Readers Insight
Publisher of open access books and journals
PJMLS OPEN ACCESS
Print ISSN: 2707-4471. Online ISSN: 2707-448X
Review Article
Pak-Euro Journal of Medical and Life Sciences

DOI: 10.31580/pjmls.v9i1.3460
Vol. 9 No. 1, 2026: pp. 165-182
www.readersinsight.net/pjmls
Revised: March 15 , 2026
Accepted: March 22, 2026
Submission: December 31, 2025
Published Online: March 31, 2026

MODIFIED RELEASE DRUG DELIVERY SYSTEMS: IMPACT ON PHARMACOKINETICS, THERAPEUTIC EFFICACY AND PATIENT COMPLIANCE

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Abstract
Modified Release Drug Delivery Systems (MRDDS) are significant advancements in pharmaceutical formulation, enhancing pharmacokinetic modulation and therapeutic efficacy while improving patient compliance. This review assesses literature from 2016 to 2026, highlighting that MRDDS modify drug absorption by delaying Tmax, lowering Cmax, and maintaining therapeutic drug levels, leading to better therapeutic predictability and reduced toxicity. Especially beneficial for chronic conditions like hypertension and diabetes, MRDDS support once-daily dosing, improving adherence and patient satisfaction. Although challenges in manufacturing and costs persist, innovations in nanotechnology and personalized medicine are setting the stage for enhanced controlled drug delivery, positioning MRDDS as a key strategy for optimizing long-term pharmacotherapy and improving patient-centered care.
Keywords: *Adherence, Bioavailability, Chronic disease management, Controlled release, Extended-release formulations, Modified release drug delivery systems, Patient compliance, Pharmacokinetics, Precision medicine, Therapeutic efficacy*

INTRODUCTION

EVOLUTION OF ORAL DRUG DELIVERY SYSTEMS

Oral drug delivery is preferred because it is easy to use and doesn't hurt. Traditional immediate-release forms can cause blood levels to change and side effects to get worse (1).This has led to a shift toward modified-release systems that let you better control when and how quickly the drug is released (2). IR drugs dissolve quickly, which frequently results in a short half-life, frequent dosing, and significant changes in plasma levels, all of which might exacerbate adherence and adverse effects (3, 4). Low bioavailability and poorly soluble medications are problems for conventional oral formulations (5). These restrictions are especially difficult for chronic illnesses including epilepsy, arthritis, and hypertension (6).

CONVENTIONAL IMMEDIATE-RELEASE DOSAGE FORMS

At first, the main oral dosage forms were IR tablets, capsules, and syrups that dissolve quickly and release the whole dose at once. Because of their problems, like needing to take them often, having side effects, and not sticking to the schedule, controlled, sustained, prolonged, and modified-release systems were developed over time to lower the frequency of doses and keep drug levels more stable (4).

After they are given, IR forms are made to melt and break down quickly, without slowing down or speeding up absorption (7).Syrups, pills, and capsules are some of the most common types (8). People often use super disintegrants to speed up the breakdown of fluids in the stomach and intestines helpful when you need an effect to start right away (like pain relief) (4). Pattern of Plasma Level (IR) : After each dose, the blood level quickly rises to a peak and then quickly falls, often dropping below the effective level before the next dose (8).

Fluctuating plasma drug levels: IR causes wide swings from peak to trough. The peaks may be above the therapeutic window (toxicity), and the troughs may be below it (loss of efficacy) (9). Regular dose: Because the medicine leaves the body quickly, you need to take it multiple times a day to keep it working (10). Inadequate patient compliance: Adherence is lowered by complicated, frequent regimens, particularly in chronic illnesses (9). Toxicity associated to dosage: High peaks from each IR dose might exacerbate side effects linked to concentration and, in the case of certain medications, dependency or resistance (11).

EMERGENCE, CONCEPT, AND REGULATORY FRAMEWORK OF MODIFIED-RELEASE DRUG DELIVERY SYSTEMS

Modified-release (MR) systems (sustained-, extended-, and controlled-release) were created starting around 1950 to solve IR restrictions, and they have developed across numerous "generations" (12). Keep medication levels within the therapeutic window for an extended period of time .Cut down on the number of pills and frequency of doses. Reduce peak-trough variations and associated toxicity (9).

In order to achieve therapeutic or convenience goals not possible with immediate-release (IR) products, modified-release (MR) oral medicines are designed to purposefully alter the time-course and/or site of drug release (13). Extended-release (ER) and delayed-release (DR/enteric-coated) medicines are examples of MR solid oral dose formulations (5).

MR forms are defined as those "whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms" (14). USP employs "extended-release" and "modified-release," and in monographs (e.g., USP <724>, <1088>) it provides test requirements for each (5). As long as the release pattern is purposefully changed in contrast to IR, MR also includes designs that change the release of some fast-dissolving forms and poorly water-soluble medications (6). Table I. Comparative Characteristics of Immediate-Release (IR) and Modified-Release (MR) Drug Delivery Systems. It describes how each system adjusts the time, place, or rate of medication release to maximize therapeutic results.

Table I. Comparison between Immediate-Release and Modified-Release Drug Delivery Systems

Parameter	Immediate-Release (IR)	Modified-Release (MR)	References
Drug Release Rate	Rapid release after administration	Controlled, delayed, or sustained release	(13)
Onset of Action	Quick	Slower but prolonged	(2)
Plasma Concentration	High peak (Cmax) with fluctuations	Reduced peak, stable plasma levels	(15)
Dosing Frequency	Multiple daily doses	Reduced dosing frequency	(16, 17)
Patient Compliance	Moderate	Improved	(18, 19)
Risk of Side Effects	Higher (due to peak concentration)	Lower (controlled plasma levels)	(20)
Therapeutic Control	Limited	Optimized and sustained	(21)

METHODOLOGY

The systematic review was performed by employing the PRISMA-guided narrative review technique. An extensive search was performed for peer-reviewed scientific articles published during the period from January 2015 through January 2025 from the PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar electronic databases. "Modified release drug delivery systems," "controlled release," "pharmacokinetics," "active targeting," "therapeutic efficacy," and " bioavailability" were some search terms that have been employed by combining the Boolean logic.

An extensive literature search was performed for peer-reviewed scientific articles published between January 2016 and January 2026 using electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The following search terms were used in various combinations with Boolean operators (AND, OR): "Modified Release Drug Delivery System," "Sustained Release," "Controlled Release," "Extended Release," "Pharmacokinetics," "Therapeutic Efficacy," "Patient Compliance," and "Drug Delivery Technology. "All identified records were imported into a reference management system, and duplicate articles were removed prior to screening.

A total of 1,284 records were initially identified. After removal of 252 duplicate records, 1,032 articles were screened by title and abstract. Following screening, 214 full-text articles were assessed for eligibility. Finally, 96 studies met the inclusion criteria and were included in the qualitative synthesis. Due to heterogeneity in drug classes, formulation strategies, outcome parameters, and study designs, a quantitative meta-analysis was not performed. Instead, a qualitative narrative synthesis approach was adopted. The detailed study selection process, including database search, removal of duplicates, screening, eligibility assessment, and final inclusion of studies, is illustrated in Fig. 1.

INCLUSION AND EXCLUSION CRITERIA

Peer-reviewed original research articles, systematic reviews, or clinical studies published between 2016 and 2026 were included in this review. Modified-release formulations, such as sustained-release, controlled-release, extended-release, or delayed-release systems, were the subject of eligible investigations. Studies assessing patient compliance, safety profiles, therapeutic efficacy, or pharmacokinetic factors related to modified-release drug delivery systems were also taken into consideration for inclusion.

Studies that were published in languages other than English, conference abstracts, editorials, commentary, or non-peer-reviewed journals were not included. Additionally, articles that only discussed immediate-release formulations devoid of any modified-release mechanism were not included. Additionally, this analysis did not take into account papers that were published before 2016.

EXAMINE THE SELECTION AND SCREENING PROCEDURE

PRISMA guidelines were followed in selecting the study for the review. Every study entry that was obtained from the databases had to be imported, and duplicate articles had to be removed. The procedure also included independently evaluating the abstracts and titles to ensure they were relevant to the review's objective in order to avoid duplication. The full-text articles that were selected for evaluation used the inclusion and exclusion criteria, and the authors reached a consensus on any conflicts that might have arisen, particularly with regard to the selection of papers for assessment.

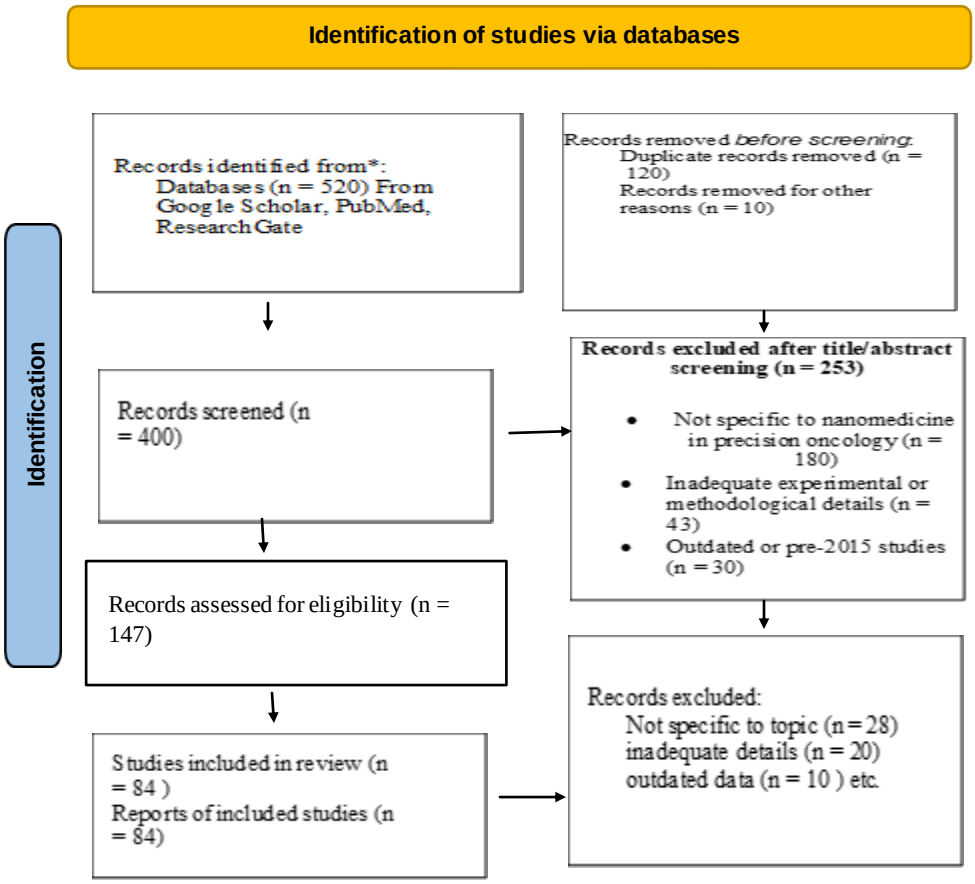

Fig. 1. Steps involved in choosing a study, such as database searches, eliminating duplicate and ineligible records, determining eligibility, and adding the studies to the systematic review

COMPARISON BETWEEN IMMEDIATE-RELEASE AND MODIFIED-RELEASE DRUG DELIVERY SYSTEMS

Immediate-release (IR) formulations are designed to disintegrate and release the drug rapidly after administration, resulting in quick onset but significant plasma concentration fluctuations and frequent dosing requirements (22). In contrast, modified-release (MR) formulations intentionally alter the rate, time, or site of drug release to prolong therapeutic levels, reduce dosing frequency, and minimize peak-trough variations. Therefore, while IR emphasizes rapid therapeutic action, MR systems focus on pharmacokinetic optimization and long-term therapeutic stability (22).

Fig. 2 illustrates Comparison of immediate-release, sustained-release, and zero-order drug delivery systems showing plasma drug concentration–time profiles and release kinetics. Modified-release formulations maintain plasma drug concentration within the therapeutic window for prolonged periods while minimizing peak–trough fluctuations and toxic effects.(23).

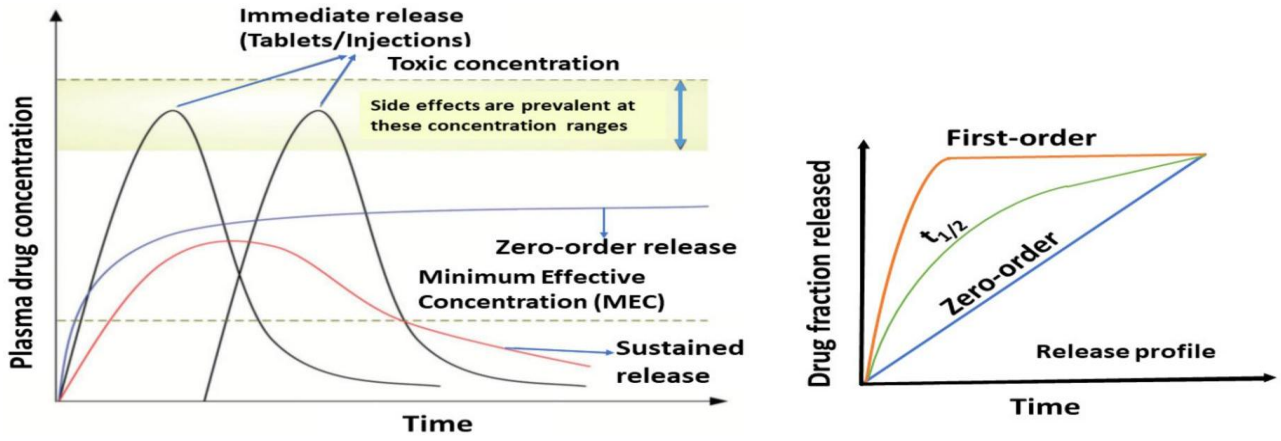

Fig. 2. Illustrates Comparison of immediate-release, sustained-release, and zero-order drug delivery systems showing plasma drug concentration–time profiles and release kinetics. Modified-release formulations maintain plasma drug concentration within the therapeutic window for prolonged periods while minimizing peak–trough fluctuations and toxic effects [*Adapted from Narayan R et al., 2018* (24)]

EVOLUTION, CLASSIFICATION, AND TECHNOLOGICAL ADVANCEMENTS IN MODIFIED-RELEASE DRUG DELIVERY SYSTEMS

The goals of sustained, extended, and controlled release (SR/ER/CR) are to minimize peak-trough fluctuations, lower dosage frequency, and sustain therapeutic levels for longer (25). Hydrophilic matrices, reservoir/osmotic systems, mucoadhesive and pH-dependent systems, multiparticulates, nanofibers, and lipid or nanoemulsion systems are among the designs (2).

By flattening concentration profiles, ER/SR formulations for NSAIDs and epilepsy lessen pill load and may reduce side effects (1). Alginate, hydrophilic matrices, and other modified polymers provide customized erosion-based release, swelling, and diffusion (16). Short GI transit and local pH/barriers are addressed via floating, mucoadhesive, unfoldable, and colon-targeted systems (26). Accurate, patient-centered release profiles are made possible via hot-melt extrusion, 3D printing, electrospinning, and quality by design (27).

BIOPHARMACEUTICAL AND PHARMACOKINETIC FOUNDATIONS OF MODIFIED-RELEASE DRUG DELIVERY SYSTEMS

MR systems are created by aligning the drug's release from the dosage form with the body's processes of absorption, distribution, metabolism, and elimination (ADME). Concentrations in the therapeutic window are maintained for as long as necessary without toxicity by a well-designed MR (28, 29). Oral MR shapes the input rate into systemic circulation by altering the location and pace at which the medication becomes available in the GI tract.For MR, GI transit duration, regional permeability, and food/pH effects are crucial, particularly for extended-release drugs (30, 31).

The amount of medication in plasma required for action is determined by volume of distribution and tissue binding; in order to sustain goal levels, MR input must match these disposition characteristics (32, 33).Steady-state concentrations are determined by intestinal and hepatic metabolism (clearance) as well as input rate; when metabolism is rapid, MR can smooth exposure and lessen peak-driven negative effects (34). The length of time a drug remains in the body is determined by its elimination half-life and clearance. MR is most helpful for medications with short half-lives or for lowering fluctuations in medications with long half-lives (35).

BIO PHARMACEUTICS CLASSIFICATION SYSTEM (BCS), THERAPEUTIC WINDOW, DRUG HALF-LIFE AND FIRST-PASS METABOLISM CONSIDERATIONS IN MODIFIED-RELEASE DRUG DELIVERY SYSTEMS

Biopharmaceutics Classification System (BCS) categorizes drugs based on solubility and permeability, affecting their absorption and overall therapeutic efficacy. The therapeutic window refers to the range of drug doses that provide effective treatment without causing toxicity. Drug half-life is crucial for determining dosing frequency and duration of action. First-pass metabolism significantly impacts the bioavailability of orally administered drugs, necessitating careful consideration in the design of modified-release drug delivery systems to optimize therapeutic outcomes(30). MR seeks to minimize peak-trough variation and maintain concentrations within the therapeutic window, particularly for medications having a narrow therapeutic index (32, 36). To prevent sub-therapeutic intervals between doses for medications with short half-lives, regulated input is required; PK-based models are employed to create such profiles (35, 37).

In order to prevent excessive presystemic loss while preserving exposure, MR must take into account where in the GI tract the medication is delivered and how slowly, as significant first-pass metabolism reduces systemic bioavailability (29). Whether delayed or extended release will increase or harm overall bioavailability depends on regional permeability and enzyme expression (stomach vs. gut vs. colon) (31).

THE THERAPEUTIC AND SOCIOECONOMIC RATIONALE FOR MODIFIED-RELEASE SYSTEMS

Modified-release (MR) systems are designed to optimize how a drug works in the body by smoothing exposure over time, reducing dosing burden, and improving real-world use. Their rationale spans clinical, patient, and economic benefits (4).The goal of MR systems is to improve the management of chronic conditions like rheumatoid arthritis and epilepsy by maintaining drug levels within the therapeutic window for a longer period of time (38, 39).Controlled or extended-release designs can enhance symptom control and better align with circadian or illness cycles (e.g., hydrocortisone for adrenal insufficiency, melatonin for sleep) (40, 41). By improving targeting and bioavailability, advanced DDS can increase drug at the site of action and boost efficacy (29).

MR formulations can reduce peak-related toxicity, tolerance, dependency, or resistance (e.g., opioids, some antibiotics) by minimizing peak-trough variations (11). When compared to immediate-release (IR) formulations, modified-release hydrocortisone and tacrolimus may reduce some side effects (42).Compared to IR, MR pills usually enable a minimum two-fold decrease in dose frequency. This schematic Fig. 3 illustrates summarizes the clinical and therapeutic rationale for developing modified-release drug delivery systems, highlighting improved efficacy, reduced toxicity, enhanced patient adherence, and prolonged maintenance of drug concentrations within the therapeutic window(43). It features a multi-layered capsule in the center surrounded by annotated icons and graphs that highlight the advantages for patients, clinicians, and the economy. Antiepileptic's and tofacitinib are examples of once-daily MR formulations that simplify regimens and lessen pill load (13, 39).

Fig. 3. Rationale for the development of modified-release drug delivery systems. Modified-release formulations are designed to maintain therapeutic drug concentrations for extended periods, reduce dosing frequency, minimize adverse effects and plasma concentration fluctuations, improve patient compliance, and enhance overall therapeutic outcomes *[Adapted from Adepu and Ramakrishna 2021 (43)]*

SOCIOECONOMIC IMPACTS: ENHANCING PATIENT ADHERENCE AND REDUCING HEALTHCARE COSTS

Treatment failure is largely caused by poor adherence, which is directly improved by DDS that lessen adverse effects and dosage frequency. Compared to multiple-daily IR regimens, once-daily MR products are linked to higher adherence for chronic illnesses like hypertension, RA, and epilepsy (44). Hospitalizations, complications, and overall healthcare expenses can all be decreased with improved adherence and more consistent control (45). Large system-level savings could result from even modest increases in pharmaceutical use brought on by simpler DDS. In many sectors, cost-effectiveness assessments are still required to weigh downstream savings against increased formulation costs (46).

CLASSIFICATION OF MODIFIED RELEASE DRUG DELIVERY SYSTEMS

The primary way that modified release systems regulate drug release—by encasing the drug in a matrix, encasing it in a membrane, employing osmotic pressure, or changing the GI residence or mode of administration—is how they are categorized (47, 48).

MATRIX SYSTEMS

The drug is evenly distributed within a polymer/lipid "block," and it is released through erosion and/or diffusion (49). Make use of swellable polymers, such as carbopol, natural gums, and cellulose derivatives. They swell and create a gel layer when they come into contact with GI fluids; the medicine is released by diffusion through and erosion of this gel (50, 51). The first oral extended-release platform (such as plastic matrices or wax/fat) Between insoluble polymers or waxes (such as fatty alcohols, waxes, and ethylcellulose), the drug diffuses through channels filled with water (48). A rate-controlling polymer covering envelops a drug core, and release happens via diffusion via this membrane (52). Common in some transdermal/implantable systems, coated pellets, and multi-layer tablets (53).

OSMOTIC PUMP SYSTEMS

Drug and osmogen-containing tablet or implant core covered in a semi-permeable membrane with one or more tiny holes (54). The classification of Modified Release Drug Delivery Systems, such as Reservoir systems (drug core with rate-controlling membrane), Matrix systems (drug dispersed in polymer matrix), Osmotic systems (semi-permeable membrane with laser-drilled orifice), and Ion-exchange systems (drug bound to resin), with labeled cross-sectional diagrams and drug release vs. time, is shown in Fig. 4. Osmosis allows water to enter, creating pressure that forces medication solution or suspension out at a roughly zero-order rate that is mostly unaffected by GI hydrodynamics and pH (55, 56). The Fig. 4 outlines a two-compartment osmotic controlled-release drug delivery system. It consists of a rigid tablet capsule divided by a flexible partition, with an osmotic agent in Compartment 1 (push layer) and the active drug in Compartment 2 (pull layer). When gastrointestinal fluids enter Compartment 1 via a semi-permeable

membrane, the osmotic agent swells, generating pressure that compresses Compartment 2, thereby expelling the drug through a laser-drilled orifice at a constant rate, following zero-order kinetics (43).

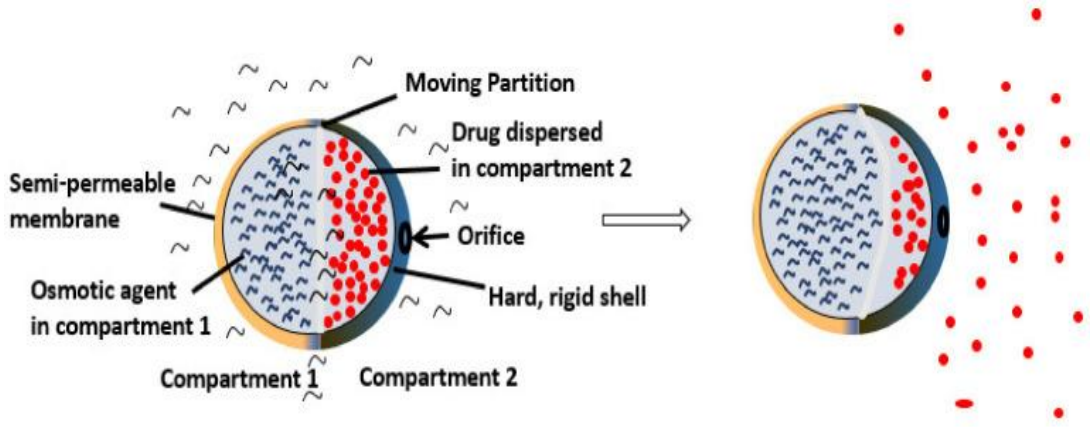

Fig. 4. Schematic illustration of a push-pull osmotic pump (PPOP) drug delivery system, showing water influx expanding the osmotic compartment to steadily push the drug formulation out through a laser-drilled delivery orifice *[Adapted from Adepu and Ramakrishna 2021(43)]*

MULTIPARTICULATE SYSTEMS

The several MR system types, such as: Matrix systems (drug distributed in a polymer matrix), many tiny units, such as pellets, mini-tablets, and beads, are frequently compacted into tablets or put into capsules. Each unit can be reservoir-coated or matrix-type, which reduces the possibility of dose dumping and allows for customizable and repeatable release profiles (52, 53).

GASTRORETENTIVE DRUG DELIVERY SYSTEMS

This system designed to increase the absorption of medications with limited upper-GI "absorption windows" by extending gastric residency. Methods include expandable devices, mucoadhesive, and floating systems (57). For local illnesses or delayed systemic absorption, strive for site-specific release in the colon.Techniques: time-dependent systems, pH-dependent coatings, and polysaccharide-based multiparticulates broken down by colonic enzymes.

TRANSDERMAL AND IMPLANTABLE MODIFIED RELEASE SYSTEMS

Transdermal patches are medication administered via the skin in a matrix or reservoir with a rate-controlling membrane or adhesive (56).Implantable systems include intrauterine devices, parenteral depots (such as PLGA-based microspheres) for long-term regulated release in chronic treatment, and biodegradable or non-biodegradable implants.

MECHANISMS OF MODIFIED RELEASE AND THEIR IMPACT ON PHARMACOKINETIC PROFILES

Modified release systems regulate the rate and mode of medication release from the dose form. Although a number of fundamental processes frequently work simultaneously, one is typically "rate-controlling" (8). Through a polymer membrane or matrix, the drug travels from a high concentration area (within the matrix or reservoir) to a low concentration area (the surrounding fluid) (58). The drug is either encased in a semi-permeable membrane or distributed in an insoluble matrix (12). Fick's rules of diffusion control release rate, which is influenced by drug diffusivity, matrix porosity, and route length (58).

Drug and/or polymer dissolution is the rate-limiting step in this case (59).Water permeates, the substance dissolves, and the drug is released when the drug is in a slowly dissolving matrix or covered with a slowly dissolving membrane (30).Controlled by the dissolving layer's thickness, porosity, wettability, and solubility (16). The medicine diffuses via the enlarged network once the polymer swells and becomes rubbery due to water penetration. Cross-link density, ionic strength, and polymer hydrophilicity all affect swelling (60).When the polymer breaks down or erodes, the medication is released through pores. Can entail surface or bulk erosion; frequently significant in nanoparticles and biodegradable implants (59).

Osmotic pressure forces the drug solution or suspension out through an aperture at a roughly constant pace after water passes through a semipermeable membrane into a core containing the medication and osmogen (61). "Smart" systems in which pH, temperature, enzymes, ions, or other stimuli cause or speed up release(62), for examples of triggers include localized heat, GI pH variations, acidic tumor pH, and certain enzymes (63-65). Impact of modified release on pharmacokinetics is In contrast to immediate-release (IR) dose forms, modified-release (MR) and sustained/extended-release (SR/ER) dosage forms are intended to alter the rate and duration of a drug's appearance in the blood. They seek to extend the action, smooth out plasma levels, and occasionally enhance absorption and adherence (8, 30).

INFLUENCE ON CMAX, TMAX AND AUC

Modified-release systems primarily alter Cmax and Tmax while maintaining comparable or improved AUC. Their major pharmacokinetic advantage lies in reducing plasma fluctuation index and maintaining concentrations within the therapeutic window, thereby enhancing safety and therapeutic predictability. Modified-release systems employ different mechanisms to regulate drug release and optimize pharmacokinetic behavior. The major classifications, mechanisms of release, key characteristics, and examples of modified-release drug delivery systems are summarized in Table II. (66, 67).

Table II. Classification and mechanisms of modified-release drug delivery systems

Type of MRDDS	Mechanism of drug release	Key features	Examples	References
Matrix System	Drug dispersed in polymer matrix	Diffusion-controlled release	Hydrophilic matrix tablets	(68)
Reservoir System	Drug core surrounded by membrane	Membrane-controlled release	Coated tablets	(69)
Osmotic System	Osmotic pressure-driven release	Zero-order release kinetics	Osmotic pump tablets	(70)
Ion-Exchange System	Drug-resin complex exchange	pH-dependent release	Ion-exchange resins	(71)
Multiparticulate System	Pellets or beads in capsule	Uniform GI distribution	Sustained-release capsules	(72)

STABILIZATION OF STEADY-STATE PLASMA CONCENTRATIONS

Semaglutide MR: 24-hour controlled release decreased variability and fluctuations in plasma concentration MR is specifically used to reduce peak-trough swings and maintain more stable levels ER/DR FDA-approved products typically show a decrease in degree of fluctuation vs. IR; even when fluctuation increased, they still provided benefits like reduced dosing frequency Compared to other formulations, tacrolimus LCPT and some MR antiepileptics shown less intraday volatility (73).

MR formulations assist maintain concentrations within the therapeutic window for extended periods of time by extending the input rate (often approximating zero-order or slow release) (23). In order to enable steady-state maintenance with fewer doses, once-daily ER/DR medications are usually formulated so that dissolution length matches dosing interval (e.g., 24-hour dissolution for 24-hour dosing) (74). Formulations with greater Cmax can still have a larger fluctuation index, although variations in Tmax may not be as clinically significant at steady state. With reduced Cmax and extended release, hydrogels and long-acting systems can sustain drug exposure (AUC) many times greater over time (74).

BIOAVAILABILITY AND BIOEQUIVALENCE DYNAMICS IN MODIFIED-RELEASE SYSTEMS

Increased bioavailability is by prolonging residence time and regulating release, MR can improve absorption for poorly soluble or permeable medications (semaglutide MR had approximately 2.4 times greater relative bioavailability vs. solution, for example).AUC was around five times greater for several hydrogels than for solutions (67, 74). Reduced bioavailability **is** Due to slower and insufficient absorption, ER/MR acetaminophen exhibited reduced bioavailability compared to IR in overdose/very high dosages (AUC <80% and <70% of IR for ER and MR) (75). Bioequivalency focus on GI physiology and food can

drastically change the bioavailability of MR products by altering dissolution, transit, and solubilization (76). Many MR products are designed so that AUC and Cmax fall within 80–125% of reference; this is common for MR antiepileptics, metformin MR, dexamphetamine MR and others (77-79).

CLINICAL SIGNIFICANCE OF MODIFIED RELEASE SYSTEMS

Extended-release (ER) and modified-release (MR) systems regulate the rate and timing of medication delivery. They are particularly helpful in chronic illnesses when higher adherence, fewer dosages, and stable blood levels are essential. Hypertension **occur** When compared to immediate-release (IR) formulations, MR diuretics such indapamide MR exhibit comparable overall cardiovascular protection and mortality; prolonged treatment may marginally lower cardiovascular events (mostly myocardial infarction), but results require validation (44). The goals of MR systems for additional antihypertensives, such as furosemide in sericin/alginate beads, include fewer daily dosages, smoother, delayed diuresis, and less adverse effects (44).

Diabetes in order to improve glucose management and flexibility, insulin formulations have been developed into rapid-, intermediate-, and long-acting forms that mirror natural basal and meal-related insulin patterns (80). In animals, glucose-responsive long-acting insulin complexes may keep blood sugar levels close to normal for around a week. They only release more insulin when glucose levels are high, which lowers the risk of hypoglycemia(81).

Epilepsy is ER oral antiepileptic medications (AEDs) can enhance seizure control, adverse-effect profile, adherence, quality of life, and costs while lowering peak-trough blood level variations and pill load (4). Similar to commercial controlled-release solutions, modified-release carbamazepine matrices offer regulated, sustained doses. Nowadays, MR once-daily AEDs are widely used and frequently chosen by patients (82, 83).

Psychiatric Disorders is Long-term treatment is necessary for chronic mental diseases; evaluations of chronic disease delivery point to long-acting injectable (LAI) formulations that lower dosage frequency, although real-world adherence can still be inconsistent (84).

CHRONOTHERAPEUTIC APPLICATIONS

Drug release is timed by chronotherapeutic devices to correspond with the circadian cycles of disease activity. Timed release can decrease toxicity and increase effectiveness if symptoms change over a 24-hour period (85). For instance: Customized timing for Addison's disease is made possible by a 3D-printed programmable delayed-release container that releases hydrocortisone after predetermined lag durations (12–28 hours) (86). Many MR designs are based on chronotherapeutic theory, which states that drug release is "programmed" in time rather than at constant levels (87).

PEDIATRIC AND GERIATRIC CONSIDERATIONS

ER oral formulations are used for epilepsy in people of all ages; smoother levels and fewer daily doses are beneficial when missing doses can quickly result in seizures, particularly in youngsters and elderly persons (4). Many older persons are included in large real-world hypertension cohorts utilizing MR vs. IR indapamide; overall efficacy is comparable, but adherence and persistence have a significant impact on results. In order to enhance compliance in groups that struggle with complex regimens, such as elderly and chronically sick patients, reviews of innovative DDS include a strong emphasis on patient-friendly methods (once-daily, long-acting, or transdermal) (88, 89).

MODIFIED RELEASE SYSTEMS AND PATIENT COMPLIANCE

Systems with modified or sustained release (MR/SR/ER) are intended to release medication gradually, maintain stable blood levels, and minimize the frequency of dosages that patients must take. This can help individuals feel better in their day-to-day lives and directly addresses frequent reasons why people do not take their medications as directed (6, 90).

Important obstacles, particularly with chronic illness:

- Conventional immediate-release pills must be taken often (3–4×/day). decreases adherence (6).
- Poor adherence and significant health and financial costs are caused by complicated regimens, pill burden, side effects, and delayed commencement (1, 11).
- Prior to switching to prolonged-release tacrolimus, non-adherence to immunosuppressants was widespread among liver transplant recipients (91).

Impact of dosing frequency on compliance is by lowering the frequency of doses, sustained/extended-release oral formulations (as well as long-acting injectables and transdermal patches) increase adherence and durability. One-weekly oral dose almost quadrupled the likelihood of adherence compared to once-daily dosing, according to a meta-analysis (92). Extended-release use in real life Extended-release users exhibited greater 2-year adherence across 15 chronic medications (MPR 57.8% vs. 49.6%) (93). Over a ten-year period, once-daily prolonged-release tacrolimus significantly decreased missed doses and timing mistakes. Metformin ER increased adherence and satisfaction while reducing the number of tablets and adverse effects (94, 95).

Quality of Life Improvements by Sustained-release pills can lessen the burden of therapy and medical expenses by reducing night or multiple daily dosages and maintaining more consistent levels (1). 76.2% of patients who switched to prolonged-release tacrolimus reported higher quality of life and greater adherence. Transdermal patches and long-acting oral or injectable systems are emphasized as means to promote general welfare, reduce everyday reminders of sickness, and make managing chronic diseases easier (96, 97).

CURRENT CHALLENGES AND RESEARCH GAPS

Although extended-release and modified-release (MR) systems have many advantages, they are not yet entirely compatible with individualized therapy, have safety issues such dosage dumping, and are technically challenging. More and more research is concentrated on safer performance, more intelligent design, and regulatory frameworks that can accommodate more customized, adaptable goods.

Manufacturing complexities are intricate materials and designs: To achieve predictable release, advanced MR systems (polymer matrices, implants, 3D-printed tablets, liposomes and nanosystems) need exact control over polymers, shape, and processing; important challenges include scale-up, batch-to-batch consistency, and excipient management (97). New fabrication methods Although they provide customizable release, new manufacturing techniques including microfabrication, powder-bed and FDM 3D printing, and lithography have drawbacks such fragility, low resolution, nozzle clogging, a limited number of printable polymers, and high cost (98). Throughput/scale-up While many oral delivery and microencapsulation methods are effective in the lab, they have poor throughput and are challenging to scale up for commercial use (11).

Dose Dumping Risks are Alcohol-induced dose dumping (AIDD) are Hydro alcoholic media can damage polymer matrices or coatings, releasing the entire dosage quickly. This is particularly risky for opioids and medications with a narrow therapeutic index (73). In vitro testing in up to 40% ethanol is currently required by regulations; many ER capsules exhibit AIDD, while other tablets are more resistant (99). Alcohol-resistant system design is still difficult, and there aren't many genuinely reliable formulations (100, 101).

NAVIGATING REGULATORY CHALLENGES AND THE SHIFT TOWARD PERSONALIZED THERAPEUTICS

Varying nations have varying dissolving settings and similarity standards for MR goods, which results in complicated and ineffective post-approval modification and registration procedures (102). Additionally, complex MR and sophisticated DDS are subject to additional scrutiny on quality by design (QbD), modeling, and consistency, which the industry occasionally perceives as resource-intensive and unclearly rewarded (103).Since existing systems authorize preset strengths rather than dosage ranges, regulatory avenues for on-demand individualized doses (such as 3D-printed PDDS) remain uncertain (104). There is a considerable drive toward patient-specific customizable release since traditional "one-size-fits-all" MR cannot accommodate individual circadian cycles, pharmacogenomics, or changing illness conditions

(105)Programmable implants and reservoir systems with adjustable microstructures that can provide patient-specific release patterns spanning days to months are examples of emerging technologies (106, 107).Although GMP-compliant printers, new materials, and new regulatory frameworks are needed, integrating PDDS with digital health (sensors, applications, and smart tracers) might result in feedback-controlled dosage (104).

IMPACT AND CLINICAL SIGNIFICANCE OF MODIFIED RELEASE DRUG DELIVERY SYSTEMS

Pharmacokinetics, therapeutic outcomes, and patient adherence are all greatly impacted by modified-release drug delivery methods (8, 23).The main areas where MRDDS (Modified Release Drug Delivery Systems) and immediate-release versions diverge are in the profiles of absorption, distribution, and elimination. MRDDS enables controlled or prolonged release, which leads to longer half-lives in the body, longer exposure times, and lower peak concentrations. Pharmacokinetic (PK), pharmacokinetic-pharmacodynamic (PK-PD), and physiologically-based pharmacokinetic (PBPK) models are used to comprehend these intricate release processes (28). By predicting the impacts on biophase and systemic bioavailability, these models aid in figuring out how much medication reaches the intended tissues (108-110).MRDDS enhances safety and efficacy by lowering variations in plasma concentration and keeping medication levels within the therapeutic window (17, 111). Drug release precision has been further improved by technological developments such as polymer science, osmotic systems, and multiparticulate formulations (112, 113).MR systems offer significant clinical benefits in the therapy of chronic diseases, despite formulation complexity and increased manufacturing costs (108, 114).

Based on recent research (2016–2026), this study attempts to provide a thorough summary of how Modified Release Drug Delivery Systems (MRDDS) affect pharmacokinetics, therapeutic efficacy, and patient compliance. Additionally, it aims to critically assess modified-release systems' technological developments, clinical applicability, and prospects for long-term medication optimization.

RESULT

The analysis of 96 studies from 2016 to 2026 indicates that Modified Release Drug Delivery Systems (MRDDS) offer significant benefits over immediate-release formulations. These advantages include improved pharmacokinetics, better therapeutic outcomes, and enhanced patient compliance due to features like delayed T_max, smoother C_max and reduced peak-trough fluctuations. MRDDS enhance bioavailability and maintain plasma concentrations within therapeutic ranges, particularly beneficial for chronic disease management. The once-daily dosing of MRDDS also boosts medication adherence and satisfaction, especially in elderly patients and those requiring long-term therapy.

DISCUSSION

By maintaining plasma drug concentrations within the therapeutic window and reducing peak–trough variations, Modified Release Drug Delivery Systems (MRDDS) offer substantial clinical and pharmacological benefits over traditional immediate-release formulations. MR systems reduce the likelihood of dose-related toxicity and breakthrough symptoms while preserving equivalent total drug exposure by lowering fast absorption peaks (C_max) and avoiding subtherapeutic trough levels. In chronic illnesses including hypertension, epilepsy, and pain disorders, where ongoing medication exposure is crucial for the best possible disease management, these pharmacokinetic advancements result in improved therapeutic predictability. Additionally, by streamlining treatment plans, lowering pill load, and improving convenience, MR formulations' lower dose frequency increases patient adherence. MRDDS not only enhances pharmacokinetic performance but also improves real-world treatment results since drug adherence is closely associated with therapeutic effectiveness and lower healthcare expenditures. All of the data points to MR technology as a successful tactic for enhancing patient-centered treatment and long-term clinical management.

CONCLUSION

By improving pharmacokinetics, increasing therapeutic efficacy, and dramatically increasing patient compliance, modified release drug delivery devices have revolutionized pharmacological therapy. Maintaining ideal plasma levels, minimizing side effects, and addressing the crucial problem of adherence are all made possible by prolonged management of drug administration. Despite several difficulties, MRDDS has an enormously good overall impact, especially for chronic conditions needing long-term therapy.

Challenges and limitations:

Modified Release Drug Delivery Systems (MRDDS) offer therapeutic benefits but encounter challenges that may hinder their implementation. Complex formulations, such as matrix tablets and osmotic pumps, require precise control over various parameters, complicating scale-up and quality assurance. The necessity for specialized equipment and thorough in vitro–in vivo correlation studies contributes to longer development times and higher costs, especially in resource-limited contexts. Physiological variability among individuals, including gastrointestinal differences, and strict regulatory demands add further complexity. Thus, while MRDDS have significant clinical advantages, successful application depends on careful optimization of formulation design and regulatory compliance.

Limitations of the review:

There are various restrictions on this review. First, there may be linguistic prejudice because only English-language articles were considered. Second, only papers published between 2016 and 2026 were included in the review, which may have left out important previous fundamental research. Third, generalizability to low- and middle-income healthcare settings may be limited because most of the included researches were from high-income nations. Lastly, no quantitative meta-analysis was carried out because of the methodological heterogeneity among the investigations, and the conclusions are based on qualitative synthesis.

Future perspectives:

The future of Modified Release Drug Delivery Systems (MRDDS) will benefit from advancements in nanotechnology, personalized medicine, and regulatory science. Nanocarrier platforms like polymeric nanoparticles and lipid-based carriers allow for precise drug release, enhancing targeted delivery while reducing systemic toxicity. The use of biodegradable polymers and implantable devices is directing MR applications toward targeted injectable therapies. Advances in pharmacogenomics and AI modeling contribute to personalized release profiles. New regulatory frameworks adopting quality-by-design and real-world evidence approaches are facilitating the approval of these innovative systems. The synergy of biotechnology, materials science, and computational pharmacology promises to revolutionize MRDDS for improved, patient-centered treatments.

Acknowledgment:

Through this study we wish to acknowledge our organization, Jinnah Sindh Medical University, Karachi, which has always motivated and supported in the whole journey of this research.

Conflict of interest:

There are no conflicts of interest for the authors.

Authors' contribution:

HA & AN Conceived the idea and designed the structure of the review; NW Analyzed recent literature; AS Data compilation, referencing and critical revision of the draft; MN & MK Literature review.

Declaration of generative AI and AI-assisted technologies in the writing process:

While the article was being prepared, the authors used Chat GPT to make it easier to read. The authors accepted full responsibility.

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