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pH-Sensitive Enteric-Coated Omeprazole Pellet Systems for Sequential Gastrointestinal Drug Delivery: Formulation Strategies, Release Mechanisms, and Recent Advances

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Abstract **Review Article**

Oral drug delivery remains the most preferred route of administration because of its convenience, non-invasive nature, cost-effectiveness, and high patient compliance. However, the successful delivery of acid-labile drugs continues to present significant formulation challenges. Omeprazole, a proton pump inhibitor widely prescribed for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger–Ellison syndrome, is highly unstable in acidic environments and undergoes rapid degradation in the stomach before reaching its primary absorption site in the small intestine. Consequently, specialized formulation approaches are required to protect the drug during gastric transit while ensuring efficient intestinal release. Among various oral delivery systems, pH-sensitive enteric-coated pellets have emerged as one of the most successful strategies for improving the stability and bioavailability of omeprazole. Multiparticulate pellet systems provide uniform distribution throughout the gastrointestinal tract, reduce variability in gastric emptying, and offer greater flexibility in controlling drug release compared with conventional single-unit dosage forms. The incorporation of pH-responsive polymers such as Eudragit® L100 and Eudragit® S100 enables site-specific release by exploiting physiological pH variations within the gastrointestinal tract. Recent developments in pelletization technology, enteric coating systems, and Quality by Design (QbD) methodologies have significantly improved the performance and reproducibility of omeprazole formulations. This review critically examines gastrointestinal physiology, pH-dependent drug delivery principles, the physicochemical characteristics of omeprazole, and the evolution of enteric-coated pellet systems. Particular emphasis is placed on sequential drug release strategies, polymer selection, formulation challenges, and emerging advances in pH-sensitive oral drug delivery. The review highlights the potential of multiparticulate enteric-coated systems to enhance therapeutic efficacy, improve patient compliance, and provide more reliable treatment outcomes for acid-related gastrointestinal disorders.

Keywords: Omeprazole, enteric coating, pH-sensitive drug delivery, multiparticulate systems, pelletization, sequential release, gastrointestinal targeting, proton pump inhibitors, Eudragit polymers, controlled release.

1. INTRODUCTION

Oral administration remains the most widely utilized route for drug delivery because of its ease of administration, patient acceptance, flexibility in dosage form design, and relatively low manufacturing costs. Despite these advantages, oral drug delivery systems must overcome numerous physiological barriers that can significantly affect drug stability, absorption, and therapeutic effectiveness. Variations in gastrointestinal pH, enzyme activity, transit time, and permeability frequently influence the performance of orally administered medications (Loke et al., 2025).

The challenges become even more pronounced for acid-sensitive drugs. Exposure to gastric acid may result in substantial degradation before the drug reaches its absorption site, thereby reducing bioavailability and therapeutic efficacy. Omeprazole represents one of the most important examples of an acid-labile pharmaceutical compound requiring specialized delivery systems for successful oral administration (Iuga and Bojita, 2010).

Although clinically effective, omeprazole exhibits poor stability under acidic conditions. The drug undergoes rapid degradation when exposed to gastric fluid, necessitating formulation approaches capable of protecting the active pharmaceutical ingredient during its transit through the stomach. Early conventional formulations often demonstrated variable therapeutic outcomes because significant portions of the administered dose were degraded before absorption could occur. These limitations stimulated the development of enteric-coated dosage forms specifically designed to prevent premature drug release within the stomach (Parihar et al., 2023).

Enteric coating technology has become a cornerstone of modern omeprazole formulation development. Enteric polymers remain intact under acidic conditions but dissolve when exposed to the higher pH environment of the small intestine. This selective dissolution behavior enables effective protection of acid-sensitive drugs while facilitating targeted intestinal release. Commercial success stories such as enteric-coated omeprazole capsules have demonstrated the clinical value of this approach and established enteric coating as an essential component of omeprazole drug delivery systems (Cui et al., 2020).

The evolution of pharmaceutical technology has further expanded the possibilities for oral drug delivery through the development of multiparticulate systems. Multiparticulate formulations consist of numerous discrete units, such as pellets, granules, or mini-tablets, that collectively deliver the therapeutic dose. Compared with single-unit systems, multiparticulate dosage forms exhibit superior gastrointestinal distribution, reduced risk of dose dumping, improved reproducibility of drug release, and greater flexibility in formulation design (Gandhi and Baheti, 2013; Chakravarthy *et al.,* 2012).

Pellets have emerged as particularly attractive multiparticulate systems because of their spherical geometry, narrow size distribution, excellent flow properties, and suitability for coating processes. These characteristics allow precise control over drug release profiles and facilitate the incorporation of multiple functional layers, including drug-containing cores, barrier coatings, and enteric coatings. Such multilayered structures are especially beneficial for acid-labile drugs like omeprazole, where both protection and controlled release are essential (Ramesh *et al.,* 2025).

Recent advances in pharmaceutical research have introduced the concept of sequential drug release, which seeks to deliver therapeutic agents at specific locations within the gastrointestinal tract according to physiological requirements. Sequential-release systems are designed to exploit regional variations in gastrointestinal pH and transit characteristics, thereby enhancing drug absorption and therapeutic effectiveness. For omeprazole, sequential release offers the possibility of maximizing intestinal absorption while maintaining protection against gastric degradation (Kuma et al., 2025).

In parallel with advances in formulation technology, pharmaceutical development has increasingly embraced systematic approaches such as Quality by Design (QbD). QbD emphasizes scientific understanding, risk assessment, and process optimization throughout product development. Application of QbD principles to pellet-based formulations has enabled improved process control, enhanced product consistency, and more efficient optimization of critical formulation variables such as polymer concentration, coating thickness, and release characteristics (Veerubhotla and Walker., 2020).

The growing interest in targeted drug delivery, personalized medicine, and controlled-release technologies has intensified research into pH-sensitive pellet systems. Modern investigations extend beyond simple enteric protection and focus increasingly on intelligent formulations capable of responding dynamically to physiological conditions. Such innovations are expected to play an important role in the future development of oral drug delivery systems for acid-sensitive therapeutic agents.

The present review aims to critically examine the scientific foundations and technological developments associated with pH-sensitive enteric-coated omeprazole pellet systems. Particular attention is given to gastrointestinal physiology, pH-dependent release mechanisms, pelletization technologies, polymer selection, and emerging trends in sequential gastrointestinal drug delivery.

2. Gastrointestinal Physiology and pH-Dependent Drug Delivery

The success of oral drug delivery systems depends largely on the physiological characteristics of the gastrointestinal tract. The gastrointestinal system is a complex and highly dynamic environment in which pH, enzyme activity, fluid composition, transit time, and permeability vary considerably between different anatomical regions. These physiological variations exert a profound influence on drug dissolution, stability, absorption, and ultimately therapeutic performance (Loke et al., 2025).

Among the numerous physiological factors affecting oral drug delivery, pH plays a particularly critical role. The human gastrointestinal tract exhibits a distinct pH gradient extending from the stomach to the colon. These gradient forms the scientific basis for pH-dependent drug delivery systems and provides opportunities for site-specific targeting of therapeutic agents.

The stomach represents the most acidic region of the gastrointestinal tract, with fasting pH values typically ranging between 1 and 3. The highly acidic environment facilitates protein digestion and serves as a defense mechanism against pathogenic microorganisms. However, this same environment poses significant challenges for acid-sensitive drugs. Omeprazole is particularly vulnerable to gastric degradation and undergoes rapid decomposition under acidic conditions, resulting in substantial loss of active drug before intestinal absorption can occur (Iuga and Bojita, 2010).

Following gastric emptying, drug-containing dosage forms enter the duodenum, where acidic gastric contents are neutralized by bicarbonate-rich pancreatic secretions. Consequently, the pH rises to approximately 5.5–6.5. Further progression through the jejunum and ileum results in gradual increases in pH, often reaching values between 6.5 and 7.5. These near-neutral conditions provide a favorable environment for the stability and absorption of omeprazole and many other acid-sensitive compounds (Loke et al., 2025).

The colon generally exhibits pH values ranging from 7.0 to 8.0, although considerable variability may occur depending on diet, microbial composition, and disease state. In addition to pH differences, the colon contains a diverse microbial population capable of metabolizing specific polymers and excipients. These unique characteristics have stimulated the development of colon-targeted drug delivery systems and advanced controlled-release formulations (Kuma et al., 2025).

The existence of physiological pH gradients within the gastrointestinal tract has enabled the development of pH-sensitive drug delivery systems. These systems utilize polymers that remain insoluble under acidic conditions but dissolve or swell when exposed to higher pH environments. Such behavior permits selective drug release within targeted gastrointestinal regions while protecting sensitive compounds during transit through unfavorable environments (Ambudkar and Chauhan, 2025).

Among the most widely utilized pH-responsive polymers are methacrylic acid copolymers marketed under the Eudragit® brand name. Eudragit® L100 dissolves at pH values above approximately 6.0 and is therefore suitable for targeting the upper small intestine. In contrast, Eudragit® S100 dissolves at pH values above approximately 7.0 and is commonly employed for distal intestinal or colonic targeting. By varying polymer composition and coating thickness, formulation scientists can precisely modulate the location and timing of drug release (Singh and Nayak, 2023).

The advantages of pH-sensitive drug delivery extend beyond protection of acid-labile drugs. These systems can reduce gastric irritation, improve bioavailability, minimize systemic side effects, and enhance therapeutic efficiency. Moreover, pH-dependent release mechanisms provide opportunities for chronotherapeutic and site-specific drug delivery applications, allowing therapy to be tailored according to physiological or pathological conditions (Kuma et al., 2025).

For omeprazole, pH-sensitive delivery is particularly important because successful therapy depends upon maintaining drug integrity until the dosage form reaches the upper intestine. Enteric-coated pellet systems accomplish this objective by combining the protective effects of pH-responsive polymers with the distribution advantages of multiparticulate dosage forms. The resulting formulations provide excellent gastric protection while ensuring rapid and efficient release within the optimal absorption region (Ambudkar and Chauhan, 2025).

Understanding gastrointestinal physiology therefore remains fundamental to the design of effective omeprazole delivery systems. Advances in polymer science, formulation technology, and controlled-release design continue to improve the ability of pharmaceutical scientists to exploit physiological pH gradients for targeted and sequential drug delivery. These developments have established pH-sensitive pellet systems as one of the most promising approaches for enhancing the therapeutic performance of acid-sensitive drugs such as omeprazole.

3. Omeprazole: Physicochemical, Pharmacokinetic, and Biopharmaceutical Characteristics

Omeprazole is a substituted benzimidazole derivative belonging to the proton pump inhibitor (PPI) class of drugs and is widely recognized as one of the most effective therapeutic agents for the management of acid-related gastrointestinal disorders. Since its introduction into clinical practice, omeprazole has been extensively prescribed for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease, Zollinger–Ellison syndrome, and Helicobacter pylori-associated gastric ulcers owing to its potent and prolonged inhibition of gastric acid secretion (Loke et al., 2025). Despite its remarkable therapeutic efficacy, the successful formulation of omeprazole remains challenging because of its poor physicochemical stability and complex biopharmaceutical behavior.

Chemically, omeprazole is designated as 5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl]-1H-benzimidazole, possessing the molecular formula $C_{17}H_{19}N_3O_3S$ and a molecular weight of 345.42 g/mol (Loke et al., 2025). The molecule consists of a benzimidazole ring connected through a sulfoxide bridge to a substituted pyridine moiety, a structural arrangement responsible for both its pharmacological activity and chemical instability. Omeprazole is typically obtained as a white to off-white crystalline powder and exhibits poor aqueous solubility

while remaining soluble in several organic solvents. More importantly, the drug displays pronounced pH-dependent stability, a characteristic that significantly influences formulation design (Iuga and Bojita, 2010).

The major pharmaceutical challenge associated with omeprazole arises from its acid-labile nature. Upon exposure to acidic environments, particularly gastric fluid, the drug undergoes rapid degradation through acid-catalyzed rearrangement reactions, producing inactive degradation products before absorption can occur (Iuga and Bojita, 2010). Consequently, conventional oral dosage forms lacking appropriate protection are unable to deliver therapeutically effective quantities of intact drug. This instability forms the primary rationale for the development of enteric-coated formulations and pH-sensitive drug delivery systems.

From a biopharmaceutical perspective, omeprazole exhibits characteristics that necessitate careful consideration during dosage form development. The drug is absorbed primarily from the upper small intestine and demonstrates significantly greater stability under neutral and alkaline conditions than in acidic environments. Effective therapy therefore depends upon protecting the drug during gastric transit while ensuring rapid release upon entry into the intestinal region (Loke et al., 2025). Furthermore, because omeprazole exhibits limited aqueous solubility, dissolution behavior may influence the rate and extent of absorption, making formulation optimization essential for achieving satisfactory bioavailability.

The pharmacological activity of omeprazole results from its ability to irreversibly inhibit the gastric H^+/K^+-ATPase enzyme system, commonly referred to as the proton pump. Following absorption and systemic distribution, omeprazole accumulates within the acidic secretory canaliculi of gastric parietal cells, where it undergoes activation and covalent binding to proton pump enzymes. Because enzyme inhibition is irreversible, restoration of acid secretion requires synthesis of new proton pumps, resulting in a pharmacological effect that persists considerably longer than the plasma half-life of the drug (Loke et al., 2025).

Pharmacokinetic studies indicate that omeprazole is rapidly absorbed after release into the small intestine, with peak plasma concentrations typically occurring within one to two hours following administration. The drug exhibits extensive plasma protein binding and undergoes significant hepatic metabolism through cytochrome P450 enzymes, particularly CYP2C19 and CYP3A4. Genetic variations affecting these enzymes may contribute to interindividual variability in therapeutic response and systemic drug exposure (Iuga and Bojita, 2010). Although the plasma elimination half-life generally ranges from 0.5 to 1 hour, acid suppression persists for substantially longer periods because of irreversible proton pump inhibition.

The physicochemical and pharmacokinetic characteristics of omeprazole collectively highlight the necessity of employing sophisticated formulation strategies. Enteric-coated multiparticulate systems have emerged as particularly suitable approaches because they simultaneously address acid instability, dissolution behavior, and site-specific delivery requirements. Understanding these fundamental properties is therefore essential for the rational development of effective omeprazole formulations.

Table 1: Physicochemical and Biopharmaceutical Characteristics of Omeprazole

Parameter	Description
Chemical Name	5-Methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl]-1H-benzimidazole
Molecular Formula	$C_{17}H_{19}N_3O_3S$
Molecular Weight	345.42 g/mol
Therapeutic Class	Proton Pump Inhibitor (PPI)
Physical Appearance	White to Off-White Crystalline Powder
Water Solubility	Practically Insoluble
Stability	Highly Acid-Labile
Primary Absorption Site	Upper Small Intestine
Bioavailability	Approximately 30–40%
Plasma Protein Binding	~95%
Elimination Half-Life	0.5–1 Hour
Major Metabolic Enzymes	CYP2C19 and CYP3A4

Source: Loke *et al.,* 2025; Iuga and Bojita, 2010

The data presented in Table 1 clearly demonstrate why conventional immediate-release formulations are generally unsuitable for omeprazole delivery. The combination of acid instability, limited aqueous solubility, and intestinal absorption requirements necessitates the use of specialized dosage forms capable of protecting the drug until it reaches favorable absorption conditions.

4. Challenges Associated with Oral Delivery of Omeprazole

Despite its proven therapeutic effectiveness, omeprazole remains one of the most formulation-sensitive drugs used in oral pharmaceutical products. The successful delivery of the drug requires overcoming multiple physicochemical, biopharmaceutical, and technological challenges. These challenges have served as major driving forces behind the development of advanced multiparticulate and enteric-coated delivery systems (Ambudkar and Chauhan, 2025).

The foremost challenge is the pronounced acid instability of the molecule. Exposure to gastric fluid results in rapid degradation, leading to substantial loss of active drug before intestinal absorption can occur. This degradation not only reduces bioavailability but may also contribute to variability in therapeutic response among patients. Studies examining the stability profile of omeprazole have consistently demonstrated that degradation occurs rapidly under acidic conditions, whereas the drug remains relatively stable at pH values above 6.0 (Iuga and Bojita, 2010). Consequently, effective gastric protection is an absolute requirement for successful oral delivery.

Another significant challenge involves incompatibility between omeprazole and acidic enteric polymers. Although enteric coatings are necessary to prevent gastric degradation, direct contact between the alkaline drug and acidic polymeric materials may accelerate degradation during manufacturing and storage (Parihar et al., 2023). To address this issue, formulation scientists commonly incorporate barrier coatings between the drug layer and enteric coating. Such protective layers minimize chemical interactions and improve long-term stability.

Moisture sensitivity further complicates formulation development. Omeprazole is susceptible to hydrolytic degradation, necessitating strict control of humidity during manufacturing, packaging, and storage. Exposure to moisture may compromise both drug stability and coating integrity, ultimately affecting product performance (DellaGreca et al., 2006). Similarly, elevated temperatures and prolonged exposure to light may accelerate degradation processes and reduce shelf life.

Variability in bioavailability also represents a significant challenge. Oral bioavailability is influenced by numerous physiological and formulation-related factors, including gastric residence time, intestinal transit, extent of acid degradation, metabolic activity, and release characteristics of the dosage form. Because omeprazole is absorbed primarily in the upper small intestine, both premature gastric release and excessive delays in intestinal release may adversely affect therapeutic outcomes (Loke et al., 2025).

Another important consideration is the requirement for site-specific delivery. Effective therapy depends upon releasing omeprazole within a relatively narrow gastrointestinal region characterized by favorable pH conditions and efficient absorption. Achieving such precise targeting requires careful selection of enteric polymers, optimization of coating thickness, and thorough understanding of gastrointestinal physiology (Ambudkar and Chauhan, 2025).

Collectively, these challenges illustrate why omeprazole formulation development remains a complex pharmaceutical undertaking. Addressing acid instability, moisture sensitivity, drug–polymer interactions, and site-specific release requirements necessitates sophisticated formulation strategies capable of providing reliable and reproducible performance.

5. Need for Enteric Protection and Multiparticulate Drug Delivery Systems

The limitations associated with conventional oral formulations have led to the widespread adoption of enteric-coated multiparticulate systems for omeprazole delivery. These systems are specifically designed to overcome the challenges posed by acid instability while simultaneously optimizing drug release within the preferred absorption region of the gastrointestinal tract.

Enteric protection constitutes the most fundamental requirement for successful omeprazole delivery. Enteric coatings remain intact in the acidic environment of the stomach and dissolve only when exposed to elevated intestinal pH conditions. This selective dissolution behavior prevents premature drug release and preserves the integrity of the active pharmaceutical ingredient during gastric transit (Parihar et al., 2023). The effectiveness of enteric protection is reflected in the commercial success of delayed-release omeprazole products, which have demonstrated superior bioavailability and therapeutic performance compared with unprotected formulations.

Multiparticulate delivery systems provide additional advantages beyond simple gastric protection. These systems consist of numerous individual pellets or granules that collectively deliver the therapeutic dose. Because each subunit behaves independently within the gastrointestinal tract, multiparticulates exhibit more uniform distribution and less variability in gastric emptying than conventional single-unit dosage forms (Gandhi and Baheti, 2013).

The pharmaceutical significance of multiparticulate systems extends to their ability to reduce the risk of dose dumping, improve coating uniformity, and facilitate the development of complex release profiles. Pellet-based formulations are particularly attractive because their spherical geometry promotes efficient coating and reproducible release behavior. Furthermore, multiple populations of pellets possessing

different release characteristics may be combined within a single dosage form to achieve sequential or pulsatile drug delivery (Kuma et al., 2025).

The convergence of enteric coating technology and multiparticulate formulation principles has therefore transformed the delivery of omeprazole. Modern pellet-based systems effectively address the major limitations associated with acid instability and variable bioavailability while providing enhanced therapeutic consistency. These formulations have become the foundation of most commercially successful omeprazole products and continue to serve as a model for the development of advanced oral drug delivery systems for acid-sensitive therapeutic agents (Chakravarthy et al., 2012; Parihar et al., 2023).

6. Multiparticulate Drug Delivery Systems: Principles and Pharmaceutical Significance

The increasing demand for oral dosage forms capable of providing predictable drug release, enhanced bioavailability, and improved therapeutic outcomes has accelerated the development of multiparticulate drug delivery systems. Multiparticulate formulations consist of numerous discrete subunits, including pellets, granules, beads, microspheres, or mini-tablets, which collectively deliver the required therapeutic dose. Unlike conventional single-unit dosage forms, multiparticulates disperse widely throughout the gastrointestinal tract following administration, thereby reducing variability in gastric emptying and promoting more reproducible drug absorption (Gandhi and Baheti, 2013).

For acid-labile drugs such as omeprazole, multiparticulate systems offer substantial advantages over conventional tablets and capsules. The distribution of numerous small units throughout the gastrointestinal tract minimizes localized drug concentration, reduces interpatient variability, and decreases the risk of dose dumping. Furthermore, the independent behavior of individual pellets allows more consistent transit through the pylorus, resulting in more uniform absorption profiles and improved therapeutic reproducibility (Chakravarthy et al., 2012).

The pharmaceutical significance of multiparticulate systems extends beyond improved gastrointestinal distribution. These systems provide exceptional formulation flexibility, allowing the incorporation of pellets exhibiting different release characteristics within a single dosage form. Such versatility enables the development of immediate-release, delayed-release, sustained-release, and sequential-release formulations tailored to specific therapeutic requirements. In the case of omeprazole, multiparticulate systems facilitate the integration of enteric protection with controlled intestinal release, thereby maximizing drug stability and bioavailability (Kuma et al., 2025).

Commercial success has further validated the effectiveness of multiparticulate technologies. Most modern proton pump inhibitor products utilize enteric-coated pellet systems because they provide superior protection against gastric degradation while ensuring reliable release in the intestinal environment. Consequently, multiparticulate delivery systems have become a benchmark platform for the formulation of acid-sensitive therapeutic agents (Ambudkar and Chauhan, 2025).

7. Pelletization Technologies for Omeprazole Formulations

Pelletization refers to the process of converting powders or granules into spherical or near-spherical particles possessing defined size, shape, and mechanical properties. Pharmaceutical pellets generally range between 500 µm and 1500 µm in diameter and exhibit excellent flowability, packing characteristics, and suitability for coating applications (Chakravarthy et al., 2012).

The choice of pelletization technique significantly influences the quality and performance of the final dosage form. Pellet morphology, size distribution, mechanical strength, porosity, and surface smoothness are all determined by the manufacturing process employed. These properties subsequently affect coating efficiency, drug release behavior, and overall product stability (Ramesh et al., 2025).

Several pelletization methods have been developed for pharmaceutical applications, including extrusion–spheronization, solution layering, powder layering, spray drying, and hot-melt pelletization. Each technique offers distinct advantages and limitations, and the selection of an appropriate method depends upon the physicochemical properties of the drug, desired release profile, production scale, and manufacturing considerations.

Table 2: Comparison of Major Pelletization Techniques Used in Pharmaceutical Formulations

Pelletization Technique	Principle	Major Advantages	Limitations	Suitability for Omeprazole Pellets
Extrusion–Spheronization	Wet mass is extruded and converted into spherical pellets through spheronization	Uniform pellet size, excellent sphericity, high drug-loading capacity, superior coating properties	Requires specialized equipment and process optimization	Excellent; most commonly used for enteric-coated omeprazole pellets

Solution/Suspension Layering	Drug solution or suspension is sprayed onto inert starter cores	High content uniformity, precise drug loading, suitable for low-dose formulations	Longer processing times and solvent requirements	Widely used in commercial formulations
Powder Layering	Drug powder and binder solution are simultaneously deposited onto starter cores	High drug-loading potential and reduced solvent use	Greater process complexity and risk of agglomeration	Suitable for poorly soluble compounds
Spray Drying	Drug solution is atomized into a heated drying chamber	Rapid production and scalability	Limited control over pellet morphology	Less frequently used for enteric-coated pellets
Hot-Melt Pelletization	Drug and excipients are processed using molten binders	Solvent-free manufacturing and shorter processing times	Thermal stress may affect drug stability	Limited applicability due to omeprazole instability

Source: Chakravarthy *et al.,* 2012; Ramesh *et al.,* 2025; Veerubhotla and Walker., 2020

As evident from Table 2, extrusion–spheronization remains the preferred technique for manufacturing enteric-coated omeprazole pellets because it consistently produces highly spherical particles with excellent mechanical strength, narrow size distribution, and superior coating characteristics. These properties are critical for achieving reproducible pH-dependent drug release and long-term product stability (Chakravarthy *et al.,* 2012; Ramesh *et al.,* 2025).

8. Extrusion–Spheronization: The Preferred Pelletization Technique

Among the various pelletization technologies available, extrusion–spheronization has emerged as the most widely accepted and commercially successful technique for the production of pharmaceutical pellets. The method is particularly attractive because it generates highly spherical pellets with smooth surfaces, excellent mechanical integrity, and uniform size distributions, all of which contribute to superior coating performance and controlled drug release (Chakravarthy et al., 2012).

The extrusion–spheronization process generally involves four sequential stages: blending, wet massing, extrusion, and spheronization. Initially, the active pharmaceutical ingredient is mixed with suitable excipients to achieve a homogeneous powder blend. A granulating liquid is then added to produce a cohesive wet mass possessing sufficient plasticity for extrusion. The wet mass is forced through a die plate to produce cylindrical extrudates, which are subsequently transformed into spherical pellets through rotational and frictional forces within a spheronizer (Chakravarthy et al., 2012).

Microcrystalline cellulose (MCC) plays a particularly important role in extrusion–spheronization. Because of its excellent plasticity and water-retention capacity, MCC facilitates pellet formation and contributes significantly to mechanical strength. The study formulation similarly employed MCC as a pelletization aid, highlighting its importance in the manufacture of omeprazole pellets (Kumisbek et al., 2024).

The resulting pellets possess several desirable characteristics, including narrow particle-size distributions, high sphericity, excellent flow properties, and smooth surfaces. These attributes not only facilitate large-scale manufacturing but also improve coating uniformity and release reproducibility. Consequently, extrusion–spheronization continues to be regarded as the gold standard for the production of enteric-coated omeprazole pellets (Ramesh et al., 2025).

9. Drug Layering Approaches and Core Pellet Design

Drug layering represents a critical stage in pellet formulation because it determines the distribution of the active pharmaceutical ingredient and influences subsequent coating performance. Layering techniques are particularly useful when drug loading onto inert starter cores is desired.

Two principal approaches are commonly employed: solution or suspension layering and powder layering. In solution layering, a drug solution or suspension containing suitable binders is sprayed onto inert cores such as sugar spheres. Successive spraying and drying cycles gradually build the desired drug layer around the core. This approach provides excellent content uniformity and precise control over drug loading, making it highly suitable for potent therapeutic agents (Ramesh et al., 2025).

Powder layering involves the simultaneous application of dry drug powder and binder solution onto starter cores. Repeated deposition cycles increase pellet size while incorporating the active pharmaceutical ingredient. This technique offers higher drug-loading capacities and may be advantageous for poorly soluble compounds; however, it generally requires more extensive process optimization to prevent agglomeration and ensure uniformity (Ramesh et al., 2025).

In omeprazole formulations, pellet core design typically involves a multilayer architecture consisting of a drug-containing layer, a barrier coating, and an enteric coating. Such arrangements provide effective protection against degradation while facilitating controlled intestinal release. Proper core design is therefore essential for ensuring product quality and therapeutic performance (Kumisbek et al., 2024).

10. Barrier Coating Strategies and Formulation Stability

One of the major challenges associated with omeprazole formulation is the potential incompatibility between the alkaline drug and acidic enteric polymers. Direct contact between these materials may promote degradation during manufacturing and storage, resulting in reduced product stability and compromised therapeutic performance (He et al., 2009).

To overcome this limitation, modern omeprazole pellet systems typically incorporate a barrier or seal coating between the drug layer and the enteric coating. This intermediate layer acts as a protective interface, preventing undesirable chemical interactions while improving coating adhesion and overall formulation robustness (Papoutsi et al., 2025).

Hydroxypropyl methylcellulose (HPMC) is among the most commonly employed barrier-coating materials because of its excellent film-forming properties, compatibility with omeprazole, and ability to provide effective separation between functional layers. The incorporation of HPMC barrier coatings has been shown to significantly improve long-term stability and reduce degradation during storage (He et al., 2009).

The importance of barrier coatings has been consistently demonstrated through accelerated stability studies, which reveal superior performance for multilayer formulations compared with systems lacking protective seal coats. Consequently, barrier coating technology has become a standard component of commercially successful omeprazole pellet formulations (DellaGreca et al., 2006).

11. Advantages of Pellet-Based Omeprazole Delivery Systems

The integration of pelletization technology with enteric coating strategies has fundamentally transformed the delivery of omeprazole. Pellet-based formulations effectively address the primary challenges associated with acid instability, site-specific release, and variable bioavailability while offering significant manufacturing and therapeutic advantages.

Compared with conventional single-unit dosage forms, enteric-coated pellets provide superior gastric protection, improved release reproducibility, enhanced gastrointestinal distribution, and reduced risk of dose dumping. Their spherical geometry promotes uniform coating application and enables precise control over release characteristics. Moreover, pellet systems offer exceptional flexibility for the development of sequential-release and controlled-release formulations (Chakravarthy et al., 2012; Kuma et al., 2025).

The widespread adoption of pellet-based technologies in commercial omeprazole products underscores their pharmaceutical significance. These systems have become the preferred platform for delivering acid-sensitive drugs and continue to serve as a foundation for innovation in oral controlled-release drug delivery. Through the combination of optimized pelletization techniques, barrier coatings, and enteric protection strategies, pellet-based formulations have established a robust and reliable approach for maximizing the therapeutic effectiveness of omeprazole (Parihar et al., 2023).

12. Enteric and pH-Sensitive Polymers in Omeprazole Pellet Formulations

The development of effective pH-sensitive drug delivery systems is fundamentally dependent on the selection of suitable polymeric materials capable of protecting the active pharmaceutical ingredient under gastric conditions while ensuring timely release at the desired intestinal location. For acid-labile drugs such as omeprazole, enteric polymers play a crucial role in maintaining drug stability, improving bioavailability, and enabling site-specific drug delivery. The growing interest in gastrointestinal targeting has led to extensive research on pH-responsive polymers that exhibit controlled dissolution characteristics in response to physiological pH variations along the gastrointestinal tract (Ambudkar and Chauhan, 2025).

Among the various polymers investigated for enteric drug delivery, methacrylic acid copolymers marketed under the Eudragit® brand have received particular attention because of their reproducible dissolution profiles and excellent film-forming properties. Eudragit® L100 is an anionic copolymer that remains intact under gastric conditions and dissolves at pH values above 6.0, making it suitable for drug release in the upper regions of the small intestine. In contrast, Eudragit® S100 dissolves at pH values exceeding 7.0 and is therefore frequently employed in formulations intended for distal intestinal or colonic delivery (Singh and Nayak, 2023). The combination of these polymers offers substantial flexibility in designing sequential-release systems capable of targeting multiple gastrointestinal regions.

In omeprazole formulations, Eudragit-based coatings have demonstrated remarkable effectiveness in preventing premature drug degradation within the stomach. Because omeprazole is highly susceptible to acid-catalyzed decomposition, the integrity of the enteric coating directly influences therapeutic performance. Studies have shown that Eudragit-coated

multiparticulate systems successfully maintain drug stability during gastric transit while enabling rapid release following exposure to intestinal pH conditions (He et al., 2009). Furthermore, variations in polymer concentration and coating thickness can be used to modulate lag time, release rate, and site of drug release, thereby providing a versatile platform for formulation optimization.

Hydroxypropyl methylcellulose (HPMC) represents another important polymer in omeprazole pellet formulations. Unlike enteric polymers, HPMC does not exhibit pH-dependent solubility; instead, it hydrates and forms a gel layer upon contact with aqueous media. This characteristic makes HPMC particularly useful as a barrier coating material. In multilayered pellet systems, HPMC is commonly applied between the drug-containing core and the enteric coating to prevent direct contact between omeprazole and acidic enteric polymers. Such barrier layers significantly improve formulation stability and reduce the likelihood of degradation during manufacturing and storage (He et al., 2009).

Ethyl cellulose has also been investigated extensively as a release-modifying polymer. Owing to its water-insoluble nature, ethyl cellulose forms semipermeable membranes that regulate water penetration and drug diffusion. Incorporation of ethyl cellulose into coating systems can prolong drug release and contribute to sustained or near zero-order release kinetics. This property is particularly valuable in sequential-release formulations where controlled drug delivery beyond the initial intestinal release phase is desired (Veerubhotla and Walker., 2020).

Other enteric polymers such as hydroxypropyl methylcellulose phthalate (HPMCP) and cellulose acetate phthalate (CAP) have historically played important roles in the development of pH-sensitive delivery systems. Although these materials continue to be used successfully in many formulations, modern research increasingly favors Eudragit-based systems because of their superior processing characteristics, predictable dissolution behavior, and broader formulation flexibility (Ambudkar and Chauhan, 2025). Collectively, these polymers provide formulation scientists with a diverse range of tools for designing sophisticated gastrointestinal drug delivery systems capable of meeting specific therapeutic objectives.

13. Sequential Drug Release Mechanisms

Sequential drug release represents an advanced strategy in oral drug delivery that seeks to release therapeutic agents at predetermined gastrointestinal locations and time intervals. Unlike conventional delayed-release systems, which typically release the entire drug dose after a lag period, sequential-release systems are designed to achieve staged or region-specific drug delivery. Such approaches have gained considerable attention because they more closely align drug release with physiological requirements and may enhance therapeutic efficacy while minimizing adverse effects (Kuma et al., 2025).

The concept of sequential release is particularly relevant to omeprazole because of the drug's acid sensitivity and site-specific absorption characteristics. Effective therapy requires that omeprazole remain protected during gastric transit and become available for absorption primarily within the upper small intestine. Sequential-release formulations accomplish this objective through the strategic combination of multiple coating layers and polymers exhibiting different dissolution characteristics (Kuma et al., 2025).

In a typical omeprazole pellet system, the drug-containing core is surrounded by a barrier layer and an outer enteric coating. During gastric residence, the enteric coating remains intact and prevents exposure of the drug to acidic conditions. Upon entry into the small intestine, the increase in environmental pH triggers dissolution of the enteric layer, exposing the underlying structures and initiating drug release. Depending on polymer composition, coating thickness, and formulation design, release may occur rapidly or continue progressively throughout the intestinal tract (Kumisbek et al., 2024).

Sequential-release systems provide several therapeutic advantages. First, they ensure protection of acid-labile drugs until favorable absorption conditions are encountered. Second, they reduce fluctuations in plasma drug concentration by controlling the rate and location of release. Third, they may improve patient compliance by reducing dosing frequency and enhancing therapeutic consistency. These benefits have stimulated increasing interest in the development of multilayered pellet formulations capable of achieving sophisticated release profiles tailored to specific clinical requirements (Kuma et al., 2025).

14. Drug Release Kinetics of Omeprazole Pellets

The evaluation of drug release kinetics is essential for understanding the mechanisms governing drug release from multiparticulate systems. Mathematical modeling provides valuable insight into formulation behavior and assists in the optimization of release profiles. Several kinetic models are commonly employed in the analysis of omeprazole pellet formulations, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models (Kumisbek et al., 2024).

Zero-order kinetics describes systems in which a constant amount of drug is released per unit time regardless of drug concentration. Such release behavior is considered highly desirable because it maintains relatively stable plasma concentrations and minimizes fluctuations associated with conventional dosage forms. In practice, achieving true zero-order release is challenging; however, appropriately designed multilayer

pellet systems may approximate this behavior over extended periods (Veerubhotla and Walker., 2020).

Among the available models, the Korsmeyer–Peppas equation is particularly useful for identifying the dominant mechanism of drug release. The release exponent obtained from this model provides insight into whether release is governed primarily by diffusion, erosion, or a combination of both processes. According to the findings, optimized omeprazole pellet formulations exhibited the highest correlation with the Korsmeyer–Peppas model, suggesting that diffusion-controlled transport played a major role in governing drug release behavior (Farmoudeh et al., 2020).

The application of kinetic modeling not only improves scientific understanding of formulation performance but also supports rational product development. By correlating release behavior with formulation variables, researchers can optimize polymer composition, coating thickness, and processing conditions to achieve desired therapeutic outcomes.

15. Quality by Design (QbD) in Omeprazole Pellet Development

Quality by Design (QbD) has emerged as a transformative approach in pharmaceutical product development. This philosophy has been strongly encouraged by regulatory agencies because it promotes robust manufacturing processes and consistent product performance (Veerubhotla and Walker., 2020). The application of QbD principles to omeprazole pellet formulations begins with the establishment of a Quality Target Product Profile (QTPP). The QTPP defines the desired characteristics of the final dosage form, including drug content, release profile, stability, and therapeutic performance. Once these objectives are established, critical quality attributes (CQAs) are identified. In pellet formulations, CQAs commonly include pellet size, coating thickness, dissolution behavior, drug content uniformity, and physical stability (Farmoudeh et al., 2020).

Risk assessment tools are subsequently employed to identify formulation variables most likely to influence product quality. For omeprazole pellets, factors such as polymer concentration, coating weight gain, drying conditions, and pellet size distribution are particularly important. Design of Experiments (DoE) methodologies are then used to systematically evaluate the effects of these variables and identify optimal processing conditions. The study demonstrated the successful use of factorial experimental designs to optimize polymer concentration and coating levels, resulting in improved release characteristics and enhanced formulation reproducibility (Veerubhotla and Walker., 2020).

The implementation of QbD offers several advantages, including improved process understanding, reduced development time, enhanced manufacturing robustness, and greater regulatory flexibility. As pharmaceutical formulations become increasingly sophisticated, QbD is expected to play an even more important role in the development of advanced multiparticulate delivery systems.

16. Stability Considerations for Omeprazole Pellet Systems

Stability remains one of the most critical considerations in the development of omeprazole formulations. Because the drug is highly susceptible to degradation through hydrolysis, oxidation, moisture uptake, and acid exposure, formulation strategies must be carefully designed to maintain product quality throughout manufacturing, storage, and administration (Papoutsi et al., 2025).

Moisture represents a particularly important stability concern. Water can accelerate hydrolytic degradation reactions and compromise the integrity of coating systems. Consequently, strict control of humidity during manufacturing and storage is essential. Similarly, elevated temperatures may increase degradation rates and negatively affect both drug potency and coating performance (DellaGreca et al., 2006).

Light sensitivity further complicates formulation development. Exposure to light may induce chemical degradation, necessitating the use of protective packaging materials. In addition, localized acidic microenvironments within the dosage form can promote degradation even when the overall formulation appears stable. The incorporation of barrier coatings and alkaline stabilizers therefore represents an important strategy for enhancing long-term stability (Parihar et al., 2023). The findings similarly indicated that optimized formulations retained their release performance and coating integrity during stability testing, confirming the effectiveness of multilayer coating strategies in preserving product quality (Papoutsi et al., 2025).

The long-term success of omeprazole pellet formulations ultimately depends on balancing protection, release performance, manufacturability, and stability. Continued advances in polymer science and coating technology are expected to further improve the robustness and shelf life of future pH-sensitive delivery systems.

17. Commercial Omeprazole Formulations and Marketed Products

The successful commercialization of omeprazole formulations has significantly influenced the development of pH-sensitive oral drug delivery systems. Since the introduction of the first omeprazole-containing products, enteric-coated multiparticulate systems have become the dominant formulation strategy for protecting the drug from gastric degradation while ensuring efficient intestinal absorption. The widespread clinical

acceptance of these products demonstrates the effectiveness of combining enteric coating technology with multiparticulate delivery platforms (Parihar et al., 2023).

One of the earliest and most influential commercial formulations was Losec®, developed by AstraZeneca. This product utilized enteric-coated pellets encapsulated within hard gelatin capsules, thereby providing effective gastric protection and targeted intestinal release. The success of Losec® established multiparticulate pellet systems as a benchmark technology for proton pump inhibitor formulations and stimulated extensive research into improved coating materials and release mechanisms (Parihar et al., 2023).

Subsequent products such as Prilosec OTC®, Omez®, and several generic formulations adopted similar design principles, emphasizing enteric-coated pellet systems capable of maintaining drug stability during gastrointestinal transit. These products have demonstrated that pellet-based formulations provide reliable therapeutic outcomes while minimizing variability associated with gastric emptying and intestinal transit (DellaGreca et al., 2006).

The commercial success of enteric-coated omeprazole products has also highlighted several critical formulation principles. First, effective gastric protection is essential for preserving drug potency. Second, uniform pellet size distribution and coating consistency contribute significantly to product reproducibility. Third, the integration of barrier coatings between the drug layer and enteric coating improves stability and extends shelf life. Collectively, these observations continue to guide the development of new-generation pH-sensitive formulations (Parihar et al., 2023).

Table 3: Representative Commercial Omeprazole Formulations

Product	Manufacturer	Dosage Form	Key Technology
Losec®	AstraZeneca	Capsule	Enteric-Coated Pellets
Prilosec OTC®	Procter & Gamble	Delayed-Release Tablet/Capsule	Enteric Protection
Omez®	Dr. Reddy's Laboratories	Capsule	Enteric-Coated Pellets
Generic Omeprazole Products	Various Manufacturers	Capsules/Tablets	pH-Sensitive Coating Systems

Source: Parihar *et al.,* 2023

The continued market dominance of pellet-based omeprazole formulations underscores the importance of pH-sensitive delivery systems in ensuring optimal therapeutic performance.

18. Patent Landscape and Intellectual Property Trends

Patent activity provides valuable insight into technological innovation within pharmaceutical formulation development. Omeprazole has been the subject of numerous patents focused on improving stability, enhancing bioavailability, optimizing release profiles, and simplifying manufacturing processes. Many of these patents have centered on enteric-coated pellet systems because of their proven effectiveness in protecting acid-sensitive drugs (Parihar et al., 2023).

Early patents primarily addressed the stabilization of omeprazole through the incorporation of alkaline excipients and protective coatings. These innovations enabled the commercialization of stable oral formulations and laid the foundation for subsequent technological advancements. Later patents introduced multilayer pellet systems incorporating drug layers, barrier coatings, and enteric coatings to further enhance stability and release control (Parihar et al., 2023).

More recent patent activity has focused on sophisticated sequential-release systems, polymer combinations, and advanced manufacturing technologies. Such developments reflect the growing interest in achieving precise gastrointestinal targeting and improved pharmacokinetic performance. The increasing complexity of modern patent filings also highlights the transition from simple delayed-release systems toward intelligent and multifunctional drug delivery platforms (Farmoudeh et al., 2020).

The patent landscape demonstrates that although the fundamental principles of enteric protection remain unchanged, substantial opportunities continue to exist for innovation in coating technologies, polymer design, and controlled-release strategies.

19. Recent Advances in pH-Sensitive Omeprazole Delivery Systems

Recent years have witnessed remarkable progress in the design of pH-sensitive oral delivery systems for acid-labile drugs. Advances in polymer science, process engineering, and controlled-release technology have expanded the capabilities of enteric-coated pellet formulations and opened new opportunities for improving therapeutic outcomes.

One important area of innovation involves the development of multifunctional coating systems. Traditional enteric coatings primarily serve as protective barriers against gastric acid. Modern coatings, however, are increasingly designed to perform multiple functions simultaneously, including stabilization, controlled

release, and site-specific targeting. The integration of different polymer layers enables the creation of sophisticated formulations capable of achieving highly predictable release profiles (Veerubhotla and Walker., 2020).

Another emerging trend is the use of polymer blends. By combining polymers with different dissolution thresholds, researchers can fine-tune release behavior and achieve more precise control over drug delivery. Blends of Eudragit® L100 and Eudragit® S100 have proven particularly useful for sequential-release applications because they permit gradual drug release across multiple intestinal regions (Singh and Nayak, 2023).

Nanotechnology has also begun to influence oral drug delivery research. Nanostructured coatings and nanoscale excipients have demonstrated potential for improving coating uniformity, enhancing stability, and increasing drug absorption. Although these technologies remain largely in the developmental stage, they represent promising directions for future omeprazole formulations.

Continuous manufacturing represents another significant advancement. Traditional pharmaceutical manufacturing often involves multiple batch-processing steps that may introduce variability. Continuous manufacturing systems offer improved process control, enhanced reproducibility, and greater production efficiency. The integration of continuous processing with pelletization and coating technologies is expected to improve both product quality and manufacturing economics (Farmoudeh et al., 2020).

Recent investigations have additionally emphasized the role of Quality by Design methodologies in formulation optimization. The combination of experimental design techniques, statistical modeling, and process analytical technologies has enabled more efficient development of robust formulations with predictable performance characteristics (Veerubhotla and Walker., 2020). These advances collectively illustrate the dynamic nature of pharmaceutical research and highlight the continuing evolution of pH-sensitive drug delivery systems.

20. Future Perspectives

Despite substantial progress in pH-sensitive drug delivery, several challenges remain. Variability in gastrointestinal physiology among patients continues to influence drug release and absorption. Differences in gastric emptying time, intestinal transit rate, pH profiles, and disease states may affect formulation performance and contribute to interindividual variability in therapeutic outcomes (Loke et al., 2025).

Future research is expected to focus increasingly on personalized drug delivery systems capable of adapting to individual physiological conditions. Such systems may utilize advanced polymers, biosensors, and responsive materials that dynamically adjust drug release according to environmental stimuli. The integration of these technologies could significantly improve therapeutic precision and patient outcomes.

Chronotherapeutic drug delivery represents another promising area of investigation. Many gastrointestinal disorders exhibit circadian variations in symptom severity and disease activity. Formulations capable of synchronizing drug release with biological rhythms may enhance treatment effectiveness while reducing drug exposure and adverse effects (Kuma et al., 2025).

Three-dimensional printing and advanced manufacturing technologies are also expected to transform pharmaceutical development. These approaches offer unprecedented flexibility in dosage form design and may facilitate the production of personalized formulations tailored to specific patient requirements. The ability to precisely control pellet architecture, coating thickness, and drug distribution could significantly enhance the performance of future sequential-release systems.

In addition, growing interest in environmentally sustainable pharmaceutical manufacturing is likely to encourage the development of greener processing methods and solvent-free coating technologies. The future of pH-sensitive omeprazole delivery systems will therefore likely involve the convergence of polymer science, advanced manufacturing, personalized medicine, and digital health technologies. Continued interdisciplinary collaboration will be essential for translating these innovations into clinically meaningful therapeutic advances.

21. CONCLUSION

The successful oral delivery of omeprazole remains a significant pharmaceutical challenge because of the drug's pronounced acid sensitivity and site-specific absorption requirements. Over the past several decades, enteric-coated pellet systems have emerged as one of the most effective solutions to these challenges, providing robust protection against gastric degradation while enabling targeted release within the intestinal environment. The combination of multiparticulate delivery systems, pH-sensitive polymers, and advanced coating technologies has significantly improved the stability, bioavailability, and therapeutic performance of omeprazole formulations.

Among the various formulation approaches, pellet-based systems offer unique advantages including uniform gastrointestinal distribution, reduced variability in gastric emptying, enhanced coating efficiency, and greater flexibility in release profile design. The incorporation of enteric polymers such as Eudragit®

L100 and Eudragit® S100 has enabled precise control over drug release location and timing, while barrier coatings have improved compatibility and long-term stability. Furthermore, the application of Quality by Design principles has facilitated systematic optimization of formulation variables and manufacturing processes, resulting in more robust and reproducible products.

The literature reviewed in this article demonstrates that pH-sensitive enteric-coated pellets represent a highly effective platform for delivering acid-labile drugs. Advances in sequential-release technologies, polymer engineering, and process optimization continue to expand the capabilities of these systems and provide new opportunities for improving therapeutic outcomes. Emerging innovations such as multifunctional coatings, nanostructured materials, continuous manufacturing, and personalized drug delivery approaches are expected to further enhance the effectiveness of future formulations.

In conclusion, pH-sensitive enteric-coated omeprazole pellet systems exemplify the successful integration of pharmaceutical science, materials engineering, and drug delivery technology. Continued research and innovation in this field will not only improve the treatment of acid-related gastrointestinal disorders but also contribute broadly to the development of advanced oral delivery systems for a wide range of therapeutic agents.

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