American Journal of Psychiatric Rehabilitation

Expert Opinion Article

Dual-Phase Extended-Release Tablets: A Comprehensive Review

Saloni Ranka[1*], Vikas Jain[2], Narendra Gehlot[3], Yogendra Malviya[4]

[1*,2,3,4]Mahakal Institute of Pharmaceutical Studies, Ujjain, Madhya Pradesh 456010, India,

***Corresponding Author:** Saloni Ranka
Research Scholar, Mahakal Institute of Pharmaceutical Studies, Ujjain, Madhya Pradesh 456010, India,
Email: saloni25700@gmail.com

Abstract

Dual-phase extended-release tablets represent a sophisticated oral drug delivery strategy, integrating the benefits of both immediate-release and sustained-release systems. These formulations, also known as biphasic or bilayer extended-release systems, are meticulously engineered to provide a rapid onset of therapeutic action via an initial drug burst, followed by prolonged drug release to maintain stable plasma concentrations over an extended period. This design addresses critical pharmacokinetic shortcomings of traditional immediate-release and single-phase extended-release formulations, such as fluctuating drug levels, sub-therapeutic troughs, and peak-related toxicities. The rationale for their development spans ensuring rapid relief, maintaining consistent therapeutic levels, reducing dosing frequency, and improving overall pharmacokinetic profiles, making them suitable for fixed-dose combinations. Various design and formulation approaches, including bilayer tablets, polymeric matrix systems, membrane-coated systems, multilayer tablets, and osmotic dual-release systems, are employed, each leveraging distinct mechanisms such as disintegration, dissolution, diffusion, erosion, and swelling. Rigorous evaluation through physical, mechanical, in vitro dissolution studies, IVIVC, and advanced analytical techniques like FT-IR and SEM, alongside stability studies, ensures their quality and performance. Dual-phase tablets find widespread applications in analgesics, antivirals, urologic, antidiabetic, cardiovascular, and antihistamine drugs. Despite challenges such as mechanical integrity issues, manufacturing complexity, and regulatory hurdles, ongoing advancements in smart polymers, in-silico modeling, and 3D printing are enhancing their feasibility. Poised to play a major role in future pharmacotherapy, these systems promise improved patient compliance, better therapeutic outcomes, and greater formulation flexibility

Keywords: Dual-phase drug delivery, Extended-release tablets, Immediate-release, Pharmacokinetics, Bilayer tablets, 3D printing.

Introduction

Oral drug delivery remains the most widely preferred route for drug administration due to its inherent convenience, cost-effectiveness, and high patient compliance. Historically, traditional immediate-release dosage forms have dominated the pharmaceutical landscape, offering rapid delivery of active drug into the systemic circulation[1]. However, this rapid release often necessitates frequent administration to maintain therapeutic efficacy and can lead to undesirable pharmacokinetic profiles characterized by sharp peaks in plasma drug levels, potentially causing dose-related side effects, and subsequent troughs, which may result in sub-therapeutic concentrations and treatment failure[2,3].

To address these significant limitations, extended-release formulations were developed. These systems are designed to deliver a drug over an extended period, thereby maintaining more stable, prolonged, and consistent therapeutic concentrations and reducing the frequency of dosing. While ER formulations improve drug exposure over time, they typically lack the rapid onset of action that is crucial for certain therapeutic needs[4,5].

This is where dual-phase extended-release tablets emerge as a significant advancement. These innovative formulations ingeniously combine the strengths of both IR and ER systems within a single dosage unit. They are typically designed as either bilayer tablets, featuring distinct immediate-release and sustained-release layers, or as monolithic matrices with two differentiated release phases. The fundamental goal of these systems is to deliver an initial loading dose rapidly to achieve a quick therapeutic effect, followed by a sustained release phase that maintains drug concentrations for hours, or even a full day[6].

Such dual-phase dosage forms are particularly beneficial for drugs that require a rapid onset of action for instance, for conditions like pain management, asthma rescue therapy, or acute allergic reactions combined with a sustained pharmacotherapy to maintain therapeutic levels throughout the day and avoid fluctuations. Specific examples include analgesics for prompt pain relief followed by prolonged comfort, antihistamines and

cough/cold formulas for continuous symptom management, and antidiabetic or cardiovascular agents requiring rapid glycemic control or consistent blood pressure regulation, respectively[7,8].

Given the increasing demand for finely tuned, controlled pharmacokinetic profiles and patient-friendly formulations that enhance adherence and improve overall therapeutic outcomes, dual-phase ER dosage forms have rapidly become a major research and development area in pharmaceutics. Their ability to provide both rapid therapeutic response and sustained drug action marks them as a sophisticated and highly valuable strategy in modern pharmacotherapy[9].

2. Rationale for Dual-Phase Drug Delivery

Dual-phase drug delivery systems are meticulously engineered to achieve a multitude of pharmacokinetic and therapeutic advantages, addressing many shortcomings of traditional immediate-release and even single-phase extended-release formulations[10]. These systems represent a sophisticated approach to optimize drug efficacy and patient experience.

2.1. Rapid Onset of Action

A primary rationale behind dual-phase delivery is to ensure a rapid onset of therapeutic action. The immediate-release portion of the tablet serves as a "loading dose," quickly delivering the drug to achieve effective plasma concentrations. This is crucial for overcoming any potential delays in drug absorption, such as those caused by gastric emptying or the slower dissolution of matrix materials inherent in sustained-release formulations. This rapid initial drug exposure is particularly essential for conditions where immediate relief or intervention is required, including pain management, asthma rescue therapy, and the administration of antihistamines or antipyretics, where symptomatic relief cannot be delayed[11,12].

2.2. Maintenance of Therapeutic Levels

Following the initial rapid burst, the sustained-release portion of the dual-phase system takes over, providing a "maintenance dose." This extended delivery is designed to compensate for the body's natural processes of drug elimination, effectively preventing the plasma drug levels from dropping below the minimum effective concentration. By sustaining drug release over an extended period, these systems eliminate the fluctuations often observed with frequent dosing of IR formulations, ensuring consistent therapeutic levels and maximizing the duration of drug action[13].

2.3. Reduced Dosing Frequency

By integrating both the rapid onset and the sustained maintenance phases into a single dosage unit, dual-phase tablets significantly minimize the need for multiple daily doses. This reduction in dosing frequency is a major advantage, directly translating to improved patient adherence to medication regimens. Patients are more likely to comply with treatments that require less frequent administration, which in turn leads to better therapeutic outcomes and enhanced overall patient convenience[14].

2.4. Improved Pharmacokinetic Profile

Dual-release systems are instrumental in optimizing the pharmacokinetic profile of a drug. They are specifically designed to reduce undesirable peak-related side effects that can occur with high drug concentrations immediately following an IR dose. Simultaneously, they prevent sub-therapeutic troughs, which can lead to treatment failure if drug levels fall below the effective range. This precise control results in a much narrower and more stable range of plasma drug concentrations, thereby reducing wide variations and promoting a safer and more effective therapeutic window[15,16].

2.5. Suitable for Fixed-Dose Combinations

Dual-phase systems, especially in the form of bilayer tablets, offer exceptional versatility for fixed-dose combinations. They can effectively separate incompatible drugs into distinct layers, preventing chemical interactions that might compromise stability or efficacy. Furthermore, these designs allow for the precise tailoring of different release kinetics for each drug within the same tablet, optimizing their individual therapeutic contributions. This capability also enables sequential delivery, where one drug is released immediately, followed by the sustained release of another, or even staggered release profiles for synchronized therapeutic effects, providing considerable flexibility in drug design[17,18].

3. Design & Formulation Approaches

Dual-phase extended-release tablets can be manufactured using a variety of sophisticated technological approaches, each designed to achieve the desired immediate and sustained release profiles (Figure 1) [19]. The choice of approach often depends on the drug's properties, the desired release kinetics, and manufacturing capabilities.

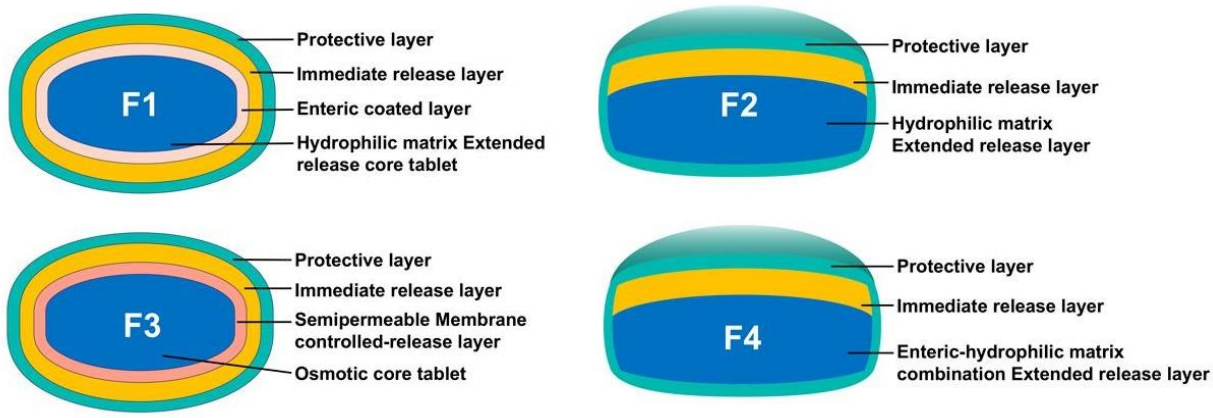

Figure 1: Different types of dual-phase extended-release tablets

3.1. Bilayer Tablet Technology

Bilayer tablet technology represents the most common and widely utilized design for dual-phase extended-release systems. This approach involves compressing two distinct layers into a single tablet. The first layer is typically an immediate-release layer, formulated to rapidly dissolve and release its drug content. This layer often incorporates superdisintegrants, such as croscarmellose sodium or sodium starch glycolate, to facilitate quick breakdown and drug release[20]. The second layer functions as the extended-release portion, designed to provide sustained drug delivery over an extended period. This ER layer is commonly constructed using polymers like hydrophilic polymers (e.g., HPMC, HPC) that form a gel layer upon hydration to control diffusion, hydrophobic matrices (e.g., ethylcellulose, stearic acid) that create water-insoluble barriers, or waxes. Key considerations in bilayer tablet manufacturing include ensuring sufficient layer adhesion strength to prevent delamination, achieving uniform die filling, preventing cross-contamination between the layers during compression, and precisely controlling the compression force applied to each layer to maintain its integrity and release characteristics[21,22].

3.2. Polymeric Matrix Systems

Polymeric matrix systems are fundamental to controlling drug release in dual-phase formulations, particularly for the extended-release component. These systems can be broadly categorized into hydrophilic, hydrophobic, and combination matrices. Hydrophilic matrices, frequently employing polymers such as hydroxypropyl methylcellulose or carbomers, function by hydrating upon contact with gastrointestinal fluids, forming a viscous gel layer. This gel layer acts as a barrier, regulating drug diffusion from the matrix. Conversely, hydrophobic matrices, often composed of materials like ethylcellulose, stearic acid, or various waxes, slow down drug release by creating water-insoluble barriers through which drug diffusion is hindered. More advanced approaches utilize combination matrices, which involve synergistic blends of polymers (e.g., HPMC, HPC, and carbomer). These blends allow for a more nuanced modulation of both diffusion and erosion mechanisms, offering greater control over the overall drug release profile[23,24].

3.3. Membrane-Coated Systems

Another effective strategy for creating dual-phase release is through membrane-coated systems. In these designs, a drug core (either an immediate-release or an extended-release core) is surrounded by one or more polymeric coatings. For instance, an immediate-release core might be coated with an enteric polymer to delay release until it reaches the intestine, or an extended-release core might be further coated with a functional polymer to fine-tune its release. This approach is particularly beneficial for drugs that require modified release triggered by specific environmental factors, such as changes in intestinal pH, allowing for targeted drug delivery or protection from the acidic stomach environment[25].

3.4. Multilayer Tablets

Extending beyond simple bilayer configurations, multilayer tablets offer even greater complexity and control. These systems can incorporate more than two layers, enabling a wider array of release profiles and drug combinations. For example, multilayer tablets might include two immediate-release layers for different active pharmaceutical ingredients, or separate layers designed for pulsatile release, where drug is released at specific intervals. They can also facilitate chronotherapeutic layers, where drug release is timed to coincide with circadian rhythms or specific physiological needs, optimizing treatment efficacy for conditions like hypertension or asthma[26].

3.5. Osmotic Dual-Release Systems

Advanced osmotic pump systems, such as L-OROS or push–pull osmotic tablets, can be ingeniously modified to achieve biphasic release. These sophisticated devices inherently control drug release by utilizing osmotic pressure. To create a dual-phase profile, an immediate-release coating can be applied to the exterior of the osmotic pump. This external coating provides the initial rapid drug release. Subsequently, the internal osmotic gradient controls the sustained release of the remaining drug from the pump's core, thereby achieving both immediate and extended therapeutic effects from a single dosage form[27,28].

4. Mechanisms of Drug Release

Dual-phase tablets are meticulously designed to achieve their characteristic biphasic release profile by relying on distinct and often synergistic mechanisms for their immediate and sustained release components.

4.1. Immediate-Release Mechanisms

The immediate-release portion of these tablets is engineered for rapid drug delivery. The primary mechanisms involved include rapid disintegration of the tablet matrix and fast dissolution of the active pharmaceutical ingredient. This quick breakdown and release are often significantly aided by the incorporation of pharmaceutical excipients such as superdisintegrants (e.g., croscarmellose sodium, sodium starch glycolate) or effervescent agents, which accelerate the tablet's breakup upon contact with gastrointestinal fluids, making the drug readily available for absorption[29,30].

4.2. Sustained-Release Mechanisms

Conversely, the sustained-release portion operates through more complex mechanisms to provide prolonged drug delivery. Key mechanisms contributing to sustained release include diffusion of the drug through hydrated polymer matrices, erosion of polymeric gel layers, and swelling of hydrophilic matrices. In diffusion-controlled systems, the drug slowly passes through a polymeric network. Erosion mechanisms involve the gradual breakdown of the polymer matrix itself, releasing the entrapped drug over time[31]. Swelling of hydrophilic polymers, upon contact with water, forms a viscous gel that acts as a barrier, regulating the rate of drug release. Advanced systems may also incorporate osmotic pumping, where osmotic pressure drives drug release at a controlled rate, or pH-dependent dissolution, where drug release is modulated by the pH environment of the gastrointestinal tract. It is common for most dual-phase tablets to combine multiple sustained-release mechanisms, such as diffusion and erosion, to achieve a precisely tailored and consistent drug release profile[32].

5. Evaluation & Characterization

The rigorous evaluation and characterization of dual-phase extended-release tablets are critical steps in their development to ensure their quality, performance, and stability[33]. A range of physical, chemical, and biological tests are employed to assess these complex formulations.

5.1. Physical & Mechanical Testing

Physical and mechanical testing is fundamental to ensuring the robustness and integrity of dual-phase tablets. Key parameters assessed include:

- **Hardness and friability:** These tests measure the tablet's resistance to crushing and its tendency to chip or break during handling and packaging.
- **Layer adhesion strength:** This is a crucial test for bilayer and multilayer tablets, assessing the force required to separate the layers, which is vital to prevent delamination during manufacturing, packaging, and patient use.
- **Thickness and uniformity:** Ensuring consistent tablet dimensions is important for packaging and consistent dosage.
- **Tablet density and porosity:** These characteristics can influence drug release kinetics and are important for ensuring consistency between batches[34,35].

5.2. In-vitro Dissolution Studies

In-vitro dissolution studies are of paramount importance for dual-phase systems as they provide insights into the drug release profile under simulated physiological conditions. These studies are critical for predicting how the drug will behave *in vivo*. Commonly used methods include:

- **USP apparatus I (basket) and USP apparatus II (paddle):** These are standard dissolution apparatuses used to determine the rate and extent of drug release.
- **Profiles tested in different pH conditions:** To mimic the transit of the tablet through the gastrointestinal tract, dissolution profiles are typically tested in various pH media, such as pH 1.2 (simulating gastric fluid) and pH 6.8 (simulating intestinal fluid). This helps to understand how both the immediate and sustained release phases perform in different environments[36,37].

5.3. In-vitro/In-vivo Correlation

Establishing an In-vitro/In-vivo Correlation is highly desirable for dual-phase extended-release tablets and is often a regulatory requirement. A successful IVIVC demonstrates a predictive mathematical relationship between an *in vitro* property (like dissolution rate) and a relevant *in vivo* response (like

plasma drug concentration). This correlation can significantly reduce the need for extensive *in vivo* bioavailability and bioequivalence studies, especially during post-approval changes or for new formulations[38,39].

5.4. Analytical Techniques

Advanced analytical techniques are employed to gain deeper insights into the tablet's structure, composition, and release mechanisms:

- **FT-IR mapping:** Fourier-transform infrared mapping can be used to study polymer interactions within the tablet layers and to identify the distribution of components.
- **SEM imaging of swelling/erosion:** Scanning electron microscopy provides visual evidence of how polymer matrices swell and erode during drug release, offering crucial information about the physical changes occurring.
- **Differential scanning calorimetry:** DSC is used to characterize thermal properties of materials, such as glass transition temperature, melting point, and drug-excipient compatibility.
- **X-ray diffraction:** XRD can assess the crystallinity of the drug and excipients, which can influence dissolution rates and stability[40,41].

5.5. Stability Studies

Stability studies are conducted in accordance with International Council for Harmonisation guidelines. These studies evaluate how the quality of the drug product varies with time under the influence of environmental factors such as temperature, humidity, and light. The goal is to establish a re-test period for the drug substance or a shelf-life for the drug product and to recommend storage conditions. For dual-phase tablets, stability across layers must be proven, ensuring that both the immediate and sustained release components maintain their integrity and functionality over time[42].

6. Applications & Case Studies

Dual-phase extended-release tablets have found diverse applications across various therapeutic areas, showcasing their versatility and effectiveness in optimizing drug delivery. The following examples illustrate how these innovative formulations are being utilized and the benefits they offer.

6.1. Analgesics (e.g., Tramadol, Aceclofenac)

In the realm of pain management, dual-phase tablets are particularly valuable for providing both rapid analgesia and prolonged pain relief. The immediate-release component quickly alleviates acute pain, while the extended-release portion ensures sustained therapeutic concentrations to manage pain over an extended duration. This dual action is crucial for conditions requiring continuous pain control, improving patient comfort and reducing the frequency of dosing. Formulations for the extended-release portion of these analgesics commonly utilize hydrophilic polymer-based matrices, such as those made from hydroxypropyl methylcellulose, which control drug diffusion and erosion to maintain consistent drug levels[43,44].

6.2. Antivirals (e.g., Oseltamivir)

Recent research has successfully applied dual-phase mechanisms to antiviral agents, demonstrating their potential to enhance treatment regimens. One notable example involves the development of a bilayer tablet combined with an enteric coating. This system was designed for an antiviral like oseltamivir, aiming to achieve near-bioequivalent results to the marketed capsule while offering the significant advantage of once-daily dosing. The bilayer design allows for precise control over the initial and sustained release of the drug, while the enteric coating protects the drug from gastric degradation and ensures targeted release in the intestine, ultimately improving patient convenience and adherence[45,46].

6.3. Urologic Drugs (e.g., Mirabegron + Fesoterodine)

Combination therapies are frequently employed in urology to manage complex conditions. Dual-phase tablets, particularly in bilayer form, are well-suited for such applications. For instance, combination tablets for urologic drugs might feature separate layers, each designed with differing dissolution mechanisms, distinct polymer matrices, and specific swelling behaviors. This allows for the simultaneous delivery of two or more drugs, each with its optimized release profile, which is crucial when drugs have different pharmacokinetic needs or when their combination provides synergistic therapeutic effects, as seen with drugs like Mirabegron and Fesoterodine[47,48].

6.4. Antidiabetic & Cardiovascular Agents

For chronic conditions such as diabetes and cardiovascular diseases, maintaining stable drug levels is paramount. Dual-phase formulations offer significant benefits for drugs like metformin, glipizide (antidiabetics), or various beta-blockers (cardiovascular agents). These tablets provide a rapid onset for immediate effects, such as glycemic control in diabetes or initial blood pressure reduction in hypertension, followed by a prolonged maintenance phase. This allows for once-daily dosing, which significantly enhances patient adherence and helps in achieving consistent therapeutic outcomes throughout the day and night[49].

6.5. Antihistamines and Cough/Cold Formulas

Dual-phase release systems are highly advantageous for over-the-counter medications like antihistamines and cough/cold formulas. These formulations are designed to provide rapid relief from symptoms initially, followed by sustained release of the active ingredients. This extended action helps maintain symptom relief overnight or throughout the entire day, preventing the recurrence of symptoms and ensuring prolonged patient comfort and well-being without the need for frequent re-dosing (Table 1) [50].

Table 1: Comparison of Major Dual-Phase Extended-Release Tablet Studies

API / Drug(s)	Dosage Form Type	Polymers / Key Excipients Used	Release Mechanism(s)	Reported Release Profile
Tramadol HCl	Bilayer tablet (IR + SR)	HPMC, MCC, PVP, superdisintegrants (CCS)	IR: fast disintegration; ER: diffusion + polymer hydration	IR layer released in ~15 min; ER over ~10 hours
Aceclofenac	Bilayer dual-release tablet	HPMC (various grades), HPC, Carbomer, PVP	Combination of diffusion + swelling + erosion	Controlled release sustained for 12 hours; comparable to marketed CR tablets
Oseltamivir Phosphate	Dual-phase ER matrix + enteric-coated system	Ethylcellulose, HPMC, enteric polymer (HPMCP), plasticizers	pH-triggered release + hydrophilic matrix diffusion	Biphasic profile: initial release after gastric transit; prolonged intestinal release; ~95% relative bioavailability to capsule
Mirabegron + Fesoterodine Fumarate	Bilayer combination tablet	EC, HPMC, HEC, PVP, hydrophobic excipients	Mirabegron: erosion-controlled; Fesoterodine: diffusion (Higuchi)	Clear dual-release behavior; interactions between layers influenced kinetics
Metformin HCl	IR + ER monolithic or bilayer	HPMC K15M/K100M, PEO, carbopol	Hydrophilic matrix swelling + diffusion	IR: immediate burst; ER maintained for 8–12 hours
Diclofenac Sodium	Bilayer dual-release	HPMC K4M, EC, sodium alginate	Diffusion-controlled + erosion	Rapid initial release + sustained 12-hr release; reduced gastric irritation
Glipizide	Biphasic matrix tablet	HPMC (multiple grades), ethylcellulose, MCC	Diffusion + controlled erosion	IR: ≤30% in 30 min; SR: linear release for 8–10 hours
Amlodipine Besylate + Atenolol	Bilayer FDC (IR + SR)	HPMC, sodium CMC, EC, SSG	Atenolol: slow release via matrix diffusion; Amlodipine: IR disintegration	Combination dual-release; compatible PK targets
Caffeine (model drug)	Bilayer model for mechanistic study	Carbomer + HPMC blends	Polymer synergy causing swelling + erosion	Distinct dual-phase release; polymer ratio controlled transition point

7. Advantages

Dual-phase extended-release tablets offer a compelling array of advantages across pharmacokinetic, clinical, and patient-centric domains, alongside significant manufacturing flexibility. These benefits collectively underscore why these formulations are a major focus in modern drug delivery.

7.1. Pharmacokinetic Benefits

One of the most significant advantages of dual-phase systems lies in their ability to optimize the drug's pharmacokinetic profile. By providing both an immediate and a sustained release component, these tablets achieve lower fluctuations in plasma concentration. This is crucial as it allows for the avoidance of high peaks in drug concentration that are often linked to toxicity and undesirable side effects. Simultaneously, they prevent sub-therapeutic troughs, which can lead to therapy failure if drug levels fall below the minimum effective concentration. This precise control over drug levels ensures that the drug remains within the therapeutic window for an extended period, leading to more consistent and effective treatment[51,52].

7.2. Clinical Benefits

From a clinical perspective, dual-phase tablets deliver substantial improvements in patient care. They enable a rapid therapeutic response due to the immediate-release portion, which is critical for conditions requiring quick symptomatic relief or intervention. This initial effect is then seamlessly followed by a precisely controlled maintenance phase, ensuring that the therapeutic benefits are sustained over many hours. This controlled delivery can also lead to a potential reduction in side effects, as drug concentrations are kept within an optimal range, mitigating dose-related adverse reactions that might occur with less controlled release profiles[53,54].

7.3. Patient-Centric Benefits

The design of dual-phase tablets brings considerable advantages for the patient experience. By consolidating both immediate and extended release into a single dosage unit, they lead to a reduced pill burden. This simplification of the medication regimen directly contributes to improved adherence, as patients are more likely to comply with treatments that require less frequent administration. The convenience of once- or twice-daily dosing significantly enhances patient quality of life, making it easier to integrate medication into daily routines and reducing the likelihood of missed doses[55-58].

7.4. Manufacturing & Formulation Flexibility

Dual-phase tablets also provide considerable flexibility in manufacturing and formulation. For instance, in bilayer tablet designs, the separation of layers allows for the incorporation of incompatible active pharmaceutical ingredients or excipients into the same tablet, preventing potential chemical interactions that could compromise stability or efficacy. Furthermore, this modular design offers the capacity to precisely tailor the desired release profile for each component, enabling drug developers to fine-tune the pharmacokinetics to meet specific therapeutic needs. This adaptability makes dual-phase systems a powerful tool for developing complex and optimized drug products[59,60].

8. Limitations & Challenges

Despite their significant advantages, dual-phase extended-release tablets present several notable limitations and challenges that require careful consideration during development and manufacturing. A primary concern is mechanical integrity, with layer separation being a major issue, often stemming from differing compression requirements between layers, poor interfacial bonding, and uneven particle size distribution of the materials used in each layer [61,62]. Furthermore, the manufacturing process is inherently complex, demanding specialized equipment such as advanced bilayer tablet presses, stringent quality control measures, and often tailored granulation processes to ensure consistency and quality. Predicting the release kinetics of these systems can also be difficult, particularly when complex polymer interactions occur or when swelling and erosion rates differ significantly between the immediate and sustained-release layers. Lastly, regulatory challenges are prominent; establishing robust In-vitro/In-vivo Correlation can be demanding, proving stability across all layers is essential, and comprehensive bioequivalence studies are often required for each distinct release phase to gain regulatory approval[63-65].

9. Future Perspectives

Dual-phase extended-release tablets are poised for continued evolution, driven by advancements in materials science, computational tools, and manufacturing technologies. Future developments will likely center around smart polymers capable of dynamic environmental response, allowing for highly precise and adaptive drug release tailored to physiological conditions. The integration of improved in-silico dissolution modeling will enhance the predictability of drug release kinetics, thereby streamlining formulation development and reducing the need for extensive *in vitro* and *in vivo* testing[66]. The advent of 3D printing offers revolutionary

potential for creating customizable therapies, enabling the design of complex tablet geometries and drug loading patterns that can be personalized for individual patient needs. Furthermore, the scope of dual-phase systems is expanding to include sophisticated combination products, such as those incorporating nutraceuticals, probiotics, or even peptides, offering synergistic therapeutic benefits within a single dosage form. The rise of digital manufacturing techniques will also pave the way for patient-specific dosing, where tablets can be manufactured on demand with precise drug quantities and release profiles optimized for each patient. As the demand for drugs that provide both rapid onset and sustained effect continues to grow, these advanced dual-phase systems are expected to become increasingly important in modern pharmacotherapy, pushing the boundaries of oral drug delivery[67-70].

10. Conclusion

Dual-phase extended-release tablets stand as a testament to the sophistication and ingenuity within oral drug delivery, representing a highly advanced strategy that seamlessly integrates the most advantageous features of both immediate-release and sustained-release systems into a single dosage form. This synergistic combination allows for an initial, rapid therapeutic onset, crucial for addressing acute symptoms or achieving immediate pharmacological effects, followed by a prolonged and controlled drug action that maintains stable plasma concentrations over an extended period. This unique capability makes them exceptionally valuable across a broad spectrum of therapeutic classes, from analgesics requiring quick pain relief and sustained comfort, to cardiovascular and antidiabetic agents demanding consistent, long-term therapeutic levels.

Despite the undeniable advantages, the development and manufacturing of dual-phase tablets are not without their inherent challenges. Significant hurdles include ensuring robust mechanical stability, particularly concerning layer adhesion in bilayer systems, navigating complex polymer compatibility issues, and overcoming the overall manufacturing complexity associated with producing multi-layered or multi-phasic dosage forms with consistent quality and performance. However, the pharmaceutical industry is actively addressing these challenges through continuous innovation. Advances in materials science are yielding novel excipients and polymers with enhanced functional properties, while the adoption of quality-by-design approaches is leading to more systematic and robust formulation development processes. Furthermore, emerging technologies such as 3D printing are revolutionizing the field by offering unprecedented precision and customization capabilities, rapidly improving the feasibility and overall performance of these complex drug delivery systems.

Looking ahead, dual-phase extended-release tablets are undeniably poised to play a major and increasingly pivotal role in future pharmaceutical development. Their capacity to enhance patient compliance through reduced dosing frequency, to deliver better therapeutic outcomes by optimizing pharmacokinetic profiles, and to offer greater formulation flexibility for a diverse range of active pharmaceutical ingredients underscores their importance. As the demand for patient-centric and highly effective drug delivery solutions continues to grow, dual-phase ER tablets will remain at the forefront of innovation, continuously pushing the boundaries of modern pharmacotherapy.

References

1. Atre P, Rizvi SAA. Advances in Oral Solid Drug Delivery Systems: Quality by Design Approach in Development of Controlled Release Tablets. BioChem 2025;5:9. https://doi.org/10.3390/biochem5020009.
2. Desrosiers A, Derbali RM, Hassine S, Berdugo J, Long V, Lauzon D, et al. Programmable self-regulated molecular buffers for precise sustained drug delivery. Nature Communications 2022;13. https://doi.org/10.1038/s41467-022-33491-7.
3. Uthman BM. Extended-release Antiepilepsy Drugs—Review of the Effects of Once-daily Dosing on Tolerability, Effectiveness, Adherence, Quality of Life, and Patient Preference. Touch Reviews in Neurology 2014;10:30. https://doi.org/10.17925/usn.2014.10.01.30.
4. Wheless JW, Phelps SJ. A Clinician's Guide to Oral Extended-Release Drug Delivery Systems in Epilepsy. The Journal of Pediatric Pharmacology and Therapeutics 2018;23:277. https://doi.org/10.5863/1551-6776-23.4.277.
5. Siegel SJ. Extended release drug delivery strategies in psychiatry: theory to practice. PubMed 2005;2:22.
6. Mzoughi J. Smart rolled-up capsules for drug release control. HAL (Le Centre Pour La Communication Scientifique Directe) 2022.
7. Serajuddin ATM. Challenges, current status and emerging strategies in the development of rapidly dissolving FDM 3D-printed tablets: An overview and commentary. ADMET & DMPK 2023. https://doi.org/10.5599/admet.1622.
8. Manandhar S, Sjöholm E, Bobacka J, M. Rosenholm J, K. Bansal K. Polymer-Drug Conjugates as Nanotheranostic Agents. Journal of Nanotheranostics 2021;2:63. https://doi.org/10.3390/jnt2010005.
9. Al-Thani AN, Jan AG, Abbas M, Geetha M, Sadasivuni KK. Nanoparticles in cancer theragnostic and drug delivery: A comprehensive

review. Life Sciences 2024;352:122899. https://doi.org/10.1016/j.lfs.2024.122899.
10. Maiti S, Sen KK. Advanced Technology for Delivering Therapeutics. 2017. https://doi.org/10.5772/62564.
11. Neeraj B, Kumar A, Abhilash C, Rubia C, Rajni B, Sai S. A review on immediate release drug delivery system. 2014.
12. Lopes CM, Lobo JMS, Pinto JF, Costa P. Compressed matrix core tablet as a quick/slow dual-component delivery system containing ibuprofen. AAPS PharmSciTech 2007;8. https://doi.org/10.1208/pt0803076.
13. Singh MC, Ranawat LS. To establish bioequivalence of 50mg Metoprolol Succinate extended release tablets in normal, healthy, adult, human subject under fasting condition. Journal of Drug Delivery and Therapeutics 2021;11:48. https://doi.org/10.22270/jddt.v11i1.4497.
14. Parashar AK, Tyagi LK, Sethi VA, Bansal K. Advanced nanotheranostics: Evolving strategies in cancer therapy and diagnosis. ijnrph. 2025;1–9. Available from: http://dx.doi.org/10.61554/ijnrph.v3i1.2025.170
15. Loftus J, Yaworsky A, Roland CL, Turner-Bowker DM, McLafferty M, Su S, et al. Experience of switching from a daily to a less frequent administration of injection treatments. PLoS ONE 2022;17. https://doi.org/10.1371/journal.pone.0278293.
16. Arroyo-Currás N, Ortega G, Copp D, Ploense KL, Plaxco ZA, Kippin TE, et al. High-Precision Control of Plasma Drug Levels Using Feedback-Controlled Dosing. ACS Pharmacology & Translational Science 2018;1:110. https://doi.org/10.1021/acsptsci.8b00033.
17. Minichmayr IK, Mizuno T, Goswami S, Peck R, Polasek TM. Recent Advances Addressing the Challenges of Precision Dosing. Clinical Pharmacology & Therapeutics 2024;116:527. https://doi.org/10.1002/cpt.3365.
18. Lee W, Yu P, Hong M, Widjaja E, Loo SCJ. Designing multilayered particulate systems for tunable drug release profiles. Acta Biomaterialia 2012;8:2271. https://doi.org/10.1016/j.actbio.2012.02.007.
19. Jain PK, Parashar AK, Shrivastava V. A review on exploring the health benefits and antioxidant properties of bioactive polyphenols. Discov Food. 2025;5(1). Available from: http://dx.doi.org/10.1007/s44187-025-00637-7
20. Pei J, Yan Y, Palanisamy CP, Jayaraman S, Natarajan PM, Umapathy VR, et al. Materials-based drug delivery approaches: Recent advances and future perspectives. Green Processing and Synthesis 2024;13. https://doi.org/10.1515/gps-2023-0094.
21. Curti C, Kirby D, Russell C. Current formulation approaches in design and development of solid oral dosage forms through three-dimensional printing. Progress in Additive Manufacturing 2020;5:111. https://doi.org/10.1007/s40964-020-00127-5.
22. Subramanian M, Sankar C, Rajaram G, Ravi V. Layered Tablets: A Novel Oral Solid Dosage Form. IntechOpen eBooks, IntechOpen; 2022. https://doi.org/10.5772/intechopen.108702.
23. Hwang K-M, Cho C-H, Lee S-H, Kim J, Park E. Preformulation and evaluation of multi-layer tablets. Journal of Pharmaceutical Investigation 2024;54:161. https://doi.org/10.1007/s40005-024-00673-y.
24. Parashar AK, Saini K, Sethi VA, Gupta C. A review on current challenges and emerging therapies in psoriasis management. Rev Recent Clin Trials. 2025;20. Available from: http://dx.doi.org/10.2174/0115748871393960250912053926
25. Pujari NM. Bilayer Tablet Technology: A Concept Of Immediate And Controlled Drug Delivery. Journal of Pharmaceutical Negative Results 2023:503. https://doi.org/10.47750/pnr.2023.14.s01.59.
26. Olsson M, Storm RS, Björn L, Lilja V, Krupnik L, Chen Y, et al. Phase-separated polymer blends for controlled drug delivery by tuning morphology. Communications Materials 2024;5. https://doi.org/10.1038/s43246-024-00678-y.
27. Nyamweya N. Applications of polymer blends in drug delivery. Future Journal of Pharmaceutical Sciences 2021;7. https://doi.org/10.1186/s43094-020-00167-2.
28. Current Update of Clinical Therapeutic Strategies for Colon-Targeted Delivery Systems. Pharmaceutical Sciences and Research 2024;11. https://doi.org/10.7454/psr.v11i1.1360.
29. Sowmya PS, DP V, Nayek S. Pulsatile drug delivery system: a formulation approach for treatment of diseases. International Journal of Current Pharmaceutical Research 2020:16. https://doi.org/10.22159/ijcpr.2020v12i3.38328.
30. Jain N, Jain N, Parashar AK. Liposome as antigen delivery system: Isolation, preparation, characterization. ijnrph. 2025;51–60. Available from: http://dx.doi.org/10.61554/ijnrph.v3i1.2025.139
31. Vitthal DA, Deokar S, Singh S. A Comprehensive Review On Osmotically Controlled Oral Drug Delivery System. Journal of Emerging Technologies and Innovative Research 2020;7.
32. Almoshari Y. Osmotic Pump Drug Delivery Systems—A Comprehensive Review.

Pharmaceuticals 2022;15:1430. https://doi.org/10.3390/ph15111430.

33. Madaan R, Bala R, Zandu SK, Singh I. Formulation and characterization of fast dissolving tablets using salvia hispanica (chia seed) mucilage as superdisintegrant. ACTA Pharmaceutica Sciencia 2020;58:69. https://doi.org/10.23893/1307-2080.aps.05805.
34. Shete MB, Saraogi GK, Parashar AK. Dengue fever: A comprehensive review of diagnosis and management. Antiinfect Agents. 2025;24. Available from: http://dx.doi.org/10.2174/0122113525366277250306072415
35. Dash GS, Murthy PN, Chowdary KA. Selection and optimization of most efficient superdisintegrant for the formulation of dispersible tablets of tramadol hydrochloride. International Journal of Pharmacy and Pharmaceutical Sciences 2022:21. https://doi.org/10.22159/ijpps.2022v14i7.43638.
36. Liechty WB, Kryscio DR, Slaughter BV, Peppas NA. Polymers for Drug Delivery Systems. Annual Review of Chemical and Biomolecular Engineering 2010;1:149. https://doi.org/10.1146/annurev-chembioeng-073009-100847.
37. Parashar AK, Hardenia A, Dwivedi SK, Saraogi GK, Hardenia S. Next-generation nucleic acid delivery: A review of nanobiosystem design and applications. Curr Gene Ther. 2025;25. Available from: http://dx.doi.org/10.2174/0115665232367377250519114910
38. Prajapat P, Agrawal D, Bhaduka G. A brief overview of sustained released drug delivery system. Journal of Applied Pharmaceutical Research 2022;10:5. https://doi.org/10.18231/j.joapr.2022.10.3.5.11.
39. Kumaravelrajan R. Asian Journal of Pharmaceutics 2016;10. https://doi.org/10.22377/ajp.v10i04.895.
40. Razavi SM, Scicolone JV, Snee RD, Kumar A, Bertels J, Cappuyns P, et al. Prediction of tablet weight variability in continuous manufacturing. International Journal of Pharmaceutics 2019;575:118727. https://doi.org/10.1016/j.ijpharm.2019.118727.
41. Bassetto R, Amadio E, Ciampanelli F, Perin S, Ilari P, Gaballo P, et al. Designing an effective dissolution test for bilayer tablets tailored for optimal melatonin release in sleep disorder management. Frontiers in Nutrition 2024;11. https://doi.org/10.3389/fnut.2024.1394330.
42. Gulati P, Chandila V, Parashar AK, Sethi VA. A review on advancements in lipid-based nanoparticles for vaccine adjuvant and antigen delivery. ijnrph. 2024;26–34. Available from: http://dx.doi.org/10.61554/ijnrph.v2i2.2024.128
43. Vyshnavi K, Sinduja Y, Adeyemi PG, Ebuka AD, Srija M, Sushma G. A Review Article on Dissolution Studies in Novel Drug Delivery System. Journal of Drug Delivery and Therapeutics 2022;12:220. https://doi.org/10.22270/jddt.v12i3.5337.
44. Bredael G, Liang S, Hahn DA. A Strategy for Quality Control Dissolution Method Development for Immediate-Release Solid Oral Dosage Forms. Dissolution Technologies 2015;22:10. https://doi.org/10.14227/dt220315p10.
45. Marroum P. Role of In Vitro–In Vivo Correlations in Drug Development. Dissolution Technologies 2015;22:50. https://doi.org/10.14227/dt220215p50.
46. Patel RS, Patel A. In vivo–In Vitro correlation (IVIVC) in drug development: bridging preclinical and clinical outcomes for regulatory approvals. World Journal of Advanced Research and Reviews 2024;22:2311. https://doi.org/10.30574/wjarr.2024.22.2.1197.
47. Sareen T, Parashar AK, Tyagi LK. Exploring the unique role of albumin as a carrier in nanomedicine-based drug delivery. ijnrph. 2024;129–37. Available from: http://dx.doi.org/10.61554/ijnrph.v2i2.2024.127
48. Salar-Behzadi S, Corzo C, Laggner P. A Package of Established Analytical Tools to Investigate the Solid-State Alteration of Lipid-Based Excipients. Journal of Visualized Experiments 2022. https://doi.org/10.3791/63993-v.
49. Mohammed EA, Alfahad M, Qazzaz ME. Solid dispersion: application and limitations. Journal of Drug Delivery and Therapeutics 2024;14:222. https://doi.org/10.22270/jddt.v14i2.6410.
50. Parashar AK, Saraogi GK, Shrivastava V, Bagri R, Tyagi LK, Sethi VA, et al. Development of Angiopep-2 targeted dendrimer-based nanotheranostic system for enhanced temozolomide delivery to glioblastoma multiforme. Bull Natl Res Cent. 2025;49(1). Available from: http://dx.doi.org/10.1186/s42269-025-01309-3
51. Ameen MSM, Ibrahim N, Omar TA. Design and Evaluation of Sustained Release Bilayer Tablets of Oxcarbazepine. Journal of Pharmaceutical Innovation 2023;18:1213. https://doi.org/10.1007/s12247-022-09694-2.
52. Brigham N, Ji R, Becker ML. Degradable polymeric vehicles for postoperative pain management.

Nature Communications 2021;12. https://doi.org/10.1038/s41467-021-21438-3.
53. Brigham N, Nofsinger R, Luo X, Dreger NZ, Abel AK, Gustafson TP, et al. Controlled release of etoricoxib from poly(ester urea) films for post-operative pain management. Journal of Controlled Release 2020;329:316. https://doi.org/10.1016/j.jconrel.2020.11.052.
54. Sharma K, Parashar AK, Saraogi GK. Solubility enhancement of BCS-class II drug resveratrol using solid dispersion. ijnrph. 2025;184–94. Available from: http://dx.doi.org/10.61554/ijnrph.v3i1.2025.166
55. Jo SD, Ku SH, Won Y, Kim SH, Kwon IC. Targeted Nanotheranostics for Future Personalized Medicine: Recent Progress in Cancer Therapy. Theranostics 2016;6:1362. https://doi.org/10.7150/thno.15335.
56. Vrettos N-N, Roberts CJ, Zhu Z. Gastroretentive Technologies in Tandem with Controlled-Release Strategies: A Potent Answer to Oral Drug Bioavailability and Patient Compliance Implications. Pharmaceutics 2021;13:1591. https://doi.org/10.3390/pharmaceutics13101591.
57. Ghanem M, Ashmawy SM, Maghraby GME. Intestinal Absorption Site-Guided Development and Evaluation of Oral Disintegrating Controlled Release Tablets of Mirabegron. AAPS PharmSciTech 2024;25:167. https://doi.org/10.1208/s12249-024-02865-z.
58. Gupta C, Sahu GK, Parashar AK, Singh K, Bukke SPN, Udom GJ. Novel curcumin floating tablets for spatial delivery in peptic ulcer. Biomed Res Int. 2025;2025(1):6622146. Available from: http://dx.doi.org/10.1155/bmri/6622146
59. Rahmani S, Park T-H, Dishman AF, Lahann J. Multimodal delivery of irinotecan from microparticles with two distinct compartments. Journal of Controlled Release 2013;172:239. https://doi.org/10.1016/j.jconrel.2013.08.017.
60. Abdellatif AAH. Microparticles Formulation as a Targeting Drug Delivery System. Journal of Nanomedicine Research 2017;6. https://doi.org/10.15406/jnmr.2017.06.00151.
61. Anusha A, Ponnekanti K, Tiwari R, Swapna LA, Hussain MM, Siddhardha A. A review of medicines with sustained release. World Journal of Biology Pharmacy and Health Sciences 2023;13:221. https://doi.org/10.30574/wjbphs.2023.13.3.0141.
62. Parashar AK. Synthesis and characterization of ligand anchored poly propyleneiminedendrimers for the treatment of brain glioma. J Med Pharm Allied Sci. 2021;10(3):2784–9. Available from: http://dx.doi.org/10.22270/jmpas.v10i3.1084
63. Durieux P, Trinquart L, Colombet I, Niès J, Walton R, Rajeswaran A, et al. Computerized advice on drug dosage to improve prescribing practice. Cochrane Database of Systematic Reviews 2008. https://doi.org/10.1002/14651858.cd002894.pub2.
64. Sanjay ST, Dou M, Fu G, Xu F, Li X. Controlled Drug Delivery Using Microdevices. Current Pharmaceutical Biotechnology 2016;17:772. https://doi.org/10.2174/1389201017666160127110440.
65. Jain N, Jain N, Parashar AK. Design and development of biosynthetic copper nanoparticles for skin diseases. ijnrph. 2025;200–6. Available from: http://dx.doi.org/10.61554/ijnrph.v3i1.2025.143
66. Sadosky A, Srivastava K, Arora A, Kataria A, Cappelleri, Peterson AM. Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis. Patient Preference and Adherence 2013:419. https://doi.org/10.2147/ppa.s44646.
67. Mohan RP, Gupta RA. Design, Development and Evaluation of Gastroretentive Drug Delivery System of Antacids. Journal of Drug Delivery and Therapeutics 2022;12:55. https://doi.org/10.22270/jddt.v12i6-s.5706.
68. Fernandes EAF, Oudtshoorn JV, Tam A, González LCA, Aurela EG, Potthast H, et al. The bioequivalence study design recommendations for immediate-release solid oral dosage forms in the international pharmaceutical regulators programme participating regulators and organisations: differences and commonalities. Journal of Pharmacy & Pharmaceutical Sciences 2024;27:12398. https://doi.org/10.3389/jpps.2024.12398.
69. Hornick T, Mao C, Koynov A, Yawman PD, Thool P, Salish K, et al. In silico formulation optimization and particle engineering of pharmaceutical products using a generative artificial intelligence structure synthesis method. Nature Communications 2024;15:9622. https://doi.org/10.1038/s41467-024-54011-9.
70. Alqahtani AS. Topical Drug Delivery in Oral Mucosal Diseases: Challenges, Carriers, and Innovations: A Comprehensive Review. Biomedical & Pharmacology Journal 2025;18:1835. https://doi.org/10.13005/bpj/3218.