMDF, ultimately leading to successful clinical trials and regulatory approval of this product.

***Keywords**: drug delivery system; gastroretentive; bioadhesive; mucoadhesive dosage forms*

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INTRODUCTION

The oral dosage form is highly favored for its convenience in storage and administration (Lopes et al., 2016; Das et al., 2021). However, it presents several challenges for medications with a limited absorption range in the stomach and duodenum region. The limited duration of stomach residency (approximately 2-3 hours) and the unpredictable rate of gastric emptying can hinder the breakdown and absorption of such medicines with a narrow absorption window (Lopes et al., 2016; Mandal et al., 2016; Das et al., 2021). Consequently, the Gastroretentive Drug Delivery System (GRDDS) was developed to address these constraints by prolonging the residence time of medication in the stomach, facilitating absorption, and controlling its release.

The GRDDS technique provides site-specific drug release and ensures targeted action in the upper gastrointestinal tract (GIT), particularly for medicines that are best absorbed in the stomach. These delivery systems are specifically developed to maintain the integrity of dosage forms and regulate the release of the drugs in the upper GIT for an extended period. This technique helps prolong the duration of medication retention in the stomach, improves drug solubility and absorption at the optimal location, and enhances the drug's bioavailability (Lopes et al., 2016; Das et al., 2021). Various strategies, such as bioadhesive/mucoadhesive, expandable, high-density, floating, super porous hydrogels, and magnetic systems, have been explored to develop GRDDS (Lopes et al., 2016). Mucoadhesive systems are a type of GRDDS designed to increase drug residence time at the application site by adhering to the gastrointestinal wall's epithelium. This allows a controlled drug release, thereby improving therapeutic outcomes (Shaikh et al., 2011; Das et al., 2021).

Over the past decade, from 2014 to 2024, a total of 93.868 publications have discussed various aspects of mucoadhesive gastroretentive systems, reflecting a growing interest in their potential (refer to Figure 1). The visual representation in the figure illustrates the significant growth in research related to these systems,

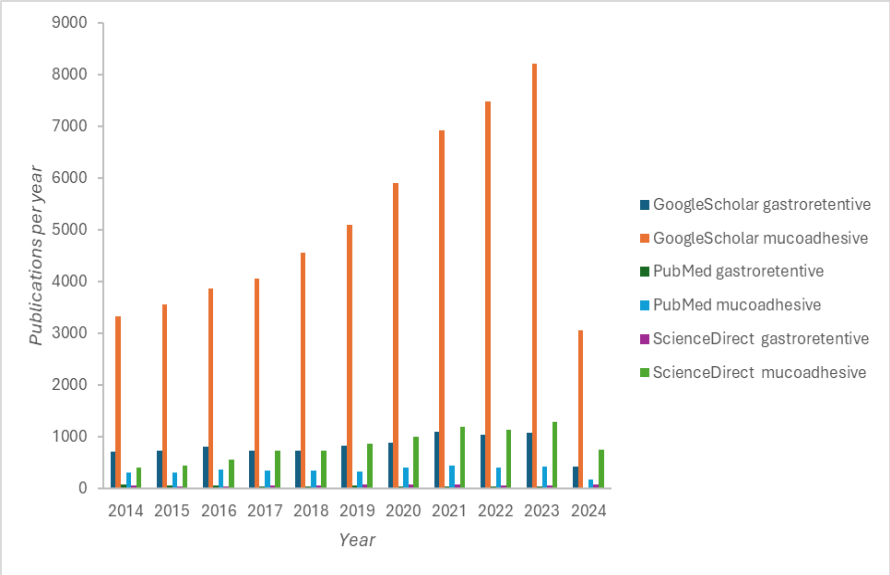

Figure 1. The number of publications related to gastroretentive mucoadhesive. The evaluation was performed by using the keywords "gastroretentive mucoadhesive" in Google Scholar, PubMed, and ScienceDirect.

highlighting their importance in improving drug delivery and bioavailability. This trend underscores the need for ongoing research and innovation in this area, indicating a shift towards clinical applications and interdisciplinary collaboration, with the potential to lead to more effective treatments and improved patient outcomes.

However, despite the extensive research in this area, the number of Gastroretentive Mucoadhesive Dosage Form (GMDF) products approved by the US FDA (United States Food and Drug Administration) and INA FDA (The Indonesian Food and Drug Authority) remains limited. This is due to several challenges in GMDF development, such as patient physiological challenges, drug formulas, production processes, product analysis, and clinical trials. As far as our search goes, literature has yet to discuss the challenges in GMDF development extensively.

This paper explores several approaches to improve the efficiency of GMDF formulation, production processes, and product analysis. It discusses the challenges associated with GMDF development and explores future opportunities. This literature review involved searches on Google Scholar, PubMed, and ScienceDirect using keywords such as "gastroretentive", "mucoadhesive", "challenge", "strategy", and "patent". Moreover, searches were also conducted on the US FDA and INA FDA Drug Approval Databases. These improvements play a critical role in facilitating successful clinical trials and obtaining regulatory approval for the sale of this product in the market.

Mechanism of Gastroretentive Mucoadhesive Dosage Forms

Upon ingestion, materials such as foods and drugs undergo the migrating myoelectric complex (MMC) within the gastric environment, which encompasses 4 phases in the stomach's mobility pattern (Lopes et al., 2016; Tripathi et al., 2019):

1. Phase I: 30–60 minutes of infrequent contractions. Phase II: 20–40 minutes of intermittent and intensified contractions.
2. Phase II: 10–20 minutes of intense contractions and a widened pylorus diameter, facilitating the transfer of food and other materials into the duodenum and small intestine.
3. Phase IV: 0–5 minutes of transitional phase.

The above phases impact the duration it takes for the stomach to empty or retain the materials. During periods of fasting, the typical cycle duration ranges from 90 to 120 minutes. However, this duration can be influenced by factors such as the type of food consumed, caloric intake, meal frequency, use of medications affecting gastrointestinal movement (e.g., anticholinergic drugs, opiates, and prokinetic agents), posture, physical activity, sleep patterns, body mass index, gender, age, illness, and emotional state (Lopes et al., 2016; Tripathi et al., 2019). Moreover, the variability of gastric residence time poses a challenge for the bioavailability of certain drugs. Therefore, it is crucial to develop gastroretentive dosage forms that can prolong drug residence time in the stomach and optimize the processes of dissolution and absorption.

Mucoadhesive gastroretentive dosage forms function by adhering to the gastrointestinal epithelium, thus prolonging the drug's residence time (Shaikh et al., 2011; Das et al., 2021). The formation of bioadhesive bonds involves three stages: initial wetting and swelling of the polymer to establish contact with biological tissues, followed by interpenetration of bioadhesive polymer chains and entanglement with mucin, and finally, the creation of weak chemical bonds between the interconnected chains (Mathiowitz et al., 1999; Sharma et al., 2012). It is essential for researchers to comprehensively understand the bioadhesive mechanism toward the gastric epithelium in order to design suitable types, systems, and formulations, as well as the polymers used in developing gastroretentive mucoadhesive dosage forms.

The mechanism of polymer adhesion in preparations with physiological mucus layers can be explained through several mechanisms, including:

a. The electronic theory

The electronic theory proposes that both the bioadhesive and the target biological material have distinct electronic structures. According to this idea, when these substances come into contact, electron transfer occurs to equalize the Fermi levels, creating an electrical double layer at the interface between the bioadhesive and the biological material. As a result, adhesion is established through attractive forces (Mathiowitz et al., 1999; Khutoryanskiy, 2014).

b. The adsorption theory

Adsorption theory explains that the bioadhesive connection between the adhesive substrate and the tissue or mucosa is a result of the interplay between hydrogen bonding and van der Waals forces. These forces are the primary factors that cause the surfaces to stick together. A subset of this theory, called chemisorption theory, posits that the interactions at the contact are due to strong covalent bonds (Mathiowitz et al., 1999; Khutoryanskiy, 2014).

c. The wetting theory

The wetting theory is utilized to study liquid systems and considers the energy associated with surfaces and interfaces. This idea pertains to the inherent capacity of a liquid to spread over a surface, which is necessary for adhesion to occur. One crucial aspect of bond formation is the capacity of a bioadhesive or mucus to effectively distribute and establish close contact with a compatible substrate (Mathiowitz et al., 1999; Khutoryanskiy, 2014).

d. The diffusion theory

This hypothesis describes the process of polymer chains diffusing through sticky contact. The driving force behind this process is the concentration disparity, and it is influenced by factors such as molecular chain length, polymer compatibility, and mobility. The extent of overlap is determined by the diffusion coefficient and the duration of contact. When there is enough depth of penetration, a semi-permanent adhesive bond is formed (Khutoryanskiy, 2014).

e. The fracture theory

The fracture theory differs slightly from previous theories by explicitly focusing on the force required to separate two adhered surfaces. It assumes that the failure of the adhesion bond occurs at the interface. However, in practice, the failure often happens at the component with the lowest strength, typically due to a cohesive failure within one of the joined surfaces (Khutoryanskiy, 2014).

f. The mechanical theory

The mechanical theory suggests that adhesion happens when a liquid adhesive becomes trapped in the unevenness of a rough surface during the setting process. Rough surfaces provide more significant amount of surface area for interaction and result in higher viscoelastic and plastic energy dissipation during joint failure. These factors are considered more significant in adhesion than mechanical impacts (Khutoryanskiy, 2014).

Drug Candidates For Gastroretentive Mucoadhesive Dosage Forms

Developing gastroretentive drug delivery systems, specifically mucoadhesive dosage forms, offers significant advantages in overcoming the limitations and improving the bioavailability of various active drug substances that encounter specific challenges in the GIT (Tripathi et al., 2019). These drug delivery systems are particularly advantageous for drugs that:

1. have a local action in the stomach, such as antacids, ranitidine, and antibiotics for *Helicobacter pylori* infection (such as amoxicillin, levofloxacin, and metronidazole);
2. are primarily absorbed in the stomach and upper intestine, like albuterol;
3. are poorly absorbed in the lower GIT, like atenolol;
4. have low solubility at alkaline pH, like ofloxacin;
5. are not stable at alkaline pH levels, like verapamil and captopril;
6. have a limited absorption range, like riboflavin, metformin, and levodopa;
7. are degraded in the colon, like metoprolol.

Despite the advantages of the aforementioned drugs, the gastroretentive mucoadhesive dosage form is not universally applicable to all drug substances. Drug substances that irritate the stomach epithelium and demonstrate instability in an acidic environment are unsuitable candidates for development into gastroretentive mucoadhesive dosage forms.

Table 1. Factors affecting the physiology of gastric

Affecting Factors	Effect on Gastric Physiology	References
Gender	Due to hormonal factors, females had longer stomach emptying durations and lower secretion of stomach acid than males.	Lopes et al., 2016; Tripathi et al., 2019
Age	Older patients exhibit a greater gastric residence time compared to younger people.	Lopes et al., 2016; Tripathi et al., 2019
Food	• The timing of dosage form administration is crucial; if it coincides with the migrating myoelectric complex (MMC), the gastric residence time is significantly reduced. In the presence of food, however, the MMC is disrupted, delaying the generation of housekeeping waves and thereby extending gastric residence time. • Higher caloric density food notably increases gastric residence time, but the type of calories has minimal effect. Moreover, higher-viscosity food can further prolong the gastric residence time. • Gastric pH is lower in the fed state compared to the fasted state.	Lopes et al., 2016; Tripathi et al., 2019
Pathological conditions	• Patients diagnosed with Parkinson's disease may experience a longer gastrointestinal transit time, which is commonly accompanied by constipation. • Patients with diabetes showed 30-50% slower gastric emptying time. • Patients with gastritis tend to have a thinner mucus layer.	Triantafyllou et al., 2007; Krygowska-Wajs et al., 2009; Lopes et al., 2016
Drug consumption	• Opiates and opiate receptor agonists, anticholinergics, and calcium channel blockers may inhibit GI motility and reduce normal peristaltic. • Prokinetic drugs may enhance GI motility.	Triantafyllou et al., 2007; Krygowska-Wajs et al., 2009; Lopes et al., 2016
Emotional state	Patients with depression had a slower gastric emptying rate. Meanwhile, those with anxiety displayed an increase in gastric emptying rate and stomach acid secretion.	Lopes et al., 2016; Tripathi et al., 2019

Furthermore, drug substances that exhibit consistent absorption throughout the gastrointestinal tract would undoubtedly not be advantageous to be developed in GMDF.

FACTORS AND CHALLENGES IN THE DEVELOPMENT OF GMDF

Physiological Factors

Given the extended drug's residence time in the gastric region, it is essential to consider the gastric pH to ensure the solubility and stability of the drug substance during its stay in the stomach. The very low gastric pH (pH 1–3.5 in a fasted state and pH 4.3–5.4 in the fed state) presents a challenge in the development of GMDF (Wen & Park, 2010). Consequently, this dosage form is only suitable for active drug substances with good solubility and stability in gastric pH. Moreover, gastric pH becomes important when selecting drug candidates for formulation and choosing appropriate excipients/polymers for GMDF. The unsuitability of polymers with high solubility and low gel strength in acidic solutions for GMDF arises from their inability to effectively prolong drug release from the dosage form.

The structure of polymers, along with the associated functional groups, significantly influence their behavior and mucoadhesive strength toward the mucin or mucus layer in the stomach. These formulations are specifically designed to interact with the mucus lining of the GIT, particularly in the stomach and small intestine. This interaction aims to prolong the residence time of the therapeutic formulation in the stomach and facilitate better absorption of the drug. Therefore, it is crucial also to consider the properties of the gastric mucin/mucus layer when developing GMDF.

The mucus layer is composed of mucin glycoproteins, water, and electrolytes, serving as a protective barrier against the stomach's acidic environment and aiding the movement of substances through the digestive tract. Mucin consists of protein-based backbones and oligosaccharide-based grafted chains. Approximately 12–17 % of the overall molecular weight of mucins is attributed to protein-based backbones, with 70% comprised of amino acids such as serine, threonine, and proline. The oligosaccharide-based grafted chains consist of N-acetylgalactosamine, N-acetylglucosamine, galactose, fucose, and N-acetylneuramic acid (sialic acid).

Table 2. Recent studies (2010-2024) on various gastroretentive mucoadhesive technologies

Types of Dosage Form	Drug Substance	Polymer	Result	Ref
Films	Captopril	Carbopol-934, hydroxypropyl methyl cellulose (HPMC), and ethyl cellulose (EC)	The captopril gastroretentive mucoadhesive films, formulated with various polymers and plasticizers, effectively administered the drug in a regulated manner. These films enhanced the drug's bioavailability by prolonging its retention in the stomach.	Anupam et al., 2013
	Furosemide	Carbopols 971P NF, Methocels E4M, Eudragits RLPO and HPMC E4M	The dosage form successfully delivers medications with narrow therapeutic windows in a regulated manner.	Darandale et al., 2012
Microspheres	Acyclovir	Chitosan, thiolated chitosan, Carbopol 71G and Methocel K15M	The extended-release profile of acyclovir from mucoadhesive microspheres leads to a notable increase in its absorption by the mouth, thanks to its improved retention in the upper gastrointestinal tract.	Dhaliwal et al., 2008
	Furosemide	Carboxymethyl starch	CMS-MS with a DS ranging from 0.6 to 1.0 is appropriate for mucoadhesive gastroretentive dosage forms. These forms are used for the controlled oral distribution of small molecules, including those with low solubility and permeability, either systemically or locally.	Lemieux et al., 2015
Beads	Emodin	Chitosan-coated pluronic F127/tween 80 beads	The beads have been demonstrated to enhance the therapeutic efficacy of the medication against stomach cancer.	Chen et al., 2019
Pellets	Metformin hydrochloride	Hydroxy propyl methyl cellulose K200M and microcrystalline cellulose	The combination of Hydroxy propyl methyl cellulose K200M with microcrystalline cellulose in a 2.80:1.00 w/w ratio proved to be a successful carrier for the regulated delivery of metformin hydrochloride in multiple units.	Ige et al., 2012
	Nifedipine	Hydroxy propyl methyl cellulose K15M and κ-carrageenan with microcrystalline cellulose	The combination of κ-carrageenan, microcrystalline cellulose, and hydroxypropyl methylcellulose K15M in a 20:35:10 w/w ratio effectively acts as a carrier to improve the roundness and prolongs the release of matrix pellets.	Ige et al., 2013
Hydrogels	Famotidine	Chitosan and Montmorillonite bio-nanocomposite hydrogels	The synthesized mucoadhesive bio-nanocomposite hydrogels can significantly enhance the effectiveness and absorption of famotidine when taken orally.	Farhadnejad et al., 2022
	Captopril	Chondroitinsulfate(CHS), polyvinylpyrrolidone (PVP), and 2-acrylamide-2-methylpropane sulphonic acid (AMPS)	CHS/PVP-co-poly (AMPS)- based hydrogel systems were suitable options for continuously releasing captopril by improving its attachment to the stomach mucus layer and reducing its dosage frequency.	Qaiser et al., 2023
Tablets	Lafutidine	Sodium alginate, xanthan gum, and karaya gum	The mucoadhesive formulation containing xanthan gum of lafutidine remained stable for 3 months when exposed to 40°C and a 75% of relative humidity. The results were deemed satisfactory.	Patil et al., 2014

Table 2. Continued

Types of Dosage Form	Drug Substance	Polymer	Result	Ref
	Rifampicin	Carbopol 71G	The device effectively delivers rifampicin to the stomach, specifically targeting its prolonged release in the region where RIF has the highest solubility and permeability.	Pund et al., 2011
	Acyclovir	Carbomer, polyethylene oxide, and sodium alginate alone and/or in combination	The gastroretentive formulation of acyclovir utilizes swelling and mucoadhesive mechanisms to prolong its retention in the upper gastrointestinal system. This formulation exhibits sustained drug release in vitro, prolonged absorption in vivo, and higher bioavailability than the immediate-release formulation. Such a composition would enhance patient adherence and enhance the effectiveness of treatment.	Jain et al., 2013
	Cephalexin	Hydroxyl propyl methyl cellulose K4M, hydroxyl propyl cellulose, chitosan, carbopol 934P, and sodium carboxymethylcellulose	The mucoadhesive drug delivery system shows promise as a highly efficient sustained release system for cephalexin, capable of maintaining drug release for up to 10 hours.	Sonani et al., 2010
Minitablets	Cefuroxime axetil	Chitosan, Hydroxyl propyl methyl cellulose K100M, and sodium carboxymethyl cellulose	The optimized mucoadhesive minitablets of cefuroxime axetil exhibited favorable formulation properties such as enhanced bioavailability, precise control over drug release rate, and increased versatility in altering both dosage and release rate. This formulation is designed specifically for the treatment of antibiotic-associated colitis.	Panda et al., 2022

Over 63% of protein-based backbones have oligosaccharide chains, while the remaining percentage remains non-glycosylated (Peppas et al., 2009; Vrettos et al., 2021; Khutoryanskiy, 2011).

The structure and properties of the mucus layer play a significant role in how the dosage form interacts with it. The thickness and viscosity of the mucus layer can affect the drug's diffusion rate from the dosage form into the bloodstream. Thicker and more viscous mucus can slow down the diffusion rate, while thinner and less viscous mucus can expedite the process. Additionally, the mucus layer's composition also impacts the adhesion of the dosage form to the mucosal surface. Specific mucin molecules, such as mucin recognition molecules like lectins, fimbrial proteins, and chitosan, can enhance the adhesion of the dosage form by forming specific bonds with the mucin molecules on the surface of the mucous gel layer (Peppas et al., 2009; Vrettos et al., 2021). The stomach has a two-layered mucus system with a turnover time of about an hour, which can pose challenges in designing GMDF formulations (Johansson et al., 2013).

In the design process of GMDF, it is important to consider various physiological aspects of the stomach, including pH, mucus viscosity and turnover, and gastric residence time. These aspects are influenced by a range of factors, such as:

1. Gender, age, posture, physical activity, sleep position, and body mass index.
2. Fasted or fed state, dietary habits, caloric intake, and frequency of food consumption.
3. Bacteria-derived substances, toxins, cytokines, and pathological conditions.
4. The use of drugs that impact gastrointestinal motility and mucin secretion, such as anticholinergic drugs, opiates, and prokinetic agents.
5. The individual's emotional state.

Table 1 illustrates the impact of each factor on pH, mucus viscosity and turnover, and gastric residence time (Triantafyllou et al., 2007; Krygowska-Wajs et al., 2009; Johansson et al., 2013; Lopes et al., 2016; Tripathi et al., 2019; Melhem et al., 2021).

Considering the factors that influence gastric pH, mucus, and residence time, developing a GMDF formula is quite challenging. Therefore, improving the effectiveness of GMDF may involve manipulating physiological conditions, such as controlling dietary and caloric intake and frequency, as well as avoiding the consumption of drugs that affect gastrointestinal motility and mucin secretion during GMDF administration. These strategies are crucial for ensuring optimal drug release and bioavailability in the gastric region (Tripathi et al., 2019; Bahadur et al., 2020; Vinchurkar et al., 2022).

Dosage Forms, Formulations, and Production Process

Numerous studies have explored the development of GMDF in various dosage forms, including mucoadhesive tablets and mini-tablets (Boddupalli et al., 2010), microspheres, pellets, and beads (Das et al., 2021), as well as hydrogels and films (Boddupalli et al., 2010). GMDF dosage forms can be designed in a matrix, reservoir, or hybrid system, each impacting the drug release profile. A summary of recent studies (2010-2024) on various gastroretentive mucoadhesive technologies is presented in Table 2.

Each type of dosage form discussed in Table 2 has its own advantages and limitations when it comes to gastroretentive mucoadhesive dosage forms. Hydrogels are considered promising materials for GMDF due to their ability to easily spread on the mucus layer. However, the semisolid nature of hydrogels makes it difficult to perfectly control prolonged drug release as intended. On the other hand, film dosage forms may be capable of extending drug release, but the administration of this form through the oral route might be inconvenient for patients (Boddupalli et al., 2010; Hanafy et al., 2019; Bej & Haag, 2022; Raeisi & Farjadian, 2024).

Recent studies have shown that mucoadhesive bio-nanocomposite hydrogels can significantly enhance the effectiveness and absorption of drugs when taken orally. For instance, Farhadnejad et al. (2022) synthesized mucoadhesive bio-nanocomposite hydrogels that improved the absorption of famotidine. Similarly, in 2023, Qaiser et al. developed CHS/PVP-co-poly (AMPS)-based hydrogel systems that continuously released captopril by improving its attachment to the gastric mucus layer and reducing its administration frequency (Bej & Haag, 2022; Liu et el., 2023; Raeisi & Farjadian, 2024). These advancements highlight the potential of hydrogels in optimizing drug delivery systems. However, there are still challenges to overcome, such as ensuring biocompatibility and stability, as well as simplifying synthesis methods of hydrogels to reduce costs. Future research should focus on addressing these issues to make hydrogels more practical for clinical applications (Liu et al., 2023; Raeisi & Farjadian, 2024).

Tablets are widely favored by patients as an oral dosage form due to their ease of handling and administration. Upon oral administration, tablets can soften, adhere, and reside in the mucosa until the disintegration or release process is completed (Boddupalli et al., 2010). This phenomenon contributes to the prolonged drug release profile of tablets. Moreover, the compression force applied during the tableting process, in conjunction with the gel strength of the polymers, also influences the extended drug release profile associated with this dosage form.

Numerous studies have demonstrated that mucoadhesive tablets are not only effective in achieving sustained release profiles, but also in increasing drug stability, solubility, bioavailability, efficacy, and the potential for improving patient adherence and treatment outcomes (Debotton & Dahan, 2016; Goldoozian et al., 2021; Karalia et al., 2021; Blynskaya et al., 2022). For instance, Patil et al. (2014) developed mucoadhesive tablets containing xanthan gum and lafutidine, which remained stable for 3 months when exposed to a temperature of 40°C and a relative humidity of 75%. This stability is crucial for maintaining the efficacy of the formulation over an extended period. Another study by Pund et al. (2011) focused on the delivery of rifampicin, aiming for its prolonged release in the stomach where it has the highest solubility and permeability. The tablets effectively delivered rifampicin to the stomach, achieving prolonged release in the desired region (Debotton & Dahan, 2016). A recent study by Panda et al. (2022) has also concentrated on optimizing mucoadhesive minitablets for specific medications. For example, the mucoadhesive minitablets of cefuroxime axetil, optimized for antibiotic-associated colitis treatment, exhibited favorable formulation properties such as enhanced bioavailability, precise control over drug release rate, and increased flexibility in adjusting both dosage and release rate (Debotton & Dahan, 2016).

Tablets serve as a suitable dosage form for GMDF; however, microspheres, beads, and granules offer distinct advantages over tablets due to their small and free-flowing characteristics. The smaller the dosage form, the larger its surface area, providing a greater contact area for the mucoadhesive site. Consequently, microspheres, beads, and granules offer enhanced adhesion and longer retention to the gastric mucus layer, which is particularly useful for GMDFs. Research by Dhaliwal et al. (2008) has demonstrated that the prolonged release of acyclovir from mucoadhesive microspheres leads to increased absorption in the mouth. Furthermore, beads developed by Chen et al. (2019) have been shown to enhance the therapeutic efficacy of medications against stomach cancer. However, there are certain challenges associated with these dosage forms, including the difficulties in controlling drug release and the complexity of dosage forms.

Table 3. Recent patents on gastroretentive mucoadhesive technologies

Patent Number	Year	Title	Brief Description	Ref.
US 9931405	2018	Pharmaceutical compositions for gastrointestinal drug delivery	Three innovative pharmaceutical formulations are designed to enhance the duration of action of active ingredients within the gastrointestinal tract. The initial composition comprises a prompt release/fast release component and a controlled release component, whereas the second composition comprises a prompt release/fast release component and a bioadhesive component. The third formulation incorporates both a controlled-release component and a bioadhesive component. All three formulations are formulated to prolong the duration of active ingredients in the gastrointestinal tract. In addition, the text mentions a composition that consists of multiple layers, including an instant release or controlled release layer and a layer that enhances the amount of time the composition stays in the gastrointestinal tract.	Jahagirdar et al., 2018
US 8974825	2015	Pharmaceutical composition for the gastrointestinal drug delivery	This pharmaceutical composition is a novel formulation designed to enhance the effectiveness of active ingredients in the gastrointestinal tract. It consists of multiple entities, including immediate-release/fast-release components, controlled-release agents, and bioadhesive elements. The composition aims to prolong the residence time of the active ingredients in the gastrointestinal tract, ensuring optimal therapeutic outcomes. A multilayered structure is incorporated to provide immediate and controlled release of active principles while promoting extended residence time within the GI tract.	Jahagirdar et al., 2015
US 6306789	2001	Mucoadhesive granules of carbomer suitable for oral administration of drugs	The granules should also contain a pharmacologically active substance appropriate for slowly releasing into the gastrointestinal tract or precisely delivering to the gastrointestinal mucosa.	Dettmar et al., 2001
US 6303147	2001	Bioadhesive solid dosage form	The present invention relates to bioadhesive pharmaceutical compositions that contain an adequate amount of an active ingredient, 80% to 98.8% (w/w) pre-gelatinized starch, and 1% to 10% (w/w) of a hydrophilic matrix-forming polymer. These compositions include 0.2% to 5% (w/w) alkyl fumarate as a lubricant. The invention also encompasses solid dosage forms, such as tablets, that can be administered orally, nasally, rectally, or vaginally. Additionally, the invention covers the processes involved in preparing these compositions and solid dosage forms.	Gilis, 2001

Table 3. Continued

Patent Number	Year	Title	Brief Description	Ref.
US 5900247	1999	Mucoadhesive pharmaceutical composition for the controlled release of active principles	The current invention pertains to a novel mucoadhesive pharmaceutical formulation that enables the extended release of active pharmaceutical ingredients in the buccal cavity or through the transmucosal pathway.	Rault et al., 1999
US 5571533	1996	Controlled-release mucoadhesive pharmaceutical composition for the oral administration of furosemide	Presented are controlled-release mucoadhesive pharmaceutical formulations designed for the oral delivery of furosemide. This composition consists of many microgranules of lipophilic substance covered with a mucoadhesive covering. This innovation mitigates or eliminates the excessive urine production peak and lowers the variability in response between different individuals that often occurs with this medication's standard treatment.	Santus et al., 1996
US 5472704	1995	Pharmaceutical controlled-release composition with bioadhesive properties	A pharmaceutical composition that may release medicinal medications in a controlled manner and can stick to biological tissues. The composition is characterized by the presence of several small units that are capable of gradually releasing the active component they contain. These units are coated with a layer of bioadhesive polymer. The composition enables the separation of the release-controlling function from the function of producing adhesion. It can be adjusted to various methods of delivery, such as oral, ophthalmic, rectal, vaginal, nasal, or periodontal. Furthermore, a beneficial method for producing the mixture is also revealed.	Santus et al., 1995

The greater surface area of microspheres, beads, and granules complicates the control of the drug release rate, leading to inconsistent and potentially variable therapeutic effects. On the other hand, tablets are generally easier to swallow and have a simpler dosage form. The choice of dosage form depends on the specific needs of the medication and the targeted population of the patient (Shahi et al., 2015; Blynskaya et al., 2022; Anjasmara et al., 2023).

The mucoadhesive mechanism of the dosage form can be explained by the wetting theory, which suggests that the dosage form should be easily hydrated. As described in Table 2, hydrophilic polymers, whether they are applied as matrix-forming material or as coating material for the dosage forms, have become the main excipient for GMDF. These include natural polymers (such as chitosan, alginate, carrageenan, and xanthan gum), semisynthetic polymers (such as chondroitin sulfate, hydroxyl propyl methyl cellulose, and sodium carboxymethyl cellulose), and synthetic polymers (e.g., carbopol and polyvinyl pyrrolidone). Hydrophilic polymers have several hydroxyl groups in their structure, enabling them to form strong bonds with mucus through hydrogen bonding and van der Waals interactions. Additionally, when considering gastric mucin, which is composed of various ionic molecules such as N-acetylglucosamine and sialic acid, polymers containing ionic groups, such as the amine group in chitosan and the carboxylic group in alginate, have a tendency to bind more strongly in the mucus layer through an electronic mechanism (Mathiowitz et al., 1999; Khutoryanskiy, 2014).

It is important to ensure that GMDF exhibits a prolonged drug release profile. This means that the polymers used in the formulation should possess high gel strength to achieve the desired drug release profile. As a result, high-viscosity polymers are preferred for GMDF formulation. For polymers with chemical groups that can promote mucoadhesive bonding but exhibit weak gel strength

(such as chitosan and starch), it is necessary to either modify the polymers (e.g., carboxymethyl starch) or combine them with high gel strength polymers (e.g., a combination of chitosan and HPMC). The modification and combination of polymers themself present challenges due to numerous factors that can impact the success of the process. Despite the challenges in designing GMDF, several patents on GMDF formulation and production processes have been registered, as detailed in Table 3.

The choice of dosage form during the development of GMDF will eventually impact the production processes. Therefore, it is crucial to consider the production steps and critical parameters for each step when scaling up the formulation to the production scale. A more straightforward production process requires fewer critical parameters that should be observed carefully, making the scale-up and validation process of the dosage forms more feasible.

Several key challenges should be considered during the scale-up including formulation and material selection, optimization and validation of manufacturing process, and regulatory compliance. The choice of mucoadhesive polymers, excipient ratios, and the dimension and shape of dosage forms are crucial parameters to be considered for ensuring consistent quality and availability. Following regulatory compliance such as Good Manufacturing Practices (GMPs) guidelines is crucial while performing the formulation optimization, scale-up, and validation of the production process. Understanding these challenges enables manufacturers to formulate strategies to overcome them and develop high-quality GMDF products with ensured efficacy and safety (Sankar et al., 2013; Bahadur et al., 2020; Vinchurkar et al., 2022; Turac et al., 2024).

Preclinical and Clinical Trials

Despite numerous studies and efforts to develop gastroretentive mucoadhesive dosage forms, and despite several formulas being patented, there are only a limited number of regulatory-approved GMDF products on the market. One GMDF product that has received regulatory approval is Xifaxan®, a Rifaximin-containing tablet produced by the Lupin Pharmaceutical Industry in India. However, we have not yet identified GMDF products registered on INA FDA.

This big discrepancy implies challenges in the downstream development process of GMDF. In the development of preclinical and clinical trials of GMDF, there are two important aspects that will affect the results, including the product's residence time and the controlled/extended drug release profile during its residence time in the stomach. Product residence time in the stomach is difficult to measure due to the highly variable nature of gastric transit time, which is influenced by several physiological factors, such as age, body posture, gender, osmolarity, and food intake. For instance, human gastric transit time can range from several minutes to several hours, with a median time of around 1.5 hours in the fasted state and up to 6 hours in the fed state. Additionally, the time of administration is found to be associated with an individual's bowel movements and gender. Females are found to have a significantly longer colonic transit time, which also affects gastric transit time. These factors contribute to the complexity of accurate measurement of the residence time of GMDF products in the stomach (Hua, 2020; Maurer et al., 2015; Katona et al., 2022; Gazzaniga et al., 2022; Shinde et al., 2011).

On the other hand, other factors, including the formulation design, the drug's physicochemical properties, polymer content, matrix properties, initial concentration distribution, release mechanisms, and some environmental factors, contribute to the challenges while measuring the drug's release profile in the stomach. These factors can interact with each other or with the specific characteristics of the drug and matrix, creating a unique release profile for each formulation. Accurately measuring the drug release profile is crucial to ensure the efficacy and safety of the drug, as well as to optimize the formulation and manufacturing process (Varma et al., 2004; Raval et al., 2010; Frenning et al., 2011; Parojčić et al., 2004).

The varying gastric sizes and mucus layer thickness between humans and animal models (such as rodents) complicate the correlation between *ex vivo/in vivo* studies in animals and clinical trials in humans. Designing clinical trials is highly complex due to these multiple influential factors. A well-designed in vivo study in either animal models or humans is essential to prove the effectiveness of GMDF. The initial prerequisite for a successful in vivo investigation is the careful selection of an appropriate animal model. Small-sized animals such as mice, rats, guinea pigs, and rabbits pose challenges, particularly when administering large dosage forms, making the assessment of gastric residence time and bioavailability difficult. Additionally, methods to observe product residence time in the stomach remain challenging (Mishra, 2018; Tripathi et al., 2019).

The intricate interactions among the delivery system, the gastrointestinal (GI) tract, and the administered drug present numerous challenges in the bioanalysis of the gastroretentive mucoadhesive systems. Issues that need resolution include linking in vitro and in vivo data, understanding mucus interaction with substances, considering the pH and enzymatic effects, ensuring proper sample collection and preparation, validating methods, and adhering to regulatory standards.

Table 4. Strategies in designing gastro-retentive mucoadhesive dosage form

Aspect	Strategies
Active Drug Substance	One of the physiological challenges in the development of GMDF is very low gastric pH (pH 1 – 3.5 in a fasted state and pH 4.3 – 5.4 in the fed state). Therefore, this dosage form is only suitable for active drug substances with good solubility and stability in gastric pH. It is not recommended that an active drug substance that can cause gastric irritation be formulated into GMDF.
Gastric residence time	The GMDF must remain in the stomach for at least 6 hours, ideally while the patient is fasting. However, some studies have also shown that taking the GMDF product with a meal can prolong the gastric residence time. Furthermore, considering phase I of the migrating myoelectric complex (MMC), which consists of 30 – 60 minutes of rare contractions, GMDF should be able to bind to gastric mucosa within 30 – 60 minutes. Therefore, it can be suggested that GMDF can be orally administered 1 hour before meal. This 1 hour served as the time for the dosage form to bind to the gastric mucosa firmly, and the meal was administered later to delay gastric emptying time.
Dosage forms	Tablets or capsules containing microspheres/beads/granules are still considered the most suitable dosage forms for GMDF, not only due to their easy distribution and administration but also due to the relatively simple production process required.
Formulation/ Polymers	The drug substance should be released at a controlled rate, and the dosage forms should form a strong bond with the gastric mucus layer. Therefore, hydrophilic polymers with high viscosity, gel strength, and mucoadhesive/mechanical strength should be applied as the leading excipients for GMDF. To obtain controlled-rate drug release, dosage forms can be prepared in a matrix, reservoir, or hybrid system.
Animal models	For conducting proof-of-principle experiments in designing gastroretentive mucoadhesive dosage forms, a suitable animal model is crucial to ensure the efficacy and feasibility of the formulation. The choice of animal model depends on several factors, including the specific requirements of the study, the complexity of the formulation, and the desired outcome. The most commonly used animal models for gastro-retentive mucoadhesive dosage forms are rats and rabbits. These animals are suitable for initial tests regarding the functionality of a gastroretentive concept, especially for multi-particulate mucoadhesive systems. In the context of gastroretentive mucoadhesive dosage forms, the rabbit model is often used due to its relatively close gastric pH values to those of humans. This similarity in pH is important because it allows for a more accurate assessment of the dosage form's ability to adhere to the mucosa and prolong gastric residence time. Additionally, the rabbit model is relatively small, which makes it easier to handle and study compared to larger animals like dogs or pigs.
In vivo study	Mucoadhesive gastroretentive preparations on mucous membranes can be evaluated in vivo by direct observation (i), by gamma scintigraphy (ii), and by using insoluble markers (iii). These tests are conducted to determine the residence time period as well as the increase in residence time of mucoadhesive preparations in the gastrointestinal tract.
Feasibility	The design must be viable in terms of materials, equipment, and technology.

To address these challenges, scientists and analysts employ sophisticated analytical methods, such as liquid chromatography-mass spectrometry (LC-MS), and rigorous protocols for method validation to guarantee precise and reliable outcomes. Furthermore, the use of animal models and human clinical trials helps to gain a more comprehensive understanding of these systems' in vivo functionality, thereby improving bioanalytical techniques (Jangdey et al., 2014; Kumar & Kaushik, 2018; Vrettos et al., 2021; Das et al., 2021; Tripathi et al., 2019).

STRATEGIES IN DESIGNING GMDF

Following the identification of all challenges in the development of GMDF, we have outlined several strategies to optimize the design of GMDF in Table 4**.** The table highlights the urge of physiological challenges, including low gastric pH, which requires good solubility and stability of the active drug substance. The GMDF needs to be retained in the stomach for at least 6 hours, making it preferable to be administered while the patient is fasting. Choice of dosage forms is also important, for instance, tablets or capsules are the most suitable dosage forms due to their ease of administration. Utilization of polymers in GMDF formulations is crucial as it should allow controlled drug release and forming a strong bond with the gastric mucus layer. All in all, the choice of animal model and the correct in vivo study should be properly designed to evaluate the efficacy and feasibility of GMDFs in delivering active drug substances effectively.

FUTURE PERSPECTIVE

Gastroretentive mucoadhesive dosage forms (GMDF) hold great promise for improving the therapeutic efficacy of medications with limited absorption ranges, high solubility in acidic pH conditions, and susceptibility to destabilization in alkaline pH environments. Prior knowledge in anatomy, physiology, and pathologies of the stomach, as well as how formulation and process variables affect the quality of dosage forms, is essential for designing successful gastric modified release formulations. Although various types of GMDF, such as tablets, mini-tablets, films, beads, microspheres, and pellets, have been described in literatures, more clinical testing is still needed. Developing a robust bioanalysis method to measure product residence time in the gastric for a certain period is also important. Additionally, detection methods like gamma scintigraphy are interesting to apply for this purpose.

From the pharmaceutical perspective, a combined approach to dosage form, formulation, and production process is essential to achieve better quality of GMDF products. Furthermore, implementing the quality by design (QbD) approach can enhance our understanding of how formulation and process variables impact the product's performance, thereby streamlining the development and scaling-up process of GMDF products.

CONCLUSION

The effectiveness of Gastroretentive Mucoadhesive Dosage Forms (GMDF) in enhancing the bioavailability of drugs with narrow absorption windows has been demonstrated in numerous in-vitro, ex-vivo, and in-vivo studies. GMDF products extend the drug's residence time in the gastric system, optimizing its dissolution and absorption processes. However, there is still a need for a better correlation between results from animal and human studies, as well as addressing the bioanalysis and detection of the drug in both animal models and human patients. Overcoming these challenges presents opportunities for further research into GMDF, which could expedite the preclinical and clinical study of this product and provide the necessary evidence for GMDF products to be approved by regulatory bodies such as the US FDA and INA FDA.

AUTHOR CONTRIBUTION

RA searched the data and wrote the manuscript. HS, BPM, and RI critically revised the manuscript. KSSP designed the content, conceived the structure, supervised the process, critically revised it, and gave final approval for the manuscript. All authors have read and approved the final manuscript.

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