Available online on 15.07.2026 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Review Article

Multiparticulate Dual-Release Combination Tablets: A Promising Approach for Chronomodulated and Patient -Centric Drug Delivery

Prerona Das [1]*, Jyoti Gupta [1], Rambabu Sharma [2]

[1] Department of Pharmacy, IEC University, Baddi, Himachal Pradesh, India

[2] Department of Pharmacy, Himalayan Institute of Pharmacy, Kala-Amb, Himachal Pradesh, India

Article Info:

Article History:

Received 30 April 2026
Reviewed 29 May 2026
Accepted 24 June 2026
Published 15 July 2026

Cite this article as:

Das P, Gupta J, Sharma R, Multiparticulate Dual-Release Combination Tablets: A Promising Approach for Chronomodulated and Patient -Centric Drug Delivery, Journal of Drug Delivery and Therapeutics. 2026; 16(7):285-291
DOI: https://doi.org/10.22270/jddt.v16i7.7893

For Correspondence:

Prerona Das, Department of Pharmacy, IEC University, Baddi, Himachal Pradesh, India.

Abstract

Multiparticulate dual-release combination tablets represent an advanced drug delivery platform designed to optimize therapeutic outcomes and enhance patient compliance by synchronizing drug release with the body's circadian rhythms. These systems incorporate both immediate-release (IR) and controlled/modified-release (CR/MR) components within a single dosage form, ensuring a rapid onset of action followed by sustained drug release over an extended period. This dual functionality is particularly beneficial in managing chronic and time-dependent diseases such as hypertension, asthma, and arthritis, where symptom severity varies throughout the day. Typically, these formulations employ multiparticulate technologies such as pellets, granules, or mini-tablets, which are either filled into capsules or compressed into tablets. Such approaches provide several advantages, including uniform drug distribution, reduced risk of dose dumping, improved gastrointestinal transit, and flexible modulation of release profiles. Various formulation strategies—such as polymer coating, extrusion-spheronization, and compression coating—are used to achieve the desired release kinetics. Evaluation of these systems involves parameters like flow properties, hardness, friability, drug content, dissolution studies, and stability testing to ensure consistent performance and product quality. Importantly, multiparticulate dual-release systems offer patient-centric benefits, including reduced dosing frequency, minimized side effects, and improved adherence to therapy. With ongoing advancements in novel polymers and drug delivery technologies, these systems hold significant promise for chronotherapeutic applications and personalized medicine, paving the way for more effective and targeted treatment strategies .

Keywords: Multiparticulate system, Dual release tablet, Immediate release, Sustained release, Diltiazem hydrochloride, Hydrochlorothiazide, Combination therapy.

1. Introduction

Oral drug delivery remains the most preferred route due to ease of administration and patient compliance. However, conventional dosage forms fail to address circadian variations in disease conditions[1]. Chemotherapeutic systems are designed to align drug release with biological rhythms, thereby improving therapeutic efficacy and minimizing adverse effects [2,3]. Multi particulate drug delivery systems, such as pellets and mini-tablets, offer advantages including predictable gastric emptying, reduced variability, and minimized risk of dose dumping compared to single-unit systems[4]. The integration of dual-release mechanisms further enhances therapeutic performance. The Following Diagram Figure.1 shows the comprehensive significance of multi-particulate drug delivery system.

Examples of marketed preparation of different pharmaceutical companies are given in Table 1.

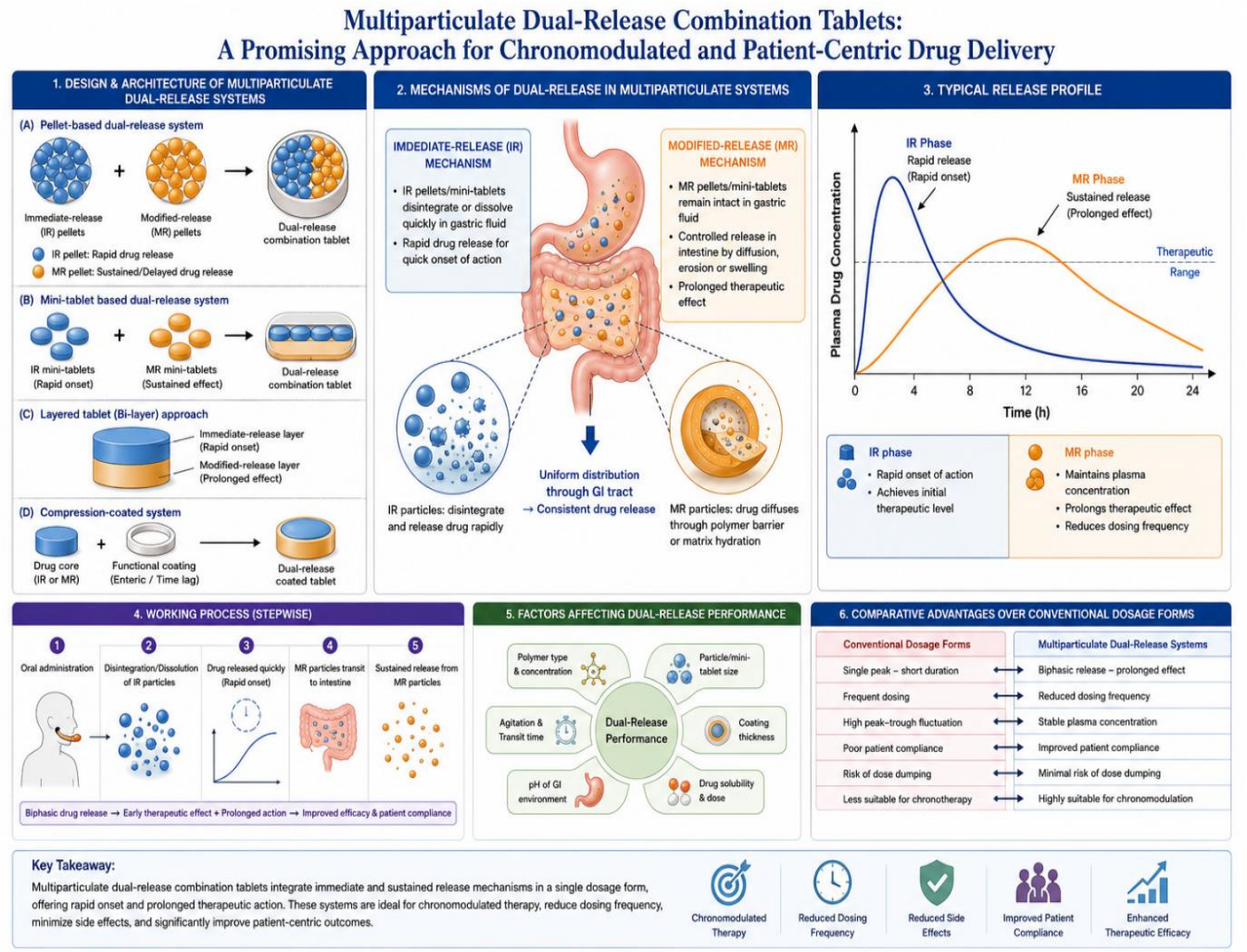

Figure 1: A comprehensive significance of multi-particulate drug delivery system.

Table 1: Marketed preparation of different pharmaceutical companies[5-10]

Drug / Combination	Therapeutic Use	Dosage Form / Technology	Release Pattern	Marketed / Research Status
Metformin HCl (IR + SR)	Type 2 Diabetes	Bilayer tablet / multiparticulate matrix	Immediate + sustained release	Marketed (e.g., Glucophage XR variants)
Amlodipine + Atenolol	Hypertension	Bilayer / pellet-based system	Rapid onset + prolonged effect	Marketed combination
Tramadol HCl	Pain management	Dual-release tablet (IR + ER)	Biphasic release	Marketed (e.g., Ultram ER)
Diclofenac Sodium	Anti-inflammatory	Pellet-filled capsule / tablet	Immediate + delayed release	Marketed (enteric-coated pellets)
Verapamil HCl	Hypertension	Chronotherapeutic coated pellets	Delayed + sustained release	Marketed (Covera-HS)
Theophylline	Asthma / COPD	Pellet-based sustained system	Pulsatile / sustained release	Marketed formulations
Ramipril + Hydrochlorothiazide	Hypertension	Bilayer tablet	Immediate + sustained release	Marketed
Glimepiride + Metformin	Diabetes	Bilayer / multiparticulate tablet	Rapid + prolonged hypoglycemic effect	Marketed
Pantoprazole + Domperidone	GERD	Capsule with IR + enteric pellets	Immediate + delayed release	Marketed
Aspirin (IR + enteric)	Cardioprotection	Compression-coated tablet	Immediate + delayed intestinal release	Marketed

2. Concept of Dual-Release Multiparticulate Systems

The significance of dual-release systems are as follows:

- Immediate drug release for rapid onset
- Sustained or delayed release for prolonged action

These systems can be developed by combining differently coated multiparticulates or blending IR and MR units into a single tablet[11]. Such designs enable precise control over drug release kinetics.

3. Rationale for Chronomodulated Drug Delivery

Biological rhythms regulate physiological functions, affecting drug pharmacokinetics and disease progression. Conditions such as asthma, hypertension, and arthritis exhibit circadian patterns in symptom severity[12-14]. Chronotherapeutic drug delivery aims to synchronize drug release with these rhythms, ensuring drug availability at the time of maximum need, thereby improving efficacy and reducing toxicity[15-17].

4. Advantages of Multiparticulate Dual-Release Tablets

- Reduced dose dumping risk
- Uniform distribution in gastrointestinal tract
- Improved bioavailability
- Reduced inter- and intra-subject variability
- Enhanced patient compliance
- Flexible drug release profiles[18]

These systems are particularly beneficial for chronic diseases requiring time-dependent therapy.

5. Formulation Strategies

5.1 Pellet-Based Systems

Pellet-based multiparticulate systems are widely utilized due to their excellent control over drug release characteristics. Pellets are typically prepared by techniques such as extrusion–spheronization, powder layering, or solution/suspension layering onto inert cores. These methods produce spherical units with uniform size distribution, which can be subsequently coated with functional polymers to achieve immediate or modified drug release. The application of polymeric coatings allows precise modulation of drug release through mechanisms such as diffusion and erosion, making pellet systems highly suitable for dual-release and chronomodulated drug delivery[19-20].

5.2 Mini-Tablets

Mini-tablets, usually ranging from 1 to 3 mm in diameter, offer significant advantages in terms of dose uniformity, flexibility, and reproducibility. These small-sized tablets can be filled into capsules or compressed into a larger tablet to create multiparticulate systems. By combining mini-tablets with different release profiles—such as immediate-release and sustained-release units—a dual-release system can be effectively achieved. Their uniform geometry and ease of coating further enhance their suitability for controlled and chronotherapeutic drug delivery applications[21,22].

5.3 Layered Tablets

Layered tablet systems, including bilayer and multilayer tablets, are designed to incorporate two or more distinct layers within a single dosage form. Typically, one layer provides immediate drug release for rapid onset of action, while the other layer ensures sustained or controlled drug release over an extended period. This physical separation of drug components allows for better control of release kinetics and minimizes drug–drug interactions, making layered tablets a practical approach for combination therapy and dual-release formulations[23,24].

5.4 Compression-Coated Systems

Compression-coated tablets, also known as press-coated tablets, consist of an inner core surrounded by an outer coating layer formed by compression rather than solvent-based coating. This technique is particularly useful for achieving delayed, pulsatile, or site-specific drug release. The outer layer acts as a barrier that controls the lag time before drug release from the core, enabling synchronization of drug delivery with circadian rhythms. Such systems are extensively explored in chronotherapeutic applications where time-dependent drug release is critical[25,26].

6. Polymers Used in Multiparticulate Dual-Release Systems**

Polymers play a critical role in designing multiparticulate dual-release systems by controlling drug release kinetics through mechanisms such as swelling, diffusion, erosion, and pH-dependent solubility. Selection of appropriate polymers is essential to achieve both immediate-release (IR) and modified-release (MR) phases within a single dosage form[27,28].

Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), Carbopol, and polyethylene oxide (PEO) are widely used in sustained-release formulations. These polymers hydrate upon contact with gastrointestinal fluids, forming a gel layer that regulates drug diffusion and erosion, thereby prolonging drug release[29,30]. HPMC is particularly preferred due to its reproducibility, safety, and versatility in controlling release rates.

Hydrophobic polymers including ethyl cellulose and hydrogenated castor oil, are commonly employed to retard drug release by forming water-insoluble matrices or coatings. These polymers act as diffusion barriers, slowing drug permeation and providing sustained therapeutic effects [31,32].

pH-dependent (enteric) polymers, such as methacrylic acid copolymers (Eudragit L100, S100) and cellulose acetate phthalate (CAP), are extensively used for delayed or site-specific drug release. These polymers remain intact in the acidic environment of the stomach and dissolve in the higher pH of the intestine, making

them ideal for chronotherapeutic and pulsatile delivery systems[33,34].

Biodegradable polymers, including polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), and polycaprolactone (PCL), are gaining increasing attention for advanced drug delivery applications. These polymers degrade into biocompatible by-products and are particularly useful in long-term and targeted delivery systems, including chronomodulated therapies[35,36].

In addition, stimuli-responsive or smart polymers** have emerged as promising materials for chronomodulated drug delivery. These polymers respond to environmental triggers such as pH, temperature, or enzymatic activity, enabling precise control over drug release timing and location [37].

The strategic combination of different polymer classes allows the development of sophisticated dual-release multiparticulate systems capable of delivering drugs in a controlled, time-dependent manner aligned with circadian rhythms[38].

7. Evaluation Parameters

The evaluation of multiparticulate dual-release tablets is a critical step to ensure the quality, performance, and reproducibility of the formulation. These parameters are broadly categorized into pre-compression and post-compression studies, which assess the physical, mechanical, and pharmaceutical properties of the dosage form[39].

7.1 Pre-Compression Studies

Pre-compression parameters are essential for evaluating the flowability and compressibility of powder blends or granules prior to tablet formulation.

7.1.1.Flow Properties

Flow characteristics of the powder blend are evaluated using parameters such as angle of repose, Carr's index, and Hausner ratio. Good flowability ensures uniform die filling during compression, leading to consistent tablet weight and drug content uniformity. Poor flow properties may result in weight variation and content inconsistency in the final product[40].

7.1.2. Bulk Density

Bulk density and tapped density measurements provide insight into the packing ability and compressibility of the powder blend. These parameters are crucial for determining die fill volume and predicting compaction behavior, which directly influences tablet hardness and uniformity[41].

7.2 Post-Compression Studies

Post-compression evaluation ensures that the final dosage form meets pharmacopeial standards and performs as intended.

7.2.1.Hardness:

Tablet hardness, also known as crushing strength, indicates the mechanical integrity of the tablet and its ability to withstand handling, packaging, and transportation. Adequate hardness is necessary to maintain structural stability while still allowing proper disintegration and drug release[42].

7.2.1Friability:

Friability testing evaluates the tablet's resistance to abrasion and mechanical stress. It is usually expressed as percentage weight loss after tumbling in a friabilator. A friability value below 1% is generally considered acceptable, indicating sufficient mechanical strength[43].

7.2.1.Drug Content (Content Uniformity):

Drug content analysis ensures uniform distribution of the active pharmaceutical ingredient within the dosage form. It is typically determined using analytical techniques such as UV spectrophotometry or HPLC. Uniform drug content is essential for dose accuracy, therapeutic efficacy, and patient safety[44].

7.3 Dissolution Studies

Dissolution studies are essential for evaluating the rate and extent of drug release from dosage forms. They are performed using USP Apparatus I (basket) or USP Apparatus II (paddle) at 37 ± 0.5°C in suitable media such as 0.1 N HCl or phosphate buffer (pH 6.8), depending on drug properties [45]. The Figure 2 shows the release of drug delivery syetem.

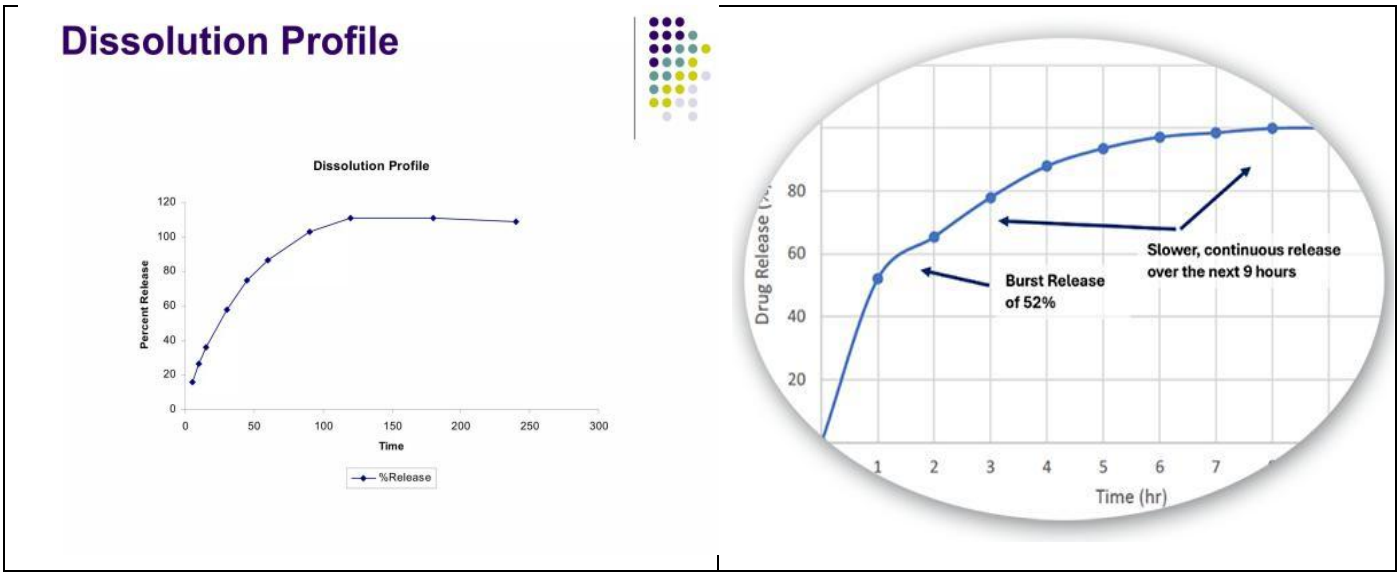

Figure 2: Dissolution pattern and release of drug delivery system.

Samples are withdrawn at predetermined intervals and analyzed using UV spectrophotometry or HPLC to determine cumulative drug release. The data are plotted as drug release versus time and fitted to kinetic models such as zero-order, first-order, and Higuchi models to understand the release mechanism[46.,47]. Dissolution testing is also important for quality control, formulation optimization, and establishing in vitro–in vivo correlation (IVIVC) [48].

7.4 Stability Studies

Stability testing ensures the robustness, safety, and efficacy of a pharmaceutical formulation under various environmental conditions. It is conducted according to regulatory guidelines (such as ICH) using accelerated conditions (e.g., 40°C ± 2°C / 75% ± 5% RH) to predict the product's shelf life in a shorter duration [49,50].

During stability studies, formulations are periodically evaluated for parameters such as physical appearance, drug content, dissolution behavior, and degradation products. These studies help identify changes caused by temperature, humidity, and light, ensuring that the product maintains its quality, purity, and performance throughout its intended storage period [51,52].

8. Applications

Multiparticulate dual-release systems are used in:

- Cardiovascular diseases
- Diabetes
- Asthma
- Rheumatoid arthritis

These diseases exhibit circadian variation, making them ideal targets for chronotherapy[53,54].

9. Challenges

- Complex manufacturing processes
- Scale-up difficulties
- Stability issues in combination formulations
- Higher production costs

Despite these challenges, technological advancements are improving feasibility[55].

10. Future Perspectives

Recent developments in chrono-tailored delivery systems and nanocarriers have enhanced the ability to deliver drugs at specific times and sites [56]. Integration with smart technologies and personalized medicine will further revolutionize this field.

11. Conclusion

Multiparticulate dual-release combination tablets represent a promising approach for chronomodulated and patient-centric drug delivery. Their ability to provide controlled, site-specific, and time-dependent drug release makes them highly valuable in modern therapeutics

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