RESEARCH PAPER

Dual-Release Gastro-Resistant Platforms Using Tablet-in-Tablet Drug Delivery Systems: A Comprehensive Review

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ABSTRACT

Oral drug delivery systems remain the most widely used pharmaceutical dosage forms due to their convenience, cost-effectiveness, and high patient compliance. However, conventional oral formulations often fail to provide site-specific drug delivery and controlled drug release required for optimal therapeutic outcomes. Tablet-in-tablet (TNT) drug delivery systems have emerged as an innovative strategy that enables sequential, delayed, or dual drug release within a single dosage form. These systems incorporate an inner core tablet surrounded by an outer tablet layer, allowing the delivery of multiple drugs or release phases. In particular, dual-release gastro-resistant platforms have gained significant attention because they protect acid-labile drugs from degradation in the gastric environment while ensuring targeted drug release in the intestinal region. The use of pH-dependent enteric polymers enables selective drug release in the gastrointestinal tract. This review provides a comprehensive overview of tablet-in-tablet technology, focusing on the design principles, formulation approaches, manufacturing techniques, and drug release mechanisms involved in dual-release gastro-resistant platforms. The review also discusses commonly used polymers, evaluation parameters, advantages, limitations, and pharmaceutical applications of TNT systems. Furthermore, recent technological advances including 3D printing, smart polymers, and nanotechnology-based strategies are highlighted. The future potential of tablet-in-tablet drug delivery systems in developing advanced oral dosage forms and personalized medicine is also explored.

Keywords: Tablet-In-Tablet Technology, Dual-Release Systems, Gastro-Resistant Drug Delivery, Compression-Coated Tablets, Enteric Polymers, Modified-Release Oral Dosage Forms.

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INTRODUCTION

Oral administration is the most preferred route for drug delivery because of its simplicity, non-invasiveness, and high patient acceptance [1,2]. Solid oral dosage forms such as tablets and capsules dominate the pharmaceutical market due to their ease of manufacturing, accurate dosing, and stability during storage [3]. Conventional tablets typically release the active pharmaceutical ingredient (API) rapidly after ingestion, resulting in immediate drug absorption in the gastrointestinal tract [4].

However, immediate-release formulations are not suitable for all drugs. Certain drugs are unstable in the acidic environment of the stomach or may cause gastric irritation [5]. Acid-labile drugs such as proton pump inhibitors degrade rapidly in gastric pH, reducing their therapeutic effectiveness [6]. Similarly, drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) may cause gastric irritation or ulceration when released in the stomach [7]. In such cases, gastro-resistant drug delivery systems are required to protect the drug from gastric conditions and allow drug release in the intestine [8].

Over the past few decades, pharmaceutical scientists have developed numerous modified-release technologies to address these challenges. Examples include multilayer tablets, matrix tablets, coated tablets, osmotic pump systems, and compression-coated tablets [9]. Among these approaches, tablet-in-tablet (TNT) drug delivery systems have gained increasing attention because they allow the incorporation of multiple release mechanisms within a single dosage form [10,11].

Tablet-in-tablet systems consist of a smaller inner core tablet embedded within a larger outer tablet. This structural design allows the formulation of dual-release systems, where one drug or portion of the drug is released immediately while another portion is released after a delay [12,13]. Such systems are particularly useful for designing dual-release gastro-resistant platforms.

Dual-release gastro-resistant tablet-in-tablet systems represent an advanced oral drug delivery approach that integrates enteric protection with programmed, sequential drug release. In these systems, the external layer or enteric coating effectively inhibits drug release under acidic gastric conditions, thereby safeguarding acid-labile compounds. Upon transition to the intestinal environment, the inner core is activated to release the drug in a controlled manner. This design not only enhances drug stability but also improves therapeutic efficacy by targeting site-specific release. Furthermore, such systems contribute to better patient compliance by reducing dosing frequency and minimizing gastrointestinal side effects [14].

CONCEPT AND STRUCTURE OF TABLET-IN-TABLET DRUG DELIVERY SYSTEMS

Tablet-in-tablet (TNT) technology is an advanced pharmaceutical formulation strategy developed to achieve controlled, sequential, and site-specific drug delivery within a single oral dosage form. In this approach, a pre-compressed inner core tablet is embedded within an outer tablet during the compression process, forming a composite system with distinct functional layers. This configuration allows for the design of dosage forms capable of delivering drugs in multiple phases, such as immediate and sustained release, or targeting specific regions of the gastrointestinal tract. Additionally, TNT systems provide protection for sensitive drug molecules against adverse environmental conditions, including gastric acidity, thereby enhancing drug stability and bioavailability. Owing to these advantages, tablet-in-tablet technology has emerged as a promising platform in the development of novel and patient-compliant drug delivery systems [15].

The tablet-in-tablet system is commonly described using terms such as compression-coated tablets, press-coated tablets, or core–shell tablet systems, reflecting its structural and functional characteristics. Unlike conventional film coating methods, which depend on the application of polymeric coating solutions, compression coating is a solvent-free process that involves the mechanical compression of a powder layer around a preformed core tablet. This technique eliminates the need for aqueous or organic solvents and avoids exposure to elevated temperatures during processing. As a result, it is particularly advantageous for formulating drugs that are sensitive to heat, moisture, or solvent-induced degradation. Moreover, compression-coated systems offer flexibility in designing modified release profiles and protecting active pharmaceutical ingredients until they reach the desired site of action within the gastrointestinal tract [16].

The tablet-in-tablet (TNT) system offers several advantages in pharmaceutical formulation, making it a versatile platform for advanced drug delivery. One of its key benefits is the ability to physically separate incompatible drugs within a single dosage form, thereby preventing potential interactions and enhancing formulation stability. Additionally, TNT systems enable the development of dual or multi-phase drug release profiles, allowing precise modulation of drug release kinetics. This approach is particularly beneficial for drugs that are sensitive to gastric conditions, as the outer layer can provide protection while the inner core ensures targeted release. Depending on the formulation design, tablet-in-tablet systems can be tailored to achieve immediate, delayed, sustained, or pulsatile drug release, offering significant flexibility in therapeutic applications.

Structurally, a typical tablet-in-tablet dosage form consists of two primary components:

1. inner core tablet
2. outer compression-coated layer.

The inner core is initially prepared using conventional tablet compression techniques. Subsequently, this core tablet is positioned centrally within a die that is partially filled with the outer layer powder. Additional coating material is then added, and the entire assembly is subjected to compression to produce the final tablet-in-tablet structure. To ensure accurate core placement and uniform coating thickness, specialized tablet presses or modified compression equipment are often employed. This structural configuration enables precise control over drug release characteristics by adjusting the composition and properties of both the inner core and the outer layer, thereby enhancing therapeutic efficacy and formulation performance [17].

2.1 Structural Design

A typical tablet-in-tablet drug delivery system comprises multiple structural components that function synergistically to achieve controlled drug release and protect the active pharmaceutical ingredient from degradation. These components generally include an inner core tablet, **an outer**

compression-coated layer, and, in certain formulations, an intermediate barrier layer designed to further modulate drug release.

Inner Core Tablet

Among these, the inner core tablet represents the central and functionally critical element of the system. It typically contains the primary active pharmaceutical ingredient and is formulated to provide delayed, sustained, or otherwise controlled drug release depending on specific therapeutic objectives.

To regulate drug release kinetics, the core tablet is often composed of various excipients, including **hydrophilic and hydrophobic polymers, matrix-forming agents, and release-modifying materials**. Hydrophilic polymers such as Hydroxypropyl methylcellulose, Polyethylene oxide, and Carbopol are widely employed due to their ability to control drug release through matrix swelling and diffusion mechanisms. In contrast, hydrophobic materials such as Ethyl cellulose and waxes are utilized to retard drug dissolution and prolong release duration. The composition and design of the core tablet play a decisive role in determining key parameters such as lag time, release rate, and overall duration of drug delivery.

Furthermore, in combination therapy approaches, the inner core tablet may incorporate a second active pharmaceutical ingredient. In such cases, the system is engineered so that the core tablet releases the drug after a predetermined lag phase, while the outer tablet layer facilitates immediate drug release. This sequential release strategy enhances therapeutic effectiveness by synchronizing drug availability with physiological needs [18].

Outer Tablet Layer

The outer tablet layer, commonly referred to as the compression-coated layer, envelops the inner core tablet and forms the protective shell of the tablet-in-tablet (TNT) system. This layer may incorporate active pharmaceutical ingredients, protective polymers, buffering agents, and other excipients that collectively influence the timing, rate, and site of drug release within the gastrointestinal tract. Functionally, the outer layer serves multiple roles:

1. Protection of the inner core from gastric acid
2. Immediate drug release after tablet disintegration
3. Delayed release triggered by pH or enzymatic conditions
4. Prevention of interaction between incompatible drugs

In gastro-resistant formulations, the outer layer is often composed of enteric polymers such as **Cellulose acetate phthalate**, **Eudragit**, and **Hydroxypropyl methylcellulose phthalate**. These materials are specifically designed to remain intact in the low pH conditions of the stomach while dissolving at the higher pH levels encountered in the intestinal environment, thereby ensuring site-specific drug release. The thickness and composition of the outer layer play a crucial role in modulating drug release characteristics. By carefully adjusting these parameters, formulators can achieve precise control over drug release profiles, optimizing therapeutic outcomes and enhancing formulation performance [19].

Barrier Layer

In certain tablet-in-tablet (TNT) formulations, an intermediate barrier layer is incorporated between the inner core tablet and the outer compression-coated layer to enhance formulation stability and control drug release behavior. The primary function of this barrier layer is to prevent direct contact between two active pharmaceutical ingredients that may be chemically incompatible or prone to degradation when combined. In addition to its protective role, the barrier layer can be engineered to introduce a time-delay mechanism by restricting the penetration of gastrointestinal fluids into the core tablet. This feature is particularly advantageous in pulsatile drug delivery systems, where drug release is required after a predefined lag time to match circadian rhythms or specific therapeutic needs.

The barrier layer is generally composed of inert polymers or hydrophobic materials that limit drug diffusion and modulate fluid ingress. Commonly used materials include **Ethyl cellulose**, **Hydroxypropyl cellulose**, and **Polyethylene glycol-based systems**. The selection and thickness of the barrier layer significantly influence the lag time and overall drug release profile, allowing formulators to design dosage forms with precise temporal control over drug delivery [20].

PRINCIPLES OF DUAL-RELEASE GASTRO-RESISTANT DRUG DELIVERY

Dual-release gastro-resistant drug delivery systems represent an advanced pharmaceutical strategy aimed at protecting drug substances from the harsh gastric environment while enabling controlled and sequential drug release within the gastrointestinal tract. These systems integrate the principles of enteric coating with modified-release technologies, thereby allowing the administration of either two distinct doses of a single drug or two different drugs within a single

dosage form. The primary objective of such systems is to ensure that the active pharmaceutical ingredient remains intact during gastric transit and is released only upon reaching the more favorable pH conditions of the small intestine. This approach is particularly advantageous for acid-labile drugs, drugs associated with gastric irritation, and those requiring site-specific intestinal delivery.

Furthermore, by incorporating sequential release mechanisms, dual-release systems can enhance therapeutic efficacy by maintaining optimal drug concentrations in systemic circulation over extended durations. These systems are commonly developed using tablet-in-tablet architectures, multilayer tablets, or compression-coated formulations, wherein each layer is engineered to release the drug at specific times or in response to distinct physiological triggers. In tablet-in-tablet configurations, the outer layer typically provides immediate or delayed release following gastric transit, while the inner core tablet delivers a second dose after a predefined lag time. Such systems have found widespread application in the management of gastrointestinal disorders, inflammatory diseases, and infections, where controlled drug exposure is essential for achieving optimal therapeutic outcomes [21].

3.1 Gastro-Resistant Mechanism

Gastro-resistant drug delivery systems primarily utilize pH-sensitive polymers, commonly referred to as enteric polymers, which are specifically engineered to remain stable and intact under acidic gastric conditions while undergoing dissolution at the higher pH levels encountered in the intestinal environment. This pH-dependent solubility enables effective protection of acid-labile drugs and facilitates site-specific drug release within the gastrointestinal tract [22]. The use of these polymers enables selective drug release within specific segments of the gastrointestinal tract.

The human gastrointestinal tract exhibits pronounced variations in pH, which play a critical role in the design of site-specific drug delivery systems. The stomach presents a highly acidic environment, with pH values typically ranging from 1 to 3 under fasting conditions and increasing slightly following food intake. In contrast, the pH of the small intestine progressively rises from approximately 6 in the duodenum to about 7.5 in the ileum. These physiological pH gradients provide a valuable basis for the development of drug delivery systems that respond selectively to environmental conditions within different regions of the gastrointestinal tract.

Enteric polymers are specifically engineered to exploit this pH-dependent variation. Under acidic gastric conditions, these polymers remain insoluble and intact, forming a protective barrier that prevents premature drug release. This property is particularly important for drugs that are acid-labile or capable of causing irritation to the gastric mucosa. Upon transition to the higher pH environment of the small intestine, the enteric polymers undergo ionization and subsequent dissolution, allowing gastrointestinal fluids to penetrate the dosage form and initiate drug release. The efficiency of this gastro-resistant mechanism is influenced by several formulation variables, including the type of polymer, coating thickness, core tablet composition, and gastric residence time.

Commonly employed enteric polymers include **Cellulose acetate phthalate**, **Hydroxypropyl methylcellulose phthalate**, **Eudragit**, and **Polyvinyl acetate phthalate**. These materials provide effective protection against gastric acid while enabling predictable and reproducible drug release in the intestinal environment. Consequently, gastro-resistant systems are widely utilized in pharmaceutical formulations to enhance drug stability, improve therapeutic outcomes, and reduce gastrointestinal side effects [23].

3.2 Dual-Release Mechanism

The dual-release mechanism is an advanced drug delivery approach designed to administer either two distinct doses of a single drug or two different drugs in a sequential and controlled manner within a single dosage form. This strategy enhances therapeutic efficacy by maintaining optimal plasma drug concentrations over prolonged periods. In tablet-in-tablet systems, drug release typically occurs in two distinct stages, each governed by the structural design and composition of the formulation.

Stage 1: Initial Drug Release

The first stage of drug release is triggered when the dosage form reaches the intestinal environment, where the enteric coating dissolves due to the elevated pH. This dissolution exposes the outer tablet layer to gastrointestinal fluids, resulting in the release of the initial dose of the drug. This phase is generally formulated to provide immediate or moderately controlled release, enabling a rapid onset of action and quick attainment of therapeutic plasma levels. In some formulations, the outer layer may contain the same drug in a rapidly dissolving form or a different drug intended for combination therapy.

Stage 2: Delayed or Sustained Release from Core Tablet

The second stage involves drug release from the inner core tablet, which is designed to release the drug after a specific lag time or in a sustained manner. This release is controlled by mechanisms such as polymer swelling, matrix erosion, diffusion, or the dissolution of additional coating layers. Hydrophilic polymers such as Hydroxypropyl methylcellulose are commonly employed due to their ability to form a gel barrier upon hydration, thereby regulating drug diffusion. Alternatively, hydrophobic polymers or wax-based materials may be used to further retard drug release and extend the duration of therapeutic action.

This biphasic release pattern ensures prolonged maintenance of therapeutic drug concentrations, reduces dosing frequency, and improves patient compliance. As a result, dual-release tablet-in-tablet systems offer significant advantages in optimizing pharmacokinetic profiles and enhancing overall therapeutic outcomes [24].

FORMULATION STRATEGIES FOR TABLET-IN-TABLET SYSTEMS

The successful development of dual-release gastro-resistant tablet-in-tablet systems is largely dependent on the formulation strategy adopted during product design. These strategies involve the judicious selection of excipients, polymers, and structural configurations to precisely regulate the rate, timing, and site of drug release within the gastrointestinal tract. By modulating the composition and properties of both the outer tablet layer and the inner core tablet, it is possible to engineer dosage forms capable of delivering drugs in a controlled and sequential manner. Such systems offer considerable flexibility, enabling the incorporation of multiple release profiles within a single dosage unit, including immediate release followed by sustained release, pulsatile delivery, or site-specific intestinal targeting. The choice of formulation strategy is influenced by factors such as the physicochemical characteristics of the drug, therapeutic objectives, gastrointestinal transit behavior, and the desired pharmacokinetic profile.

In dual-release gastro-resistant systems, the outer tablet layer typically functions as a protective barrier against the acidic gastric environment and may also provide an initial dose of the drug. In contrast, the inner core tablet is formulated to achieve delayed or sustained drug release. Various formulation approaches are employed to achieve these release patterns, among which the design of an immediate-release outer layer is one of the most commonly utilized strategies.

4.1 Immediate-Release Outer Layer

In this approach, the outer tablet layer is formulated to release the drug rapidly once the dosage form reaches the intestinal environment and the enteric polymer coating dissolves. The outer layer is generally composed of rapidly disintegrating and dissolving excipients, enabling prompt drug release and absorption into the systemic circulation, thereby producing an immediate therapeutic effect. To facilitate rapid disintegration, superdisintegrants such as **Sodium starch glycolate**, **Croscarmellose sodium**, and **Crospovidone** are commonly incorporated. In addition, water-soluble diluents such as Lactose and Mannitol are frequently used to enhance drug dissolution and improve formulation performance.

The immediate-release outer layer provides several advantages in dual-release tablet-in-tablet systems. It ensures rapid drug availability following gastric transit, facilitates the delivery of an initial loading dose to achieve therapeutic plasma concentrations quickly, and allows for the incorporation of a second active pharmaceutical ingredient in combination therapy. Furthermore, the thickness and composition of the outer layer can be optimized to achieve uniform coating around the core tablet and to fine-tune drug release characteristics [25].

4.2 Sustained-Release Core Tablet

The sustained-release core tablet constitutes the second phase of drug delivery in tablet-in-tablet systems and is primarily designed to maintain therapeutic drug concentrations in the systemic circulation over an extended period. By enabling the gradual and controlled release of the drug, this component minimizes fluctuations in plasma drug levels, reduces dosing frequency, and enhances patient compliance. Such systems are particularly beneficial for drugs requiring prolonged therapeutic action and stable pharmacokinetic profiles.

Sustained-release core tablets are typically formulated using release-retarding polymers that regulate drug diffusion and dissolution. Hydrophilic matrix-forming polymers such as **Hydroxypropyl methylcellulose**, **Hydroxypropyl cellulose**, and **Polyethylene oxide** are widely utilized due to their ability to control drug release through swelling and gel formation. Upon exposure to gastrointestinal fluids, these polymers hydrate and form a viscous gel layer around the tablet, which acts as a diffusion barrier, thereby modulating the rate of drug release.

Drug release from such hydrophilic matrices generally occurs through a combination of diffusion, polymer swelling, and matrix erosion mechanisms.

As the outer gel layer gradually dissolves or erodes, subsequent layers are exposed to the surrounding medium, allowing continuous and controlled drug release over time. In addition to hydrophilic systems, hydrophobic materials such as **Ethyl cellulose**, hydrogenated vegetable oils, and waxes may also be incorporated to further retard drug dissolution and extend the release duration.

Furthermore, formulation variables including the drug-to-polymer ratio, compression force, and matrix composition play critical roles in determining the overall release kinetics of the sustained-release core tablet. Through careful optimization of these parameters, formulators can achieve desired release profiles that ensure prolonged therapeutic activity and reduce the need for frequent drug administration [26].

4.3 Delayed-Release Core Tablet

In certain tablet-in-tablet formulations, the inner core tablet is specifically designed to provide drug release only after a predetermined lag time, thereby achieving delayed drug delivery. This approach is particularly advantageous in site-specific drug delivery systems, where the therapeutic agent must be released in the distal regions of the gastrointestinal tract, such as the ileum or colon, to maximize therapeutic effectiveness. Delayed-release systems are also widely employed in chronotherapeutic applications, where synchronization of drug release with circadian rhythms is essential for optimal clinical outcomes.

Delayed-release core tablets are commonly formulated using pH-dependent or time-dependent polymer coatings that prevent premature drug release during transit through the upper gastrointestinal tract. These coatings remain intact in the acidic environment of the stomach and begin to dissolve only when exposed to higher pH conditions in the intestine. Polymers such as **Eudragit** are frequently utilized for this purpose due to their well-defined pH-dependent solubility profiles. In colon-targeted drug delivery, such polymers are selected to dissolve at the elevated pH levels characteristic of the distal intestine.

In addition to pH-responsive systems, time-dependent coatings can be employed to introduce a predictable lag phase prior to drug release. These systems rely on the gradual erosion or swelling of polymer layers to control the onset of drug release. Alternative strategies include the incorporation of barrier layers, erodible polymer coatings, and osmotic pressure-based mechanisms, all of which contribute to precise modulation of drug release timing. By enabling accurate control over the onset of drug release, delayed-release core tablets significantly enhance the effectiveness of therapies requiring site-specific or time-dependent drug delivery [27]

POLYMERS USED IN GASTRO-RESISTANT TABLET SYSTEMS

Polymers play a pivotal role in the design of gastro-resistant drug delivery systems, as they govern both the protective capability of the dosage form and the spatial and temporal control of drug release within the gastrointestinal tract. In tablet-in-tablet formulations, polymers are primarily responsible for preventing premature drug release in the acidic gastric environment while enabling drug release upon exposure to the higher pH conditions of the intestinal region. This functionality is essential for safeguarding acid-labile drugs and for minimizing drug-induced gastric irritation.

Gastro-resistant formulations predominantly employ enteric polymers, which are pH-sensitive materials that remain intact under acidic conditions but dissolve at elevated pH levels. These polymers form a protective barrier around the drug, thereby preventing degradation and ensuring site-specific drug release. The selection of an appropriate polymer depends on several critical factors, including drug stability, desired release profile, coating integrity, compatibility with excipients, and the pH threshold required for polymer dissolution. In tablet-in-tablet systems, enteric polymers may be incorporated into the outer compression layer, applied as coating layers, or used as intermediate barrier layers to regulate drug release behavior. Commonly utilized enteric polymers include **Cellulose acetate phthalate**, **Hydroxypropyl methylcellulose phthalate**, **Eudragit**, and **Polyvinyl acetate phthalate**.

5.1 Cellulose Acetate Phthalate (CAP)

Cellulose acetate phthalate (CAP) is one of the earliest and most extensively used enteric polymers in pharmaceutical formulations. It is a cellulose-derived polymer obtained by the esterification of cellulose acetate with phthalic acid groups, which confer pH-dependent solubility characteristics. CAP remains insoluble in acidic environments but dissolves at pH values typically above 6, making it suitable for targeted drug release in the intestinal region.

CAP has been widely applied in enteric coating formulations for tablets and capsules due to its ability to form a stable and protective film that effectively resists gastric fluids. This impermeable barrier

prevents the ingress of acidic media and protects the active pharmaceutical ingredient from acid-induced degradation. Additionally, CAP exhibits good film-forming properties and is compatible with a variety of plasticizers, such as diethyl phthalate and triethyl citrate, which enhance the flexibility and mechanical strength of the coating.

Despite its advantages, CAP presents certain limitations, including sensitivity to moisture and reduced stability under high humidity conditions. These drawbacks have led to the development of alternative enteric polymers with improved physicochemical properties. Nevertheless, CAP continues to be widely utilized in gastro-resistant drug delivery systems due to its well-established performance and reliability in pharmaceutical applications [28].

5.2 Hydroxypropyl Methylcellulose Phthalate (HPMCP)

Hydroxypropyl methylcellulose phthalate (HPMCP) is a widely utilized enteric polymer in pharmaceutical drug delivery systems. It is a semi-synthetic cellulose derivative obtained by the esterification of hydroxypropyl methylcellulose with phthalic acid groups, which impart pH-dependent solubility characteristics. As a result, HPMCP remains intact in acidic gastric conditions and dissolves at the higher pH levels encountered in the intestinal environment, enabling site-specific drug release.

HPMCP is highly regarded for its excellent film-forming ability, physicochemical stability, and reproducible dissolution behavior. Compared to earlier enteric polymers, it offers improved mechanical strength and enhanced resistance to environmental factors, making it particularly suitable for coating applications in gastro-resistant formulations. The dissolution pH of HPMCP typically ranges between 5.5 and 6.5, depending on the degree of substitution and polymer grade, allowing drug release to occur in the upper regions of the small intestine where absorption is often optimal.

An additional advantage of HPMCP is its compatibility with aqueous coating systems, which reduces or eliminates the need for organic solvents during processing. This feature not only improves safety in pharmaceutical manufacturing but also aligns with environmentally sustainable formulation practices. Owing to these favorable properties, HPMCP is extensively employed in enteric-coated tablets, capsule coatings, and various modified-release oral dosage forms [29].

5.3 Methacrylic Acid Copolymers

Methacrylic acid copolymers are a widely utilized class of synthetic polymers in enteric and controlled drug delivery systems due to their well-defined pH-dependent solubility characteristics. These polymers are commercially available under the brand name **Eudragit** and include multiple grades that dissolve at specific pH thresholds, enabling precise control over the site of drug release within the gastrointestinal tract.

Among the commonly used grades, **Eudragit L** dissolves at pH values above approximately **6**, making it suitable for drug release in the upper small intestine. In contrast, **Eudragit S** dissolves at pH values above approximately **7**, which facilitates drug delivery to the distal intestine or colon. The selection of an appropriate polymer grade allows formulators to design dosage forms with targeted and site-specific drug release profiles.

Methacrylic acid copolymers offer several advantages, including excellent film-forming properties, high chemical stability, and compatibility with a wide range of pharmaceutical excipients. Additionally, these polymers can be applied using both aqueous and organic solvent-based coating techniques, providing versatility in formulation and manufacturing processes. Owing to these characteristics, methacrylic acid copolymers are extensively employed in enteric coatings, modified-release formulations, and targeted oral drug delivery systems [30].

5.4 Polyvinyl Acetate Phthalate (PVAP)

Polyvinyl acetate phthalate (PVAP) is another widely used enteric polymer in gastro-resistant pharmaceutical formulations. It is synthesized by the modification of polyvinyl acetate with phthalic acid groups, which impart pH-dependent solubility characteristics similar to other enteric polymers. As a result, PVAP remains insoluble under acidic gastric conditions but dissolves at intestinal pH values typically above 5–6, thereby facilitating controlled drug release in the small intestine.

PVAP is extensively utilized due to its excellent resistance to gastric fluids and its ability to provide effective protection against acid-induced drug degradation. The polymer forms robust and durable coating films that prevent premature drug release during gastric transit, ensuring that the active pharmaceutical ingredient is released only upon reaching the intestinal environment. In addition, PVAP exhibits favorable mechanical properties, including good flexibility and strength, which reduce the likelihood of film cracking or damage during handling and storage. It also demonstrates strong

adhesion to tablet surfaces and can be applied using conventional coating techniques.

However, similar to other enteric polymers, PVAP coatings often require the incorporation of plasticizers and stabilizers to enhance film flexibility, improve coating uniformity, and optimize overall performance. Despite these considerations, PVAP remains a valuable polymer in the development of gastro-resistant and modified-release oral dosage forms [31].

MANUFACTURING METHODS FOR TABLET-IN-TABLET SYSTEMS

The manufacturing process of tablet-in-tablet (TNT) drug delivery systems is a key factor influencing the structural integrity, drug release kinetics, and overall performance of the final dosage form. These systems are primarily produced using compression coating techniques, in which a pre-formed core tablet is enclosed within an outer powder layer and subsequently compressed to form a unified tablet structure. This method enables the development of dosage forms capable of delivering drugs in a controlled and sequential manner, making it particularly suitable for dual-release and site-specific drug delivery applications.

Unlike conventional film-coating processes that rely on the application of polymer solutions and often require solvents and elevated temperatures, compression coating is a dry process that avoids such conditions. Consequently, it is highly advantageous for formulating moisture-sensitive and thermolabile drugs. Furthermore, compression coating allows the physical separation of incompatible active pharmaceutical ingredients within a single dosage form, thereby enhancing formulation stability and expanding the scope of combination therapies.

Manufacturing approaches for tablet-in-tablet systems can generally be categorized into conventional compression coating techniques and advanced pharmaceutical technologies, each offering varying levels of precision, scalability, and process efficiency [32].

6.1 Conventional Compression Coating

Conventional compression coating is the most widely employed technique for the production of tablet-in-tablet (TNT) dosage forms. In this method, a pre-compressed core tablet is centrally positioned within a die cavity and subsequently surrounded by an outer powder layer, which is compressed to form a unified tablet structure. This approach enables the development of multilayered dosage forms with distinct functional regions, allowing controlled or sequential drug release.

The manufacturing process involves a series of well-defined steps. Initially, the core tablet is prepared using standard tableting techniques such as direct compression, wet granulation, or dry granulation. The formulation of the core typically includes the active pharmaceutical ingredient along with suitable excipients such as binders, diluents, disintegrants, lubricants, and release-modifying polymers, depending on the intended release profile.

Following core preparation, a portion of the outer layer powder blend is introduced into the die cavity to form a base layer. The pre-compressed core tablet is then carefully placed at the center of this partially filled die. Accurate positioning of the core is essential to ensure uniform coating thickness and structural integrity of the final dosage form. In large-scale manufacturing, specialized tablet presses equipped with automated core placement systems are often utilized to achieve precise alignment and high production efficiency.

Subsequently, the remaining outer layer powder is added to completely cover the core tablet. The quantity and composition of this outer layer influence the mechanical strength and drug release behavior of the final product. In the final stage, the entire assembly undergoes compression using upper and lower punches, resulting in a cohesive tablet structure. The applied compression force must be optimized to achieve adequate interlayer bonding without causing deformation or damage to the core tablet. Improper compression parameters may lead to issues such as core fracture, lamination, or inadequate mechanical strength.

Conventional compression coating remains widely used in pharmaceutical manufacturing due to its simplicity, cost-effectiveness, scalability, and compatibility with existing tablet production equipment.

6.2 Advanced Manufacturing Technologies

In recent years, advanced pharmaceutical manufacturing technologies have been introduced to enhance the precision, flexibility, and efficiency of tablet-in-tablet drug delivery systems. These technologies provide improved control over tablet architecture, drug distribution, and release kinetics compared with conventional compression coating methods. Approaches such as multilayer tablet presses, programmable compression systems, and emerging techniques like three-dimensional (3D) printing enable the fabrication of complex dosage forms with tailored release profiles and improved

reproducibility. As a result, advanced manufacturing technologies are increasingly being explored to overcome the limitations of traditional processes and to support the development of next-generation oral drug delivery systems [33].

3D Printing Technology

Three-dimensional (3D) printing, also known as additive manufacturing, represents a significant advancement in pharmaceutical formulation. This technique enables the layer-by-layer fabrication of dosage forms based on computer-aided design (CAD) models, allowing precise control over tablet geometry, internal architecture, and drug distribution. Through this approach, complex structures such as multilayer tablets, multi-compartment systems, and tablet-in-tablet configurations can be produced with high reproducibility. Various 3D printing methods have been explored for pharmaceutical applications, including fused deposition modeling (FDM), inkjet printing, selective laser sintering, and stereolithography. These technologies facilitate the incorporation of multiple active pharmaceutical ingredients within a single dosage form and support the development of personalized medicines tailored to individual patient requirements.

Hot-Melt Extrusion (HME)

Hot-melt extrusion is another advanced technique widely used in the development of modified-release drug delivery systems. In this process, a mixture of drug and polymer is heated and extruded through a die to produce a homogeneous matrix system. The resulting extrudates can be further processed into solid dosage forms with controlled drug release characteristics. HME offers several advantages, including improved drug dispersion, enhanced solubility of poorly water-soluble drugs, and suitability for continuous manufacturing processes, making it highly attractive for industrial-scale production.

Automated Core Placement Systems

Modern tablet manufacturing equipment incorporates automated core placement systems to improve the precision and efficiency of tablet-in-tablet production. These systems utilize mechanical or robotic mechanisms to accurately position the pre-compressed core tablet at the center of the die cavity during the compression process. This automation ensures uniform coating thickness, consistent tablet quality, and enhanced production speed, particularly in large-scale manufacturing environments.

Collectively, these advanced technologies provide greater control over dosage form design and performance, thereby facilitating the development of next-generation drug delivery systems with improved therapeutic outcomes [34].

EVALUATION OF TABLET-IN-TABLET SYSTEMS

The evaluation of tablet-in-tablet (TNT) drug delivery systems is a crucial step in pharmaceutical formulation development to ensure the quality, safety, and performance of the final dosage form. Due to their complex, multilayered structure, TNT systems require extensive characterization to assess both their physical properties and drug release behavior. These evaluations are necessary to verify that the formulation meets regulatory and pharmacopeial requirements while delivering the desired therapeutic performance in terms of drug stability, mechanical strength, and controlled or sequential drug release.

The evaluation of TNT systems is typically divided into three main categories: pre-compression studies, post-compression studies, and in vitro dissolution testing. Pre-compression evaluation focuses on the properties of powder blends, such as flowability, compressibility, and bulk density, which influence the uniformity of die filling and tablet formation. Post-compression tests are conducted to assess parameters including hardness, friability, weight variation, thickness, and content uniformity, ensuring the structural integrity and consistency of the dosage form. In vitro dissolution studies are performed to evaluate the drug release profile under simulated gastrointestinal conditions, providing critical information on release kinetics and the effectiveness of the formulation design [35].

7.1 Pre-Compression Parameters

Pre-compression studies are conducted to evaluate the flow properties and compressibility of the powder blends used in the preparation of both the core tablet and the outer compression layer. Proper flow characteristics are essential for achieving uniform die filling during tablet compression, which ensures consistent tablet weight, uniform drug distribution, and reproducible tablet quality.

Several standard parameters are used to assess powder flow properties:

Angle of Repose

The angle of repose is a widely used parameter that indicates the flowability of powder materials. It is defined as the maximum angle formed between the surface of a pile of powder and the horizontal plane. Powders with good flow properties typically exhibit a lower angle of repose, whereas poor-flowing powders show higher angles.

The angle of repose can be calculated using the following equation:

Angle of Repose (θ) = $\tan^{-1}$ (h / r)

Where: h = height of the powder pile r = radius of the powder pile

Generally, an angle of repose less than **30° indicates good flow properties**, while values above **40° suggest poor flowability**.

Bulk Density

Bulk density refers to the mass of powder divided by the total volume it occupies, including the spaces between particles. It provides information about the packing characteristics of powder particles.

Bulk Density = Mass of powder / Bulk volume

This parameter is useful in determining the amount of powder required to fill a die cavity during tablet compression.

Tapped Density

Tapped density is measured after mechanically tapping a graduated cylinder containing the powder until minimal volume change occurs. This test helps evaluate the compressibility of the powder.

Tapped Density = Mass of powder / Tapped volume

Carr's Compressibility Index

Carr's index provides an indication of powder flowability and compressibility by comparing bulk density and tapped density.

Carr's Index (%) = [(Tapped Density − Bulk Density) / Tapped Density] × 100

A Carr's index value below **15% indicates good flow properties**, while values above **25% indicate poor flowability**.

Hausner Ratio

The Hausner ratio is another parameter used to evaluate powder flow properties. It is calculated as the ratio of tapped density to bulk density.

Hausner Ratio = Tapped Density / Bulk Density

A Hausner ratio below **1.25** indicates good flowability, whereas values greater than **1.5** indicate poor flow characteristics.

These pre-compression tests help determine whether the powder blends are suitable for tablet manufacturing and ensure consistent tablet production [36].

7.2 Post-Compression Parameters

Post-compression evaluation involves testing the physical characteristics of the finished tablet-in-tablet dosage forms. These tests ensure that the tablets possess adequate mechanical strength, uniformity, and stability during handling, packaging, and transportation.

Tablet Hardness

Tablet hardness refers to the mechanical strength of the tablet and its ability to withstand external pressure during handling. Hardness is typically measured using hardness testers such as the **Monsanto hardness tester, Pfizer hardness tester, or digital hardness testers**.

Adequate hardness is necessary to maintain the structural integrity of the TNT system without affecting drug release properties.

Friability

Friability measures the tendency of tablets to crumble or break under mechanical stress. This test is performed using a **Roche friabilator**, where tablets are rotated at a specified speed for a fixed period.

The percentage friability is calculated as:

Friability (%) = [(Initial Weight − Final Weight) / Initial Weight] × 100

According to pharmacopeial standards, friability values should generally be **less than 1%**.

Weight Variation

Weight variation testing ensures uniform distribution of the drug within the tablet batch. Tablets are individually weighed, and their weights are compared with the average tablet weight to determine uniformity.

This test is important for ensuring accurate dosing in pharmaceutical formulations.

Tablet Thickness

Tablet thickness is measured using a **vernier caliper or micrometer screw gauge**. Consistent tablet thickness is important for maintaining uniformity in packaging and ensuring proper functioning of coating and compression processes.

Drug Content Uniformity

Drug content uniformity testing ensures that each tablet contains the intended amount of active pharmaceutical ingredient. Tablets are typically crushed, dissolved in an appropriate solvent, and analyzed using analytical techniques such as **UV-visible spectroscopy or high-performance liquid chromatography (HPLC)**.

Uniform drug distribution is particularly important in tablet-in-tablet systems because both the core and outer layers may contain active ingredients [37].

7.3 In-Vitro Dissolution Studies

In-vitro dissolution testing is one of the most important evaluation methods used to assess the drug release behavior of tablet-in-tablet formulations. This test simulates the physiological conditions of the gastrointestinal tract and helps determine whether the dosage form provides the desired gastro-resistant and dual-release characteristics.

Dissolution studies are typically conducted using pharmacopeial dissolution apparatus such as:

- **USP Apparatus I (Basket method)**
- **USP Apparatus II (Paddle method)**

The dissolution testing procedure for gastro-resistant tablets usually involves two stages:

Stage 1: Simulated Gastric Fluid (SGF)

In the first stage, the tablet is placed in simulated gastric fluid with a pH of approximately **1.2** for about **2 hours**. During this stage, the tablet should remain intact without significant drug release, confirming the effectiveness of the gastro-resistant polymer coating.

Stage 2: Simulated Intestinal Fluid (SIF)

After the gastric phase, the dissolution medium is replaced with simulated intestinal fluid with a pH of approximately **6.8 to 7.4**. At this stage, the enteric polymer dissolves, allowing the outer tablet layer to release the first dose of the drug, followed by controlled or delayed release from the inner core tablet.

The drug release profile obtained from dissolution testing helps evaluate the effectiveness of the **dual-release mechanism** and ensures that the formulation performs as intended [38].

ADVANTAGES OF TABLET-IN-TABLET DRUG DELIVERY SYSTEMS

Tablet-in-tablet (TNT) drug delivery systems offer several notable advantages over conventional single-layer tablets and other oral dosage forms. The distinctive structural configuration of these systems enables the incorporation of multiple drug release mechanisms within a single dosage unit, thereby providing considerable flexibility in the design of advanced oral drug delivery platforms. Owing to their capability to deliver drugs in a controlled and sequential manner, TNT formulations have gained increasing importance in the pharmaceutical field for improving therapeutic efficacy and enhancing patient compliance.

One of the primary advantages of tablet-in-tablet systems is their ability to protect acid-sensitive drugs from degradation in the gastric environment. Many active pharmaceutical ingredients, including proton pump inhibitors and certain antibiotics, are susceptible to instability under highly acidic conditions. Exposure to gastric fluids may result in chemical degradation, leading to reduced bioavailability and diminished therapeutic effectiveness. In gastro-resistant tablet-in-tablet systems, the outer layer—often formulated with enteric polymers—acts as a protective barrier that prevents drug release in the stomach. This ensures that the drug remains intact during gastric transit and is released only upon reaching the more favorable pH conditions of the small intestine, thereby improving drug stability and overall therapeutic performance [39].

Another significant advantage of tablet-in-tablet (TNT) gastro-resistant systems is their ability to reduce gastric irritation associated with certain drugs. Several medications, particularly non-steroidal anti-inflammatory drugs (NSAIDs) and other gastrointestinal irritants, are known to cause damage to the gastric mucosa when released in the stomach. This can lead to adverse effects such as irritation, ulceration, and gastrointestinal discomfort. In TNT-based gastro-resistant formulations, the outer layer—typically composed of enteric polymers—prevents premature drug release in the acidic gastric environment. Consequently, the drug is released only after the dosage form reaches the intestinal region, where the risk of mucosal irritation is significantly lower. This targeted release mechanism not only enhances the safety profile of such drugs but also improves their clinical acceptability and patient tolerability [40].

Tablet-in-tablet technology also allows the delivery of multiple drugs within a single tablet, which is particularly beneficial in combination therapy. In many clinical situations, patients are required to take multiple medications simultaneously for the management of complex diseases. Tablet-in-tablet systems provide a convenient platform for incorporating two or more drugs with different release profiles into one dosage form. By separating the drugs into different layers or compartments, the system prevents potential incompatibility between active ingredients while maintaining their stability and effectiveness [41].

Another key advantage of tablet-in-tablet (TNT) systems lies in their ability to achieve controlled and

sequential drug release. The unique structural arrangement of an inner core tablet enclosed within an outer layer enables the design of dosage forms that release drugs at different time intervals or at specific locations within the gastrointestinal tract. Typically, the outer layer can be formulated to provide immediate drug release upon exposure to the intestinal environment, thereby producing a rapid onset of action, while the inner core tablet is engineered to release the drug in a delayed or sustained manner over an extended period. This biphasic or multiphasic release profile allows for improved therapeutic control by maintaining consistent drug concentrations in systemic circulation, reducing fluctuations in plasma levels, and enhancing overall treatment efficacy [42].

Tablet-in-tablet drug delivery systems also contribute to improved patient compliance, which is an important factor in successful medical treatment. Complex dosing regimens that require multiple daily doses often lead to poor adherence among patients. By combining immediate and sustained drug release mechanisms within a single dosage form, TNT systems can reduce the number of tablets a patient must take each day. Simplified medication schedules improve patient convenience and increase the likelihood of consistent medication use [43].

Another important benefit of tablet-in-tablet systems is the reduction in dosing frequency. Sustained or delayed drug release from the core tablet allows therapeutic drug levels to be maintained for longer periods, thereby reducing the need for repeated drug administration. Reduced dosing frequency not only improves patient compliance but also helps maintain more stable plasma drug concentrations, which may enhance the overall therapeutic effect of the medication [44].

LIMITATIONS AND CHALLENGES

Despite their numerous advantages, tablet-in-tablet (TNT) drug delivery systems present several limitations and challenges that may affect their large-scale application. One of the primary concerns is the complexity of the manufacturing process, which involves multiple steps such as core tablet preparation, precise core placement, and compression coating. These additional processing requirements increase production time and operational complexity. Furthermore, TNT systems often incur higher manufacturing costs due to the need for specialized equipment and advanced process controls.

Achieving accurate and reproducible positioning of the core tablet within the outer layer is another critical challenge, as improper alignment can lead to non-uniform coating thickness and inconsistent drug release profiles. In addition, the availability of specialized tablet presses and automated core placement systems may be limited, particularly in smaller-scale manufacturing settings. These factors collectively pose challenges in ensuring consistent product quality, scalability, and cost-effectiveness in the industrial production of tablet-in-tablet dosage forms [45].

PHARMACEUTICAL APPLICATIONS

Tablet-in-tablet (TNT) drug delivery systems have attracted significant interest in pharmaceutical research and development owing to their versatility and capability to achieve controlled, sequential, and site-specific drug release. The distinctive structural configuration, comprising an inner core tablet enclosed within an outer tablet layer, enables the design of sophisticated dosage forms that can protect sensitive drugs from gastric degradation, minimize gastrointestinal side effects, and facilitate the co-administration of multiple therapeutic agents within a single unit.

The flexibility of TNT systems in delivering drugs through gastro-resistant, delayed, sustained, or pulsatile release mechanisms makes them particularly valuable in the management of various disease conditions requiring precise control over drug release kinetics. By tailoring the composition and functionality of both the core and outer layers, these systems can be engineered to meet specific therapeutic objectives, including improved bioavailability, reduced dosing frequency, and enhanced patient compliance. Consequently, tablet-in-tablet formulations are increasingly being explored for a wide range of pharmaceutical applications, particularly in cases where targeted or time-dependent drug delivery is essential [46]

10.1 Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are extensively used in the management of acid-related gastrointestinal disorders, including peptic ulcer disease, gastroesophageal reflux disease (GERD), and Zollinger–Ellison syndrome. Commonly prescribed PPIs include **Omeprazole**, **Lansoprazole**, **Pantoprazole**, and **Rabeprazole**. These drugs are highly acid-labile and undergo rapid degradation when exposed to the strongly acidic conditions of the stomach, which can significantly reduce their therapeutic efficacy.

Tablet-in-tablet (TNT) gastro-resistant systems offer an effective approach to overcome this limitation by protecting PPIs from gastric acid degradation. In such formulations, the active drug is typically incorporated

into the inner core tablet, which is enclosed within an outer layer containing enteric polymers. This outer layer remains intact in the acidic gastric environment and prevents premature drug release. Upon reaching the higher pH conditions of the small intestine, the enteric layer dissolves, allowing the release of the drug in a more favorable environment for absorption.

This targeted delivery strategy enhances the stability and bioavailability of PPIs by ensuring that the drug reaches the site of absorption in its active form. Furthermore, controlled or sustained release from the core tablet can help maintain therapeutic plasma concentrations over extended periods, thereby improving clinical outcomes and treatment effectiveness [47].

10.2 Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for the management of pain, inflammation, and fever. Common examples include **Ibuprofen**, **Diclofenac**, **Naproxen**, and **Aspirin**. Despite their well-established therapeutic benefits, NSAIDs are frequently associated with gastrointestinal adverse effects, including gastric irritation, ulceration, and gastrointestinal bleeding, particularly when the drug is released in the acidic environment of the stomach.

Tablet-in-tablet (TNT) drug delivery systems provide an effective strategy to minimize these limitations by enabling gastro-resistant formulations. In such systems, the drug is incorporated within a protected core or surrounded by an outer layer containing enteric polymers, which prevent premature drug release in the stomach. As a result, drug release is delayed until the dosage form reaches the intestinal environment, where the likelihood of gastric mucosal damage is significantly reduced.

Furthermore, TNT systems can be designed to achieve sustained or delayed drug release, thereby maintaining consistent therapeutic drug levels over an extended period. This controlled release profile reduces dosing frequency and enhances patient adherence, particularly in chronic conditions requiring long-term NSAID therapy. Overall, tablet-in-tablet formulations contribute to improved safety, efficacy, and patient compliance in NSAID treatment [48].

10.3 Antibiotics

Certain antibiotics require targeted drug delivery to the intestinal region to achieve optimal therapeutic efficacy. Antibiotics such as amoxicillin, metronidazole, and ciprofloxacin are often used to treat infections within the gastrointestinal tract or systemic infections that require efficient intestinal absorption.

Tablet-in-tablet drug delivery systems can be designed to release antibiotics specifically in the intestinal environment. The enteric outer layer protects the antibiotic from degradation in the stomach, while the inner core tablet releases the drug gradually after reaching the intestine. This targeted release improves drug absorption and enhances the overall therapeutic effectiveness of the antibiotic.

In addition, controlled drug release from the core tablet can help maintain effective drug concentrations in the bloodstream for longer periods. This sustained exposure may improve treatment outcomes and reduce the development of antibiotic resistance by maintaining consistent antimicrobial activity [49].

10.4 Combination Therapy

One of the most significant advantages of tablet-in-tablet (TNT) drug delivery systems is their ability to accommodate multiple drugs within a single dosage form. Combination therapy is widely employed in the management of chronic conditions such as hypertension, diabetes, cardiovascular diseases, and infectious disorders, where the simultaneous administration of multiple therapeutic agents is often required to achieve optimal clinical outcomes.

Tablet-in-tablet technology offers a versatile platform for incorporating two or more drugs with distinct release profiles into a single tablet. For instance, one drug may be formulated within the outer layer to provide immediate release, ensuring rapid onset of action, while another drug can be incorporated into the inner core tablet for delayed or sustained release. This spatial separation allows precise modulation of drug release timing and improves the overall pharmacokinetic profile of combination therapies.

Moreover, the physical separation of drugs into different compartments within the tablet helps prevent chemical incompatibility between active pharmaceutical ingredients, thereby enhancing formulation stability and preserving therapeutic efficacy. In addition to these formulation advantages, TNT-based combination systems improve patient convenience and adherence by reducing pill burden, as multiple medications can be administered in a single dosage unit rather than as separate tablets [50].

RECENT ADVANCES IN TABLET-IN-TABLET TECHNOLOGY

Recent innovations include **3D printing of pharmaceutical tablets** [51], **smart polymers responsive to environmental stimuli** [52], and

nanotechnology-based drug delivery systems that enhance solubility and bioavailability [53].

Additionally, **artificial intelligence-based formulation design** is increasingly used to optimize drug release behavior and formulation parameters [54].

FUTURE PERSPECTIVES

Advances in material science, nanotechnology, and digital manufacturing are expected to significantly improve tablet-in-tablet drug delivery systems. Integration with personalized medicine and artificial intelligence-based formulation design may further enhance therapeutic outcomes [55].

CONCLUSION

Tablet-in-tablet drug delivery systems represent a significant advancement in oral pharmaceutical formulation technology by offering improved control over drug release and enhanced therapeutic performance. Dual-release gastro-resistant platforms provide an effective strategy for protecting acid-sensitive drugs from degradation in the gastric environment while enabling controlled and sequential drug release in the intestinal region. This structural approach allows pharmaceutical scientists to design dosage forms capable of delivering multiple drugs or multiple release phases within a single tablet, thereby improving drug stability, therapeutic efficacy, and patient compliance. Furthermore, the incorporation of advanced polymers and modern manufacturing technologies has expanded the potential applications of these systems in targeted and modified drug delivery. Continued research and technological innovations are expected to further enhance the design and performance of tablet-in-tablet formulations, making them an important platform for the development of advanced oral drug delivery systems in modern pharmaceutical research and development.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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