RESEARCH PAPER

Targeted And Controlled Drug Delivery Approaches In The Management Of Gastroesophageal Reflux Disease

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Abstract

Gastroesophageal reflux disease (GERD) is a chronic gastroenterological disorder resulting from the backward flow of gastric contents into the esophagus, clinical manifestations of which may include heartburn and regurgitation, with complications including erosive esophagitis and Barrett's esophagus. While proton pump inhibitors (PPIs) are broadly used as first-line, limitations around incomplete symptom relief and long-term dependence illustrate the need for better treatment strategies. Controlled delivery systems for targeted drugs are a novel approach to increase drug stability and long-term gastric residence time, site-specific action, and prolong therapeutic effects of the system. It has been established that various systems including mucoadhesive formulations, pH-responsive carriers, raft-forming systems, gastroretentive drug delivery systems and nanotechnology-based carriers, are able to achieve higher bioavailability on GERD management which leads to therapeutic efficacy enhancement and patient compliance improvement.

Keywords: Gastroesophageal reflux disease, Targeted drug delivery Controlled release, Gastroretentive systems, Nanoparticles, Proton pump inhibitors.

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Introduction

Gastroesophageal reflux disease (GERD) is defined as a chronic state of abnormal and recurrent gastroesophageal reflux resulting in troublesome symptoms and/or complications[1]. The condition develops when the LES fails to close properly, enabling acid and other gastric contents to irritate the esophageal mucosa. Typical symptoms of GERD include heartburn and acid regurgitation, but can also manifest as chest pain, dysphagia, or extra-esophageal symptoms. Persisting reflux can create complications such as erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinom if neglected [2].

Definition and Epidemiology

It is estimated to affect 10–20% of adults in Western countries, with figures for the USA alone ranging from about 18% to 28%. In other continents, lower prevalence is evident in many countries in Asian and developing regions despite increasing incidence globally. GERD is slightly more common in male than a female for complications as erosive esophagitis and Barrett's esophagus, however, symtomatic GERD might be similarly or slightly prevalent in women [3].

The rising prevalence of gastroesophageal reflux disease (GERD) has been closely linked to risk factors including obesity, older age, smoking, and physical inactivity. GERD, due to its chronic and recurrence property, represents a significant public health burden worldwide [4].

Pathophysiological Mechanisms

The main mechanism is to compromise the function of both lower esophageal sphincter (LES) and crural diaphragm, resulting in increased acid exposure into the esophagus.

GERD arises from a dysbalance between aggressive factors (acid, pepsin, bile, transient LES relaxations, hiatal hernia and increased intra-abdominal pressure) and defense mechanisms (LES tone, esophageal clearance, salivary neutralization and mucosal integrity). Prolongation of acid contact leads to lesion formation on the esophageal mucosa in case clearance mechanisms are not effective, which is responsible for inflammation and symptoms such as heartburn and regurgitation.

Visceral hypersensitivity and neural modulation also contribute to the perception of symptoms, particularly

in patients with non-erosive reflux disease; together with structural abnormalities, these factors form an important basis for symptom perception.Thus, GERD pathophysiology is multifactorial, involving mechanical, chemical, and neurogenic components [5].

Limitations of Conventional Therapies

Standard therapy for GERD, especially proton pump inhibitors (PPIs), has many restrictions. Nonerosive reflux disease, extraesophageal manifestations (EEM) and long-term drug dependence: Despite PPI therapy, a substantial proportion of patients (40–55%) still have symptomatic GERD [6,7] even when they do not stop taking it; the majority develop this during medical treatment. While PPIs primarily inhibit gastric acid, they do not impact other important factors surrounding the pathogenesis of refractory cases, such as bile reflux, aberrant motility, or esophageal hypersensitivity [8]. Moreover, long term safety issues like its potential for nutrient deficiencies, infections, fractures, kidney disease and rebound acid hypersecretion, this highlight the need for more targeted treatment strategies [9,10].

Rationale for Targeted and Controlled Drug Delivery

Thus, the titanium dioxide-encapsulated drug delivery systems need to be implemented in a targeted manner to improve the drug stability with prolonged residence time at a specific site and sustained release of the anticancer drugs. Their advanced nanomolecule solutions, such as chitosan based nanoparticles, are notable for their mucoadhesion, protection against acid degradation, increased bioavailability and local activity [11]. These approaches have the potential to enhance therapeutic efficacy, minimize side effects, decrease dosing frequency and improve long-term patient compliance in GERD management [12,13].

Scope and Objectives

This review summarizes literature related to nanotechnology, polymers and gastroretentive systems targeting GERD. Objective: To review mechanisms, efficacy data, challenges and opportunities for clinical translation.

2. Targeted Drug Delivery Approaches for GERD

Targeted drug delivery systems for gastroesophageal reflux disease (GERD) have attracted increasing interest due to their potential as alternatives to conventional therapy, especially in terms of improving drug stability towards PRE and extending mucosal residence time with localized action at esophageal and gastric mucosa [11]. These systems overcome rapid clearance and acid degradation of drugs, enhancing the therapeutic outcome in patients suffering from refractory or chronic GERD [14]. Novel systems including mucoadhesive, pH-sensitive, raft-forming and ligand-modified are recently gaining prominence as they provide greater control over drug localization and release kinetics [15].

2.1 Mucoadhesive Drug Delivery Systems

Mucoadhesive systems are capable of prolonging the residence time of a drug to the target site by adhering to the mucus layer of either gastric or esophageal mucosa via hydrogen bond formation, electrostatic attraction and polymer chain interpenetration [16]. These systems are especially important, since the esophagus has a rapid mucus turnover and peristalsis [17], resulting in brief drug contact time.

Some of the common examples for mucoadhesive polymers are chitosan, carbopol, hydroxypropyl methylcellulose (HPMC), pectin and alginate[18]. Chitosan-based nanoparticles are promising since they possess a cationic nature that allows them to adhere better to negatively charged mucins and is also conferring protection from acidic degradation [19]. Studies show better retention time, higher bioavailability of PPIs, and reduced dosing frequency when using mucoadhesive formulations [20].

2.2 pH-Responsive Drug Delivery Systems

pH-responsive systems take advantage of the physiological changes in GI pH, releasing their drug payload in a pH-dependent manner at acidic gastric or neutral esophageal compartments based on polymer design. The pH responsive polymers Eudragit L100, Eudragit S100 and alginate disintegrate at a certain threshold of pH which can protect the drug from degradation[21].

In GERD, systems that are triggered by acid will localize drugs in the stomach where reflux originates. Such systems are particularly beneficial for acid-sensitive drugs including PPIs and specific peptides. The stability of the drug is improved from gastric acidity, and in turn controlled release is accomplished [22].

2.3 Raft-Forming Drug Delivery Systems

Raft-forming systems are alginate-based preparations having a reactant with gastric acid to form a low density, syneresis gel “raft” that floats on top of the submerged contents in stomach [23]. This floating raft acts as a mechanical barrier that would prevent the return of gastric materials into the gastrointestinal tract and providing microenvironment for localized action of incorporated drug. These systems are widely used in the treatment of mild to moderate GERD, as they significantly lower esophageal acid exposure, provide fast symptom control and improve mucosal protection. Raft formulations commonly include calcium

carbonate or sodium bicarbonate, which react in the acidic environment to promote gelation and increase buoyancy [24].

2.4 Ligand-Targeted and Surface-Modified Delivery Systems

To achieve this, the surface of drug carriers is modified with specific moieties (such as lectins, thiolated polymers, antibodies or peptides) recognized by receptors present on esophageal or gastric mucosal tissues through ligand-directed targeting [25]. This novel approach, which aims to enhance site-targeted drug delivery, has great potential in treating GERD and other upper GI diseases. Surface modifications could improve adhesion to mucosal surfaces, facilitate deeper penetration through mucosal ingestion, decrease unwanted systemic uptake, and promote localized therapeutic efficacy. Specific approaches of this nature are under investigation by polymer nanoparticles and vesicular delivery systems for targeting proton pump inhibitors (PPIs), anti-inflammatory agents, and antioxidants directly to areas affected by reflux-induced mucosal injury [21,26].

Table 1: Summary of Targeted Drug Delivery Approaches for GERD

Delivery System	Description/Key Polymers	Advantages	Ref.
Mucoadhesive Nanoparticles	Chitosan, Carbopol, HPMC	Improved residence time; additional controlled drug release	[18]
pH-Responsive Systems	Eudragit L/S, alginate	Controlled release in acidic pH	[21]
Raft Forming Systems	Sodium alginate +CaCO3	Forms floating protective raft	[24]
Ligand Targeted Systems	Lectins, thiolated polymers, peptides	Site-specific targeting	[25]

3. Controlled and sustained release formulations

Formulations that result in stable drug concentrations and/or extended gastric residence are appealing for chronic GERD, particularly β-reacting agents such as PPIs and prokinetics with short half-lives or upper-GI absorption windows. Controlled systems also enable once-daily dosing and improved adherence.

3.1 Sustained-Release Tablets and Capsules

Matrix systems & osmotic systems

Hydrophilic matrix systems containing hydroxypropyl methylcellulose (HPMC) and natural gums swell upon contact with gastrointestinal fluids, followed by the formation of a gel layer after the explosive release of water few vibrating event, which governs both drug permeation and matrix erosion and is therefore frequently used in sustained-release dosage forms: tablets as well as mini-tablets. In contrast, osmotic delivery systems employ a semipermeable membrane and precision orifice to provide near zero-order drug release by means of osmotic pressure [27]. Indeed, drugs like cisapride and esomeprazole have been developed into sustained-release matrix formulations to attain controlled drug release for over 12–24 h of time which could imply once-daily therapy for GERD [28]. Controlled-release approaches hold significant advantages of reduced dosing frequency, attenuated peak-trough plasma fluctuations, potential for decreased adverse effects and improved patient adherence in chronic disease management [27].

3.2 Gastroretentive Drug Delivery Systems (GRDDS)

3.2.1 Floating systems (low-density)

Floating or low-density gastroretentive systems are such which swells and become less density than gastric fluid that remain floating in gastric fluid for a prolonged duration. Such formulations usually constitute of hydrophilic polymers like hydroxypropyl methylcellulose (HPMC) together with gas producing agents like sodium bicarbonate. When the zero-calorie gel finally reaches your stomach and contacts gastric fluid, the sodium carbonate reacts to form carbon dioxide, which gets trapped in the gel matrix itself; this reduces the overall density of the system so that it floats on top of gastric contents. This buoyancy increases gastric residence time and enables sustained or additional controlled drug release, which is advantageous for drugs that exert their effect locally in the stomach or whose absorption is limited to the upper gastrointestinal tract [29].

3.2.2 High-density systems

High-density gastroretentive systems are designed to possess higher density (1.5–2.4 g/cm³), than that of gastric fluid so as to retain in stomach for prolonged period owing their high density. These dosage forms settle down in the stomach because of their higher density and may entrap into the gastric rugae that prevents its gastric emptying. This strategy may be beneficial for drugs that need to remain inside the body close to the pyloric region, as well as in cases where they are designed to have a local effect at the stomach or esophagus. These systems can afford extended drug release and enhanced therapeutic efficiency by staying in the lower part of the stomach [30].

3.2.3 Expanding or swelling systems

The most widely studied gastroretentive systems are the expanding or swelling types that employ polymers which swiftly swell after contact with the gastric fluids. Polymers e.g., HPMC, carbopol and superporous hydrogels absorb water and enlarge to a size larger than the pyloric opening, thus blocking their delivery into the intestine. In this way, a size increase leads to prolonged retention time in the stomach and continued

release of drugs. Such systems are especially beneficial for maintaining therapeutic ranges of drugs for long periods and are extensively researched for those drugs needing controlled release in the upper GI tract [31].

3.3 Multiparticulate Systems (Pellets, Beads, Microcapsules)

Multiparticulate systems such as pellets, beads, and microcapsules are coated for controlled drug release and can be filled into capsules or compressed into tablets. These systems provide more uniform distribution in the gastrointestinal tract, reduce inter-patient variability, and allow flexible release profiles through polymer coatings or matrix designs. Additionally, they lower the risk of dose dumping compared to single-unit tablets [32].

3.4 In Situ Gelling Systems

Various multiparticulate systems including pellets, beads and microcapsules are coated for sustained release of drug which can be filled in capsules or compressed into tablets. These systems offer better gastrointestinal tract (GIT) distribution and less inter-patient variability, besides the ability to design various release profiles by polymer coating or matrix formations. Furthermore, they decrease the risk of dose dumping compare to single-unit tablets [33].

4. Nanotechnology based delivery strategies

Nanocarriers can overcome the major GERD challenges of acidic degradation, short residence time and requirement of local mucosal action through mucoadhesion, protection and controlled release.

4.1 Polymeric Nanoparticles (e.g., Chitosan, PLGA, Eudragit)

Materials like chitosan, PLGA (poly(lactic-co-glycolic acid)) and Eudragit have been widely investigated as polymeric nanoparticles for targeted and controlled drug delivery. PLGA nanoparticles modified with chitosan or Eudragit have tunable size, variable surface charge, and high interaction with mucosal tissues. Chitosan can interact electrostatically with negatively-charged mucin due to its cationic nature, which leads to increased mucoadhesivity and better permeation through epithelial barriers.The use of PLGA or PLA cores protects against exposure of these acid-labile drugs and offers the potential for controlled and localized drug release resulting in reduced systemic exposure and toxicity while maintaining therapeutic levels of the drug at the target site [29,30]. Moreover, another type of acid-responsive coatings that pH ensures adequate protecting against gastric acid while being responsible for drug release at higher pH coating Eudragit. Studies on these polymeric nanoparticle systems have shown enhanced oral bioavailability and sustained therapeutic effects for poorly soluble or unstable drugs, supporting their potential relevance for GERD-associated drug delivery methods [34,35].

4.2 Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)

The submicron lipid-based drug carriers, such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) contain hydrophilic cores that easily entrap lipophilic drugs within them thus enhancing their solubility and oral bioavailability. Lipid-nanocarriers play a key role in enhancing gastrointestinal residence time, protecting drugs from chemical and enzymatic degradation, and enabling sustained or controlled release of the drug. Nanostructured lipid carriers, which consist of a combination of solid and liquid lipids, generally showed higher drug loading capacity, much more flexible release profile than SLN along with enhanced stability and low drug leakage. Moreover, the surface modification of these nanocarriers with chitosan and cyclodextrins can enhance mucoadhesion, improve permeability, and facilitate site-specific targeting within the gastrointestinal tract [36,37].

4.3 Liposomes and Niosomes

Liposomes are vesicles made of phospholipid bilayers that can carry both hydrophilic and lipophilic drugs; making drug solubility through them, biodistribution, and controlled drug release possible. However, niosomes are analogous vesicular systems prepared from non-ionic surfactants and cholesterol. They have a comparable bilayer structure similar to liposomes, but possess higher physical and chemical stability with lower production cost. To obtain higher active drug targeting, stimuli-responsive drug release and enhanced mucosal adhesion, both liposomes and niosomes can be surface modified via surface functionalization. Such vesicular systems have been widely studied to enhance pharmacokinetic profiles and decrease systemic toxicity of therapeutic agents [38, 39].

4.4 Nanofibers, Nanogels, and Nanoemulsions

Electrospun nanofibres have a very high surface-area-to-volume ratio, which could be ideal for localized drug depots that allow controlled and sustained release of drugs on mucosal surfaces. Nanogels and nanoemulsions are made up of nanoscale droplets or cross-linked polymeric networks, that offer a large interfacial surface area which significantly improves drug solubility, absorption and residence time at the target site. Also, these nanocarrier systems can achieve sustained or stimuli-responsive drug release thus making them potentials to approach in improving the

drug delivery system in gastrointestinal disorders like GERD[40,41]

Table 2: Key Nanocarrier Features for GERD-Relevant Delivery

Carrier Type	Advantages for GERD context	Ref.
Polymeric NPs (CS/PLGA/Eudragit)	Mucoadhesion, acid protection,pH-controlled release	[34]
SLN/NLC	Enhance Lipophillic drug solubility, sustained oral delivery	[37]
Liposomes/Niosomes	Bilayer loading/ lipophilic drugs, modifiable surfaces	[38]
Nanofibers/gels/emulsions	High surface area, local depot, prolonged retention	[39]

5. Biological & emerging delivery approaches

Therapeutics: Novel Strategies to Treat Gastroesophageal Reflux Disease Through Biologically Inspired and Responsive Delivery Systems. These include microbiome-based therapies, peptide or hormonal modulation, and smart bioresponsive drug delivery platforms designed to enhance targeting, efficacy, and long-term disease control.

5.1 Probiotic-Based Delivery and Microbiome Modulation

The gut microbiota is central in regulating intestinal inflammation, epithelial barrier integrity and immune responses that can impact GI symptoms and systemic manifestations. Challenges in probiotic therapy include maintaining bacteria viability throughout processing and storage, as well as during gastrointestinal passage with sufficient colonization time [42]. In an effort to overcome the drawbacks of both materials and methods, polysaccharides, proteins, hydrogels, nanocoatings, emulsions and core–shell microgels have been used as encapsulation technologies. These systems can use to protect the probiotic organisms from extreme conditions like low gastric pH, bile salts, digestive enzymes and oxidative stress with permit controlled release within intestine region with a delayed residence time in the gut. Probiotics could be successfully microencapsulated by nanomaterials to better survive the gastrointestinal environment and achieve targeted delivery, improving therapeutic consistency in diseases involving microbial dysbiosis. In addition, materials such as chitosan or alginate have also been used to engineer probiotics with enhanced resistance to gastric environments and the ability to modulate inflammation and microbial community signatures in experimental animal models, rationalizing the notion of "living therapeutics" [43].

5.2 Peptide, Hormonal, and LES-Modulating Therapeutics

Peptides and gut hormones are difficult to produce orally because of enzymatic degradation in the gastrointestinal tract and poor epithelial permeability. These barriers are being crossed thanks to advances in formulation technologies and medicinal chemistry. An exciting approach would be to stimulate endogenously hormone secretion, instead of direct hormone replacement. For instance, lipid-based nanocarriers have been proposed that can transport either GLP-1 or GLP-2 analogs and promote the release of endogenous hormones for gastrointestinal and metabolic disorders. Thus, a successful oral peptide delivery system must address stability, controlled release and targeting of the gastrointestinal tract for localized degradation or absorption. Peptides that have long half-lives and wide therapeutic windows make them excellent candidates towards oral delivery. An alternative and inventive method employs ingestible electroceutical capsules to electrically stimulate gastrointestinal mucosa, thereby modulating hormone release as well as the gut brain axis. These devices provide spatially and temporally controlled neuromodulation of GI motility and sphincter function, providing another option for traditional pharmacological therapies use [44,45].

5.3 Gene-Triggered and Enzyme-Responsive Systems

An additional perhaps the most promising direction for targeted gastrointestinal therapies is stimuli-responsive drug delivery systems. These platforms take advantage of some local biochemical agents such as triggers pH-responsive, redox conditions, or specific enzymes to trigger drug release exclusively at the disease site in question, thus enhancing precision and reducing systemic toxicity. An attractive approach involves the use of enzyme responsive carriers, as these carriers only release therapeutic agents in tissues where

particular enzymes are overexpressed. For example, there are enzyme-triggered adhesive oral systems that have been designed for the long-acting retention of therapeutics in the small intestine through catalase mediated in-situ gelation and mucoadhesion. Likewise, enzyme-triggered nanoconjugates have shown specific release of corticosteroids in inflamed intestinal tissues in colitis models, resulting in local drug concentrations hundreds of times higher than systemically exposed. More sophisticated systems, which integrate multiple triggers, are being researched for simultaneous and localized delivery of drugs and genetic materials using pH- or enzyme-responsive mechanisms in series. While currently investigated primarily in the context of inflammatory and neoplastic conditions, these technologies demonstrate the potential future use of gene- and enzyme-triggered delivery systems for targeted treatment of esophageal diseases as well as lower esophageal sphincter dysfunction related to GERD [46,47].

6. Pharmacokinetic and pharmacodynamic considerations

6.1 Impact of Targeted Delivery on Absorption and Exposure

Target drug delivery system (TDDS) has an enormous impact on the absorption and bio-distribution of drugs at a particular organ by ensuring high localization of therapeutic agents at the site and low exposure to other tissues. These systems can improve drug solubilization, membrane transport and penetration through various biological barriers, leading to enhanced absorption and bioavailability in the target site. Localized or organ-specific delivery strategies likewise, for the colon, kidney, as well as tumor tissues - facilitate concentrated drug levels at the desired site of action when lower circulating drugs. This strategy is helpful in improving therapeutic outcomes while limiting systemic adverse effects which highlight a more beneficial advantage for diseases that necessitate localized treatment [48,49].

6.2 Sustained Release and Steady-State Concentrations

Sustained-release (SR) and modified release formulations are intended to provide relatively constant drug concentrations in the systemic circulation over extended periods, generally over a minimum of 12 hours and up to 24 hours or more reducing peak trough fluctuations related to conventional dosing. Matrix based systems and nanotechnology driven delivery platforms have been shown to allow prolonged drug release, generate flatter plasma concentration profiles (Cmax–Cmin), and improve the concordance between exposure to drugs and pharmacokinetic targets for chronic therapy. These traits prove particularly advantageous in chronic ailments for which sustained therapeutic drug concentrations are necessary to uphold efficacy and decrease dosing frequency [50,51].

Table 3: PK/PD Benefits and Therapeutic Index

PK/PD aspect	Effect of Targeted/ SR systems	Ref.
Systemic side effects	Lower off- target exposure, less toxicity	[52]
Therapeutic index	Higher local : systemic ratio, safer higher effective doses	[52]
Dosing frequency & adherence	Less frequent dosing, better compliance	[48]
Variability	More predictable exposure, reduced interpatient fluctuation	[53]

7. Preclinical and clinical evidence

7.1 Animal Studies of Gastroretentive and Nanoformulations

Various gastroretentive systems (that is, floating, mucoadhesive and swelling) as well as nanocarrier-based formulations were evaluated using preclinical studies in animal models like rats and dogs for acid-suppressive drugs. These systems have demonstrated prolonged gastric residence, sustained plasma drug levels for up to 24 h, enhanced healing of the ulcer and reduced damage to the esophagus. Nanoparticles like chitosan and PLGA formulations increase drug stability in acidic conditions, mucosal adhesion, and bioavailability compared to conventional formulations

Table 4: Summary Animal Studies of Gastroretentive and Nanoformulations

Study focus/model	Delivery system & Key PK/PD features	Main therapeutic findings vs conventional	Ref.
GRDDS concepts (multiple species)	Floating, swellable, mucoadhesive, high density systems prolong gastric residence, enable controlled release	Enhanced gastric retention, improved bioavailability for narrow window and acid labile drugs	[54]

Ofloxacin GR nanofibers (rats)	Gellan/PVA nanofiber scaffold, mucoadhesive, gastroretentive, sustained release via Fickian diffusion	Longer gastric residence, higher antimicrobial activity and expected bioavailability vs free drug	[55]
Micro in macro GRDDS (pigs)	Ciprofloxacin loaded chitosan/Eudragit micropaticles in floating gastrosphere, 24h controlled release	Greater bioavailability and more controlled 24h profile than marleted immediate release tablets	[56]
Chitosan based GRDDS (various animals)	Mucoadhesive, expandable, superporous, density based systems using chitosan	Increased gastric retention and local action, platform for multiple nano/micro GR systems	[57]
Nanomicelles loaded GR beads (rabbits, gastric cancer models)	Floating, mucoadhesive beads containing emodin nanomicelles, anomalous transport release	More than 8h gastric retention, better antitumor efficacy than emodin suspension	[58]
Phytol nanoemulsion beads (rats)	Nano phytol in alginate beads, pH dependent controlled release	Superior protection vs free phytol against ethanol ulcers, deeper tissue penetration, and NO modulating effects	[59]
Nanofiber GRDDS review	Polymeric nanofibers for stomach specific prolonged release	Improved gastric residence, loacal action, and bioavailability vs conventional oral forms	[60]

7.2 Human Clinical Trials Using Advanced Delivery Systems

Most research on advanced delivery systems for GERD focuses on release-modified PPIs, gastroretentive tablets, in situ gelling system and multiparticular formulation. These trials demonstrate 24-hour acid control, nocturnal symptom relief, and efficient healing of erosive esophagitis. Gastroretentive and gelling systems allow for longer heartburn relief, sustained symptom control or, in some cases, improved bioavailability of acid-labile drug remained promising; however early studies on nanotechnology based formulation appeared to improve the bioavailability of acid labile drugs.

Intervention type	**Key examples & design**	**Main clinical outcomes vs standard therapy**	**Ref.**
GRDDS in humans (general)	Floating/swellable tablets, raft systems, proprietary GR products	Improved bioavailabity and once daily dosing for narrow window drugs, limited but growing clinical use	[54]
GRDDS+ controlled release products	Commercial GR controlled release tablets (e.g., metformin, others)	Better exposure in upper GI, reduced dosing frequency, improved compliance vs immediate release	[54]
Anti-reflux mucosal	Endoscopic mucosal	Durable symptom	[61]

interventions (ARMIs)	resection/ ablation techniques for GERD	score and acid exposure improvements, 2-3x higher PPI cessation, acceptable AE profile	
ARMS vs radiofrequency RCT (PPI refractory GERD)	Single center RCT, ARMS vs Stetta type radiofrequency	Similar 2 year GERD Q improvement, PPI discontinuation and satisfaction, 100% technical success	[62]
Emerging pharmacologic strategies (P-CABs, protectants)	RCTs of vonoprazan, fexuprazan, tegoprazan, PPI + mucosal protectants	P-CABs non-inferior/superior to PPIs for healing and symptoms, tegoprazan faster relief, PPI + protectant improves histologic and symptom outcomes	[63]

7.3 Comparative Outcomes vs Conventional PPIs

Such novel advanced targeted and controlled delivery systems demonstrate better pharmacokinetic profiles, improved 24-h acid control, and superior management of nocturnal symptoms compared to the traditional PPIs. They may also enhance adherence through continuous relief and once-daily dosing while preserving similar safety profiles to standard formulations.

Comparator	**Advanced system/ strategy**	**Comparative outcomes vs conventional PPI therapy**	**Ref.**
Standard PPIs	P-CABs (vonoprazan, fexuprazan, tegoprazan)	Non- inferior or superior for symptom relief and mucosal healing, faster control with tegoprazan, higher gastrin with long term vonoprazan but no malignancy seen	[63]
PPI alone	PPI + mucosal protective agents	Better symptom and histologic remission	[63]
PPI refractory on medical therapy	ARMIs (EMR/ESD/ARMA techniques)	Similar symptom relief to Nissen fundoplication and Stretta, higher chance of PPI discontinuation, shorter procedures, lower dysphagia vs surgery	[61]
PPI refractory GERD	ARMS vs radiofrequency energy	Equivalent 2 year GERD-Q scores, PPI cessation, and satisfaction	[62]

Future Perspective

Moreover, the future study on therapy of GERD will be mainly devoted to advanced targeted and controlled drug delivery systems for improving drug stabilization in GIT environments, increased mucosal adhesion, and site-specific release at the target site. Nanocarriers, gastroretentive systems, and stimuli-responsive

formulations are technologies that can be leveraged to deliver drug more optimally at the gastroesophageal junction on a localized level, instead of across the systemic circulation. Novel approaches such as microbiome-targeted therapies, peptide delivery systems and smart bioresponsive platforms could thus offer a way to advance beyond the traditional strategies of acid suppression. And for that to happen, more clinical trials, better large-scale manufacturing techniques and regulatory approval will all be required to help turn these novel delivery systems into routine clinical practice.

Conclusion

Gastroesophageal reflux disease continues to be a prevalent chronic condition with considerable effects on health-related quality of life and the health care system. Proton pump inhibitors are the first-line therapy but have limitations that call for better treatment strategies. The efficacy of these approaches has been manifested in the case of targeted and controlled drug delivery systems as mucosal, pH-sensitive, raft forming, gastroretentive and nanotechnology-based formulations that will improve drug stability long enough to propagate gastric residence (gastric retention), allowing site-specific or sustained therapeutic action at the desired physiological sites. These advanced delivery technologies may enhance therapeutic efficacy, minimize dosing complexity and systemic side effects. They represent an important future direction in long-term management in the general population.

References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R: The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006, 101:1900-20; quiz 1943. 10.1111/j.1572-0241.2006.00630.x

2 Tanvir, F., Nijjar, G. S., Aulakh, S. K., Kaur, Y., Singh, S., Singh, K., Singla, A., Sandhu, A. P. S., Luthra, S., & Antaal, H. (2024). Gastroesophageal Reflux Disease: New Insights and Treatment Approaches. *Cureus*, *16*(8), e67654. https://doi.org/10.7759/cureus.67654

3. Fass R: Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. J Clin Gastroenterol. 2007, 41:131-7. 10.1097/01.mcg.0000225631.07039.6d

4. Shaqran, T. M., Ismaeel, M. M., Alnuaman, A. A., Al Ahmad, F. A., Albalawi, G. A., Almubarak, J. N., AlHarbi, R. S., Alaqidi, R. S., AlAli, Y. A., Alfawaz, K. S., & Daghriri, A. A. (2023). Epidemiology, Causes, and Management of Gastro-esophageal Reflux Disease: A Systematic Review. *Cureus*, *15*(10), e47420. https://doi.org/10.7759/cureus.47420

5. Bertin, L., Savarino, V., Marabotto, E., Ghisa, M., de Bortoli, N., & Savarino, E. V. (2025). Pathophysiology of Gastroesophageal Reflux Disease. *Digestion*, 1–17. Advance online publication. https://doi.org/10.1159/000547023

6. Chapelle, N.; Ben Ghezala, I.; Barkun, A.; Bardou, M. The pharmacotherapeutic management of gastroesophageal reflux disease (GERD). *Expert Opin. Pharmacother.* 2021, *22*, 219–227. [Google Scholar] [CrossRef]

7. Hossa, K., & Małecka-Wojciesko, E. (2025). Advances in Gastroesophageal Reflux Disease Management: Exploring the Role of Potassium-Competitive Acid Blockers and Novel Therapies. *Pharmaceuticals (Basel, Switzerland)*, *18*(5), 699. https://doi.org/10.3390/ph18050699

8. Leowattana, W.; Leowattana, T. Potassium-competitive acid blockers and gastroesophageal reflux disease. *World J. Gastroenterol.* 2022, *28*, 3608–3619. [Google Scholar] [CrossRef]

9. Sigterman, K.E.; van Pinxteren, B.; Bonis, P.A.; Lau, J.; Numans, M.E. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane *Database Syst. Rev.* 2013, *2013*, CD002095. [Google Scholar] [CrossRef]

10. Tanvir, F.; Nijjar, G.S.; Aulakh, S.K.; Kaur, Y.; Singh, S.; Singh, K.; Singla, A.; Sandhu, A.P.S.; Luthra, S.; Antaal, H. Gastroesophageal Reflux Disease: New Insights and Treatment Approaches. *Cureus* 2024, *16*, e67654. [Google Scholar] [CrossRef] [PubMed] 10.7759/cureus.67654

11. Herdiana Y. (2023). Chitosan Nanoparticles for Gastroesophageal Reflux Disease Treatment. *Polymers*, *15*(16), 3485. https://doi.org/10.3390/polym15163485

12. Rambaran, T.; Schirhagl, R. Nanotechnology from lab to industry—A look at current trends. *Nanoscale Adv.* 2022, *4*, 3664–3675. [Google Scholar] [CrossRef] 10.1039/D2NA00439A

13. Ahire, S.A.; Bachhav, A.A.; Pawar, T.B.; Jagdale, B.S.; Patil, A.V.; Koli, P.B. The Augmentation of nanotechnology era: A concise review on fundamental concepts of nanotechnology and applications in material science and technology. *Results Chem.* 2022, *4*, 100633. [Google Scholar] [CrossRef] https://doi.org/10.1016/j.rechem.2022.100633

14. 10.1002/mabi.201000388 Advances in Mucoadhesion and Mucoadhesive Polymers
15. pH-responsive polymers for drug delivery: Trends and opportunities https://doi.org/10.1002/pol.20230403Digital Object Identifier (DOI)
16. https://doi.org/10.3762/bjnano.16.28 Development of a mucoadhesive drug delivery system and its interaction with gastric cells
17. https://doi.org/10.1016/j.ijpharm.2023.123115Get rights and content
Evaluation of bioadhesive gels for local action in the esophagus
18. 10.7569/RAA.2013.097307 Enhancement of Mucoadhesive Property of Polymers for Drug Delivery Applications: A Critical Review Inderbir Singh and Vikas Rana* Pharmaceutics Division, Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala-147002, Punjab, India
19. 10.1080/10717544.2023.2219423 Current status and advances in esophageal drug delivery technology: influence of physiological, pathophysiological and pharmaceutical factors
20. 10.3390/polym14245459 Bio-Inspired Muco-Adhesive Polymers for Drug Delivery Applications
21. https://doi.org/10.1186/s12951-025-03479-8 Advanced oral drug delivery systems for gastrointestinal targeted delivery: the design principles and foundations
22. 10.1080/03639045.2025.2536620 pH-responsive chitosan-alginate hydrogel beads: for enhanced bioavailability and controlled release of omeprazole.
23. https://doi.org/10.3390/pharmaceutics16060790 Expanding the Manufacturing Approaches for Gastroretentive Drug Delivery Systems with 3D Printing Technology
24. https://doi.org/10.1016/j.jddst.2025.107808 Raft-forming systems in GERD therapies: Formulation guidelines
25. 10.1002/adhm.202403162 "Therapies Through Gut:" Targeted Drug Delivery for Non-Gastrointestinal Diseases by Oral Administration
26. 10.1039/D5NJ00654F Tailored mesoporous silica nanoparticles for overcoming gastrointestinal barriers: a perspective on advanced strategies for oral delivery
27. https://doi.org/10.1080/10837450.2018.1534376 Controlled release drug delivery systems
28. https://doi.org/10.22159/ijpps.2021v13i9.41799 FORMULATION, EVALUATION AND OPTIMIZATION OF SUSTAINED-RELEASE DRUG DELIVERY SYSTEM OF CISAPRIDE TABLET
29. https://doi.org/10.3390/pharmaceutics11040193 Current State and Future Perspectives on Gastroretentive Drug Delivery Systems
30. https://dx.doi.org/10.33289/IJRPC.10.1.2020.10(24) GASTRO RETENTIVE DRUG DELIVERY SYSTEMS: A REVIEW
31. https://doi.org/10.22270/jddt.v12i4.5422 A review on Advanced approaches and polymers used in gastroretentive drug delivery systems
32. https://doi.org/10.3109/10717544.2010.520354 Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems
33. 10.48175/IJARSCT-8073 Review on Gastroretentive Drug Delivery System
34. https://doi.org/10.3390/pharmaceutics14010095 Chitosan/poly(lactic-co-glycolic)acid Nanoparticle Formulations with Finely-Tuned Size Distributions for Enhanced Mucoadhesion
35. https://doi.org/10.3390/polym11020304 Chitosan-Modified PLGA Nanoparticles for Control-Released Drug Delivery
36. https://doi.org/10.3390/pharmaceutics15061593 Solid Lipid Nanoparticles vs. Nanostructured Lipid Carriers: A Comparative Review
37. https://doi.org/10.3390/ijms26136509 A Review of Formulation Strategies for Cyclodextrin-Enhanced Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)
38. https://doi.org/10.1016/j.heliyon.2022.e09394 Liposomes: structure, composition, types, and clinical applications☆
39. https://doi.org/10.1016/j.mtbio.2023.100837 Current advances in niosomes applications for drug delivery and cancer treatment
40. https://doi.org/10.3390/pharmaceutics17020272 Development of an Innovative Dual Construct for Targeted Drug Delivery in the Oral Cavity
41. https://doi.org/10.1002/pat.6406Digital Object Identifier (DOI) Nanocarrier-embedded gels: Precision drug delivery via liposomal and niosomal platforms
42. https://doi.org/10.1038/s41467-022-31171-0 Programmable probiotics modulate inflammation and gut microbiota for inflammatory bowel disease treatment after effective oral delivery
43. https://doi.org/10.3390/foods14132318 Enteric Delivery of Probiotics: Challenges, Techniques, and Activity Assays
44. https://doi.org/10.1016/j.addr.2020.05.007 Systemic delivery of peptides by the oral route: Formulation and medicinal chemistry approaches

45. https://doi.org/10.1016/j.jconrel.2024.07.007 Gut hormone stimulation as a therapeutic approach in oral peptide delivery
46. https://doi.org/10.1016/j.nantod.2020.100914 Stimulus-responsive sequential release systems for drug and gene delivery
47. https://doi.org/10.1002/adhm.202301033Digital Object Identifier (DOI) Enzyme-Triggered Intestine-Specific Targeting Adhesive Platform for Universal Oral Drug Delivery
48. 10.1208/s12248-015-9814-9 Drug Delivery Approaches in Addressing Clinical Pharmacology-Related Issues: Opportunities and Challenges
49. https://doi.org/10.3390/pharmaceutics12010068 Strategic Approaches for Colon Targeted Drug Delivery: An Overview of Recent Advancements
50. https://doi.org/10.52783/jns.v14.2869 Formulation and Characterization of Sustained-Release Drug Delivery Systems for Oral Cancer
51. https://doi.org/10.70333/ijeks-04-05-016 Formulation and Evaluation of Oral Sustained Release Tablets
52. https://doi.org/10.69613/q3mj7z06 Recent Advances in Targeted Drug Delivery Systems
53. https://doi.org/10.3390/pharmaceutics17101264 Sustained-Release Oral Delivery of NSAIDs and Acetaminophen: Advances and Recent Formulation Strategies—A Systematic Review
54. https://doi.org/10.3390/pharmaceutics13101591 Gastroretentive Technologies in Tandem with Controlled-Release Strategies: A Potent Answer to Oral Drug Bioavailability and Patient Compliance Implications
55. https://doi.org/10.1016/j.msec.2016.10.051 Ofloxacin loaded gellan/PVA nanofibers - Synthesis, characterization and evaluation of their gastroretentive/mucoadhesive drug delivery potential
56. https://doi.org/10.3390/polym15061385 A Micro-In-Macro Gastroretentive System for the Delivery of Narrow-Absorption Window Drugs
57. https://doi.org/10.1016/j.ijbiomac.2020.05.104 Highlighting the impact of chitosan on the development of gastroretentive drug delivery systems
58. https://doi.org/10.1016/j.jddst.2019.03.024 Development and evaluation of a new gastroretentive drug delivery system: Nanomicelles-loaded floating mucoadhesive beads
59. https://doi.org/10.1371/journal.pone.0327368 Phytol nanoemulsions encapsulated alginate hydrogel beads for the protection and management of alcohol-induced gastric ulcer via nitric oxide synthase and NF-κB/IL-6/TGF-β modulation
60. https://doi.org/10.3109/1061186X.2014.965715 Polymeric nanofibers: targeted gastro-retentive drug delivery systems
61. https://doi.org/10.1159/000548198 Endoscopic Anti-Reflux Mucosal Interventions for Gastroesophageal Reflux Disease: A Systematic Review and Meta-Analysis of Efficacy, Safety, and Comparative Outcomes
62. https://doi.org/10.5056/jnm21240 Randomized Controlled Trial of Anti-reflux Mucosectomy Versus Radiofrequency Energy Delivery for Proton Pump Inhibitor-refractory Gastroesophageal Reflux Disease
63. https://doi.org/10.7759/cureus.84311 Comparing Proton Pump Inhibitors and Emerging Acid-Suppressive Therapies in Gastroesophageal Reflux Disease: A Systematic Review