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Modified Release Does Not Guarantee Predictable Exposure Across Food States, Gastrointestinal Physiology, Dosage-Form Failure, and Patient Variability

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ABSTRACT

Modified-release oral dosage forms are designed to control the timing, rate, or anatomical location of drug liberation, but control of release does not automatically confer equivalent control of systemic exposure. The relationship becomes conditional when formulation behavior interacts with food, gastrointestinal transit, luminal pH and fluid dynamics, regional absorptive capacity, dosage-form integrity, presystemic disposition, and patient-specific physiology. This Perspective examines those interactions by separating mechanisms that are often compressed into the single category of "modified release." Hydrophilic matrices, osmotic systems, enteric or delayed-release constructs, and multiparticulate formulations possess different dependencies and therefore different failure signatures. Food may alter exposure through several simultaneous processes, including gastric residence, luminal composition, bile-mediated solubilization, intestinal fluid redistribution, regional delivery, and metabolic or transporter effects. Exposure may also diverge from intended release when a formulation reaches intestinal regions with lower effective absorptive capacity, when release is altered by an administration vehicle or alcohol-containing medium, or when aging, gastrointestinal surgery, comorbidity, interacting medicines, or within-subject physiological variation changes the absorption environment. These observations support a mechanism-sensitive interpretation of modified-release performance in which exposure predictability must be demonstrated for the relevant combination of dosage-form behavior, physiological state, and patient context. Biopredictive dissolution, physiologically based biopharmaceutics modeling, and virtual bioequivalence can help discriminate competing explanations when their assumptions and validation ranges are explicit. Predictable exposure is therefore an evidence-supported property of a product under defined conditions rather than an intrinsic consequence of assigning a modified-release mechanism.

Keywords: Modified-release formulations, Food effect, Gastrointestinal physiology, Regional absorption, Dose dumping, Physiologically based biopharmaceutics modeling

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Introduction

Modified-release (MR) dosage forms alter the temporal or spatial liberation of drug relative to conventional immediate-release products. The category includes systems whose controlling processes differ substantially, including matrices, coated products, osmotic systems, delayed-release units, and multiparticulate preparations. Consequently, the bioavailability and bioequivalence questions surrounding MR products are inherently product sensitive [1]. Biopharmaceutical performance may depend on release mechanism, regional intestinal permeability, gastrointestinal pH, food intake, manufacturing attributes, and other formulation-specific variables [2]. A

controlled release profile should therefore be understood as one determinant of systemic drug input rather than as a complete description of the exposure process.

The physiological environment receiving that released drug is variable. Gastric emptying, intestinal transit, gastrointestinal fluids, luminal composition, intestinal permeability, disease, age, and other sources of physiological heterogeneity can alter oral absorption [3]. Some variables change between patients, whereas others change within the same patient across occasions. These sources of variability matter particularly when release is prolonged sufficiently for drug liberation to extend across physiologically different gastrointestinal regions.

Food-effect evidence illustrates the resulting heterogeneity. In a retrospective evaluation of 136 US-approved extended-release (ER) products, food increased systemic exposure for 31 products, decreased exposure for 6, and left AUC essentially unchanged for 99 [4]. The predominance of unchanged exposure argues against treating food as an inevitable destabilizer, while the bidirectional effects among affected products argue against a single fed-state mechanism. Regional absorption provides one important explanation. Mechanistic modeling of ER products has shown that colon absorption can be represented with useful accuracy in drugs with low or moderate distal absorption limitation, whereas prediction becomes substantially more difficult when colonic uptake strongly constrains exposure [5]. Release control and exposure control consequently coincide only when formulation performance and downstream absorption remain compatible.

This Perspective addresses the question: Which formulation, physiological, and patient factors break the assumed mapping between modified-release design and predictable systemic exposure? The analysis separates platform-specific release behavior, dosage-form integrity, meal-dependent physiology, luminal conditions, regional absorption, disposition, and patient variability. The objective is not to argue that MR products are intrinsically unpredictable. It is to identify the circumstances in which predictability must be demonstrated rather than inferred from the existence of a release-control mechanism.

Release mechanism determines which variables can destabilize exposure

The vulnerabilities of an MR product begin with the physical process used to control release. Hydrophilic matrices rely on hydration, swelling, diffusion, erosion, or combinations of these processes, so dissolution conditions capable of distinguishing relevant changes in matrix behavior are essential. For potassium chloride ER matrix tablets, standard compendial conditions were insufficient to establish a useful in vitro–in vivo relationship until release conditions were modified to provide discriminatory performance across formulations with different release rates [6]. The implication is narrower than a general criticism of compendial dissolution: a test can be suitable for routine quality control while remaining insufficient for predicting the physiological consequences of a particular release mechanism.

Osmotically controlled systems illustrate a different dependency. Paliperidone ER formulated using an osmotic release system showed regionally distributed absorption, and physiologically based absorption modeling indicated substantial differences between fed and fasted conditions [7]. Upadacitinib MR provides another example in which the interpretation of intestinal and colonic drug input depended strongly on the dissolution method used to parameterize the mechanistic model [8]. Together, these cases show that a formulation can impose controlled release while the resulting systemic exposure remains sensitive to the region in which drug is liberated and to whether the in vitro release representation captures in vivo-relevant conditions.

A third distinction is that changing the release profile does not remove variability generated elsewhere in the pharmacokinetic system. Tacrolimus illustrates this particularly clearly because formulation-specific absorption is superimposed on substantial effects of metabolism, genotype, drug interactions, and a narrow therapeutic index [9]. Modified-release tacrolimus products can provide clinically useful alternative exposure profiles, but reformulation does not eliminate the contribution of patient-specific metabolic and pharmacological determinants. The practical consequence is that “MR formulation” is too broad to function as a mechanistic exposure category. The relevant question is which process controls release in the specific product and which gastrointestinal or patient variables can interfere with that process or with the absorption of the released drug.

Dosage-form integrity and platform-specific failure

Predictability can be lost more abruptly when the dosage form no longer preserves the structural or functional characteristics required for intended release. Alcohol-induced dose dumping is one such failure mode. In sodium-alginate matrix tablets, exposure to high ethanol concentrations produced rapid drug liberation under particular formulation and medium conditions, while increasing the viscosity of the matrix polymer reduced the effect [10].

The finding is formulation specific and does not establish that ordinary alcohol exposure universally causes dose dumping. It demonstrates that matrix integrity can be conditionally defeated and that the vulnerability depends on material properties as well as the external medium.

Administration conditions can also compromise release before the dosage form encounters the physiological environment for which it was designed. Pantoprazole delayed-release sprinkle granules exposed to different food vehicles showed that vehicle pH and duration of contact can influence premature release and chemical stability [11]. Such interactions are distinct from classical postprandial food effects. The relevant failure occurs at the interface between administration practice and the dosage form, before broader meal-induced changes in gastrointestinal physiology become the dominant consideration.

The reverse situation is equally important: formulation architecture can protect against a defined mechanism of failure. Enteric coating of tablets containing an amorphous solid dispersion of delamanid reduced gastric crystallization and preserved subsequent in vitro release under physiologically relevant conditions [12]. Protection was therefore achieved by preventing a specific adverse interaction between the drug-rich formulation state and the gastric environment. This does not imply universal elimination of food or pH sensitivity; it shows that robustness can be engineered when the vulnerable mechanism is known.

Across these examples, structural failure, premature release, and successful protection cannot be treated as equivalent expressions of a generic "formulation effect." Their causes differ by platform. The same external condition may have little consequence for one release mechanism yet fundamentally disrupt another.

The platform-specific relationships are summarized in **Table 1**.

Table 1. Platform-specific vulnerabilities that can uncouple intended release from systemic exposure

Modified-release platform or configuration	Principal release-control feature	Critical gastrointestinal or administration dependency	Representative failure or perturbation	Plausible exposure consequence
Hydrophilic matrix	Hydration, swelling, diffusion, erosion	Medium composition, ionic environment, alcohol exposure, matrix viscosity	Accelerated erosion or disintegration; altered discriminatory release behavior	Faster or slower drug input than intended; potential peak-exposure change
Osmotically controlled tablet	Water-driven osmotic delivery through engineered membrane/orifice	Regional residence, fed-state gastrointestinal conditions, downstream absorptive capacity	Intended release persists while regional absorption changes	Altered fraction absorbed despite preserved release-control mechanism
HPMC-based extended-release matrix	Controlled matrix hydration and diffusion	Dissolution environment, intestinal transit, distal intestinal conditions	In vitro release method misrepresents regional in vivo input	Incorrect prediction of intestinal or colonic exposure
Enteric or delayed-release coated system	Suppression of gastric release followed by intestinal liberation	Gastric pH, coating integrity, food-vehicle contact, intestinal triggering conditions	Premature release, drug degradation, or failure to protect formulation state	Earlier-than-intended input, reduced available dose, or altered peak timing
Multiparticulate sprinkle formulation	Distributed coated units intended to resist gastric conditions	Vehicle composition and duration of pre-administration contact	Partial coating disruption or premature liberation before swallowing	Increased variability in release timing and delivered intact dose
Protective enteric coating over vulnerable formulation state	Barrier against gastric environment	Integrity of coating and transition to intestinal medium	Failure or success of gastric protection	Preservation or loss of release-competent drug state

The resulting vulnerabilities are platform specific: different perturbations can converge on similar exposure changes, while the same perturbation can have very different effects depending on how release is controlled (**Figure 1**).

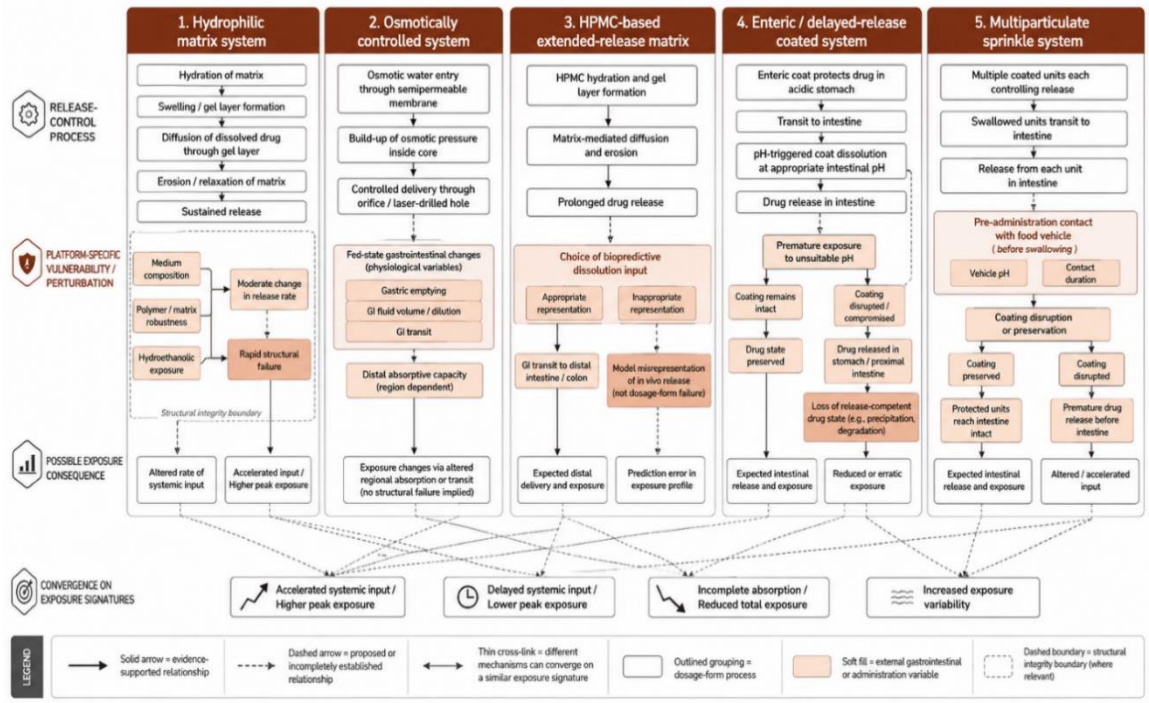

Figure 1. Platform-specific routes by which modified-release control can become exposure-vulnerable

Food effects emerge from formulation–physiology coupling

Food is often represented operationally as a binary fed-versus-fasted variable, but its pharmacokinetic consequences arise from several simultaneous physiological changes. Meals can alter gastric residence, luminal pH, bile release, intestinal fluid composition, motility, splanchnic blood flow, dissolution, membrane transport, metabolism, and elimination [13]. For an MR product, these changes occur while drug continues to be released over time, creating multiple opportunities for the fed state to interact with formulation behavior.

Dynamic characterization of the postprandial environment is therefore more informative than assuming a single static fed-state medium. A mechanistic study of six weak-base formulations found that time-dependent gastrointestinal fluid characteristics improved quantitative prediction of positive, negative, and negligible food effects [14]. Importantly, the value of the approach was not that every formulation became food sensitive; it was that formulation-specific differences could be represented using physiological changes occurring over the postprandial period.

Formulation design can also attenuate food sensitivity. Bio-enabling technologies may reduce positive food effects when the underlying mechanism involves solubility or dissolution limitations, although no single strategy applies across compounds and dosage forms [15]. In a dynamic gastrointestinal simulation comparing immediate- and sustained-release metformin, food altered the two formulations differently, with sustained release showing substantially less change in overall bioaccessibility than the immediate-release product [16]. This provides a useful counterexample to any claim that prolonging release necessarily increases vulnerability to meals.

Mechanistic modeling can help identify which fed-state process actually matters. For alpelisib, PBPK modeling reproduced clinically observed food- and pH-dependent changes and supported formulation selection by integrating solubility, permeability, bile-related effects, and gastrointestinal physiology [17]. Broader reviews of PBPK food-effect applications nevertheless show uneven model performance, particularly for some negative food effects and less well-characterized populations [18]. Successful prediction is therefore conditional on whether the model represents the dominant mechanism with adequate evidence.

Middle-out approaches make this requirement explicit. Food-effect models for different drugs have required different evidence-supported refinements, including adjustments related to clearance, solubility, or a restricted opportunity for absorption [19]. Those refinements are scientifically useful only when they are independently justified. Introducing an “absorption window” merely because it improves a fitted curve would convert a mechanistic model into an empirical explanation. Food-effect prediction is strongest when the physiological perturbation, formulation response, and resulting exposure change are linked by evidence that can be challenged independently.

Transit, pH, fluid volumes, and luminal composition

The gastrointestinal environment influencing an MR dosage form is neither chemically nor spatially uniform. Dissolution may depend on local microenvironmental conditions that are poorly represented by bulk pH alone. Work on ibuprofen showed that particle-surface pH and buffer capacity can materially alter dissolution behavior and the quality of mechanistic exposure prediction [20]. Although ibuprofen is not itself a universal proxy for MR performance, the study demonstrates a general analytical point: the physicochemical conditions immediately surrounding dissolving drug can determine whether an in vitro release profile represents what occurs in vivo.

Fluid volume presents a similar problem. The amount of liquid available for dissolution and transport changes along the gastrointestinal tract and after ingestion. Experimental work examining fluid volume and osmolality showed that luminal water movement can alter intestinal absorption, particularly when hyperosmotic solutions trigger fluid redistribution [21]. Quantitative fluid-kinetic modeling further indicates that ingestion of water predominantly changes proximal gastrointestinal volumes, whereas distal intestinal fluid behavior follows a different trajectory [22]. A single assumed intestinal fluid volume therefore cannot represent the full environment experienced by a dosage form that releases drug over several hours.

These dynamics interact with transit. A formulation that remains in the stomach longer after a meal may continue releasing into a very different fluid and pH environment than the same product under fasted conditions. Once it progresses distally, lower available fluid volume, changing buffer capacity, altered bile concentrations, and regional differences in permeability can become increasingly important. Such variables may influence matrix hydration, drug dissolution, precipitation, and the fraction of released drug that remains available for absorption.

Excipients add another layer because the formulation can sometimes alter the physiological environment acting upon it. A critical review of pharmaceutical excipients identified evidence that selected excipients can influence intestinal transit, permeability, transporters, or presystemic metabolism [23]. These effects are dose and compound dependent and should not be extrapolated to all excipients. They nevertheless weaken the assumption that the physiological environment is always external to formulation design. For some products, exposure emerges from a two-way interaction in which gastrointestinal conditions alter formulation performance while formulation components also modify local physiology.

The principal food- and physiology-dependent variables that can interact with release and absorption are separated in **Table 2**.

Table 2. Food and gastrointestinal variables that can modify the translation of release into exposure

Physiological or administration variable	Immediate change after food or fluid intake	Formulation process most directly exposed	Mechanistic route to altered absorption	Conditions in which the effect may be limited or absent
Meal composition	Changes caloric load, lipid content, viscosity, bile stimulation, and gastric processing	Release from matrices, coated units, solubility-limited formulations	Altered dissolution, solubilization, gastric residence, or regional delivery	Products whose release and uptake remain insensitive to these changes
Gastric and intestinal pH	Alters ionization and dissolution environment	pH-sensitive coatings and weakly acidic/basic drugs	Premature/late release, altered dissolution, crystallization, or precipitation	Drugs and coatings with broad pH robustness
Gastric emptying and intestinal transit	Changes time spent in individual GI regions	Long-duration ER and delayed-release systems	Shifts release into regions with different fluid, permeability, or absorption capacity	Products absorbed efficiently throughout the relevant intestinal region
Luminal fluid volume	Changes solvent available for hydration and dissolution	Hydrophilic matrices and dissolution-limited drugs	Alters matrix hydration, concentration gradients, dissolution, and transport	Highly soluble drugs or systems with limited dependence on luminal water

Fluid osmolality	Drives movement of water into or out of intestinal lumen	Drug already released into solution or suspension	Dilution or concentration changes that modify effective luminal drug concentration	Conditions without substantial osmotic fluid redistribution
Buffer capacity and local microenvironment	Alters particle-surface pH independently of nominal bulk pH	Dissolving drug released from the dosage form	Changes intrinsic dissolution behavior and therefore available concentration	Systems whose dissolution is not pH or buffer limited
Bile and other luminal constituents	Changes solubilization environment after meals	Poorly soluble drugs and formulations depending on colloidal solubilization	Increased or occasionally altered solubilization and intestinal availability	Highly soluble drugs or formulations already providing robust solubilization
Functional excipient effects	May alter motility, permeability, transport, or metabolism in selected circumstances	Formulations containing biologically active excipient levels	Physiological modification in addition to conventional release effects	Most formulations in which excipients remain functionally inert at administered exposure
Presystemic metabolic consequences of feeding	Alters enzyme, transporter, hepatic or splanchnic conditions for selected drugs	Released and absorbed drug rather than the dosage form itself	Changes first-pass extraction or downstream disposition	Drugs whose clearance and transport are insensitive to the fed state

Regional absorption and the finite opportunity for uptake

Prolonged release becomes pharmacokinetically consequential when the gastrointestinal region receiving the released drug has lower effective absorptive capacity than more proximal regions. Regional-administration studies in dogs combined with mechanistic modeling have shown substantial drug-to-drug differences in colonic absorption and in the ability of current models to reproduce those differences [24]. Similar limitations are evident when ER products are simulated using PBBM: distal exposure can be predicted adequately for some compounds, whereas strongly colon-limited drugs require substantially more product- and drug-specific information [5]. Slow release is therefore not itself a failure mechanism. The risk arises when continued release shifts a meaningful proportion of the available dose into a region where dissolution, permeability, or effective uptake is less favorable. The temporal dimension is equally important. Oral absorption cannot continue indefinitely after administration; physiological transit constrains the period during which released drug can encounter absorptive surfaces [25]. This principle should not be converted into a universal anatomical "absorption window." For some drugs, efficient uptake may extend across much of the intestine. For others, progressive distal delivery can reduce exposure because the period and region supporting effective absorption become limiting. The relevant variable is thus the correspondence among release rate, transit, and drug-specific regional uptake rather than release duration considered in isolation.

Presystemic metabolism and recirculation can re-shape release-controlled input

Systemic exposure is determined after release by more than intestinal uptake. Nalbuphine provides an instructive example in which extended-release input had to be interpreted together with glucuronidation and enterohepatic recirculation to reproduce observed pharmacokinetic profiles across clinical datasets [26]. The example is drug specific, but it demonstrates a general inference problem: an unusual concentration–time profile cannot automatically be attributed to dosage-form release when absorption and postabsorptive disposition can reshape the same input.

Food further complicates attribution because it can influence gastrointestinal release and absorption while also modifying presystemic or systemic processes [13]. Mechanistic modeling of alpelisib similarly illustrates how formulation behavior, solubility, intestinal conditions, and systemic disposition may need to be evaluated together when interpreting a food effect [17]. Consequently, comparable changes in AUC, Cmax, or Tmax can arise from mechanistically different combinations of release, absorption, metabolism, and recirculation.

These interacting layers are summarized in **Figure 2**.

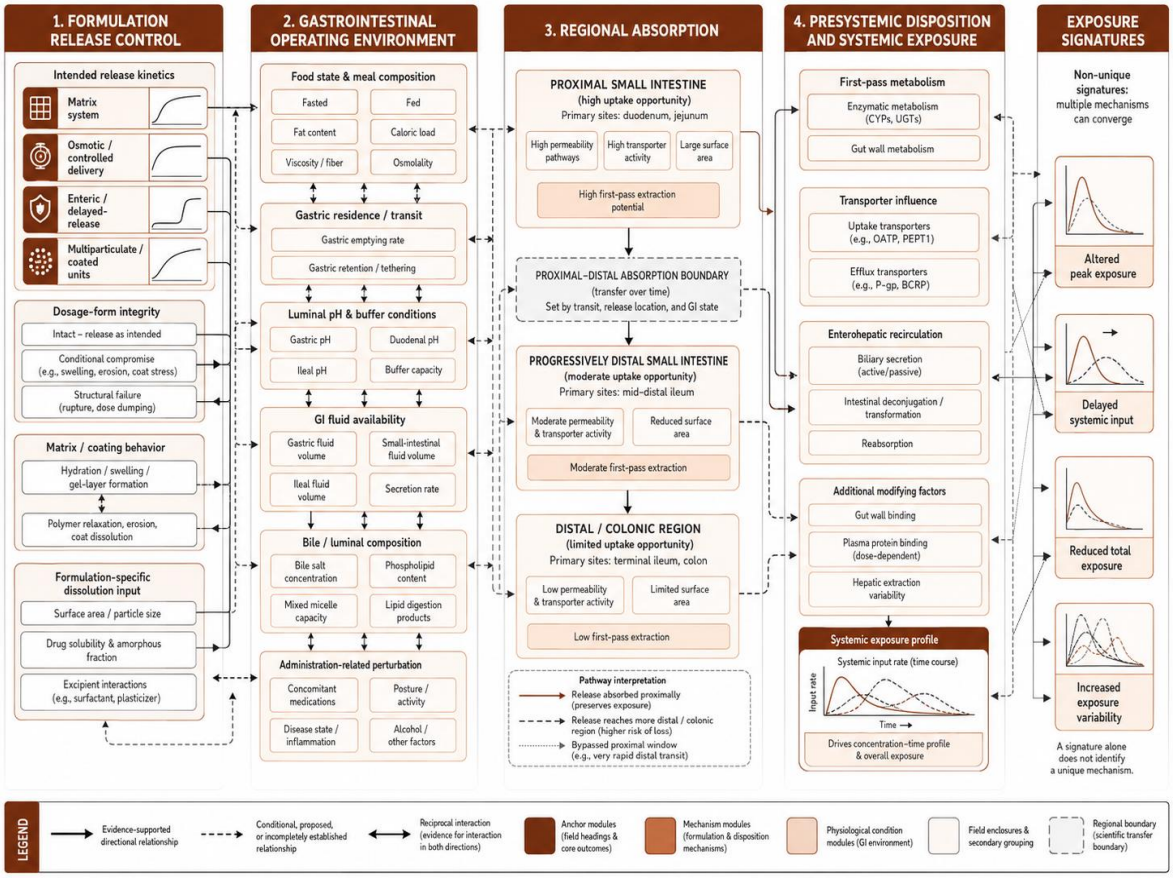

Figure 2. Conditions governing translation of modified release into systemic exposure

Patient and within-subject physiology changes the same product's exposure

The physiological context of an MR product cannot be assumed to match that of a standard healthy-adult study population. Reviews of special populations identify age, gastrointestinal disease, surgery, developmental physiology, and other conditions as potential modifiers of oral absorption [27]. The evidence is uneven, however, and the direction of change cannot be predicted reliably from the population label alone.

Advanced age illustrates this limitation. Available data on gastric emptying, intestinal fluids, permeability, and other variables are heterogeneous and sometimes conflicting [28]. PBPK models for older adults likewise remain constrained by incomplete quantitative representation of age-related gastrointestinal physiology and by substantial interindividual heterogeneity [29]. A simple rule such as “older age causes slower absorption” is therefore inadequate for MR products whose performance may depend on several competing physiological processes.

Anatomical alteration after bariatric surgery creates more obvious changes in gastrointestinal structure, yet even here ER exposure is not uniformly reduced. Drug-specific clinical evidence shows that some products change substantially after surgery whereas others retain broadly similar exposure [30]. This is an important disconfirming case for any formulation-wide rule based solely on altered anatomy.

Variability also occurs within the same individual. PBPK-based virtual bioequivalence work has shown that occasion-to-occasion variation in gastrointestinal physiology can propagate into pharmacokinetic variability and influence bioequivalence outcomes [31]. Formulation predictability should therefore be considered distributionally: a product may have a stable mean profile while remaining sensitive to physiological variation in particular patients or circumstances.

The clinically relevant sources of patient-level variability are separated in **Table 3**.

Table 3. Patient and treatment contexts that can modify exposure from the same modified-release product

Patient or treatment context	Physiological or pharmacological change	Release-to-exposure pathway potentially affected	Expected direction of exposure change	Evidence interpretation
Advanced age	Heterogeneous changes in gastric emptying, fluid environment, motility, permeability, comorbidity, and polypharmacy	Release timing, dissolution, transit, absorption, metabolism	Not reliably unidirectional	Requires drug- and patient-specific interpretation
Gastrointestinal disease or altered physiology	Changes in pH, motility, intestinal surface, secretion, or permeability	Release environment and regional uptake	Variable	Depends on disease mechanism and formulation
Bariatric surgery	Altered anatomy, gastric volume, pH, transit, intestinal access, and body composition	Release location, dissolution, uptake, and disposition	Increased, decreased, or unchanged	Effects on ER exposure are product specific; preserved exposure in some studies does not establish suitability of every product
Concomitant interacting medicines	Enzyme, transporter, pH, or motility modification	Absorption and/or systemic disposition	Interaction specific	Formulation change does not remove pharmacological interaction risk
Genetically variable metabolism	Altered metabolic capacity	Postabsorptive exposure	Genotype dependent	Particularly consequential for narrow-therapeutic-index drugs
Occasion-level GI variability	Day-to-day changes in transit, luminal conditions, or related physiological parameters	Timing and extent of absorption	Increased variability rather than fixed directional change	Relevant to repeated-dose and bioequivalence interpretation
Combined patient and formulation vulnerability	Coincidence of physiological variability with region-sensitive or integrity-sensitive release	Multiple stages simultaneously	Potentially amplified and difficult to attribute	Mechanistic discrimination is required before assigning cause

PBBM, biopredictive dissolution, and virtual bioequivalence as discriminating tests

The central methodological problem is not merely to reproduce an observed plasma profile but to distinguish why that profile occurred. Dissolution methods intended for quality control and those intended to reproduce biopharmaceutically relevant in vivo conditions therefore answer different questions [32]. Non-sink systems, dissolution–permeation approaches, physiologically relevant media, and other biopredictive methods can be valuable when their additional complexity corresponds to a known mechanism.

Mechanistic PBPK and PBBM approaches can extend this discrimination to bioequivalence assessment by linking formulation attributes with physiological variables and systemic pharmacokinetics [33]. Their value is greatest when competing explanations make different predictions—for example, when accelerated release, reduced distal absorption, altered gastric residence, or a disposition process would produce distinguishable responses under specified conditions.

Model complexity alone does not establish credibility. Contemporary PBBM practice emphasizes explicit context of use, mechanistic justification, verification, validation, sensitivity analysis, and risk-based interpretation [34]. The challenge is especially relevant for MR products because regional absorption, prolonged input, food effects, and product-specific dissolution can interact. A credible model should therefore identify the conditions under which exposure is expected to remain stable and the conditions under which its own predictions become unreliable.

Results and Discussion

The available evidence supports a product-specific interpretation of exposure predictability. Modified release can produce highly reproducible exposure when the controlling release mechanism remains intact, relevant gastrointestinal conditions are sufficiently characterized, and absorption is maintained throughout the regions receiving drug. At the same time, food-effect data show that ER products respond heterogeneously [4], colon-absorption modeling identifies predictable and poorly predicted cases [5], and bariatric evidence shows that major anatomical change does not generate a uniform ER response [30]. Predictability is therefore a property demonstrated for a product under defined conditions, not an intrinsic property conferred by the MR label.

An important implication is that similar pharmacokinetic signatures should not be treated as mechanistically interchangeable. Rapid release caused by loss of matrix integrity [10], dissolution altered by local physicochemical conditions [20], regional uptake limitations investigated in dogs [24], and recirculation or disposition effects [26] can all reshape systemic profiles through different routes. A high Cmax, delayed Tmax, or reduced AUC identifies an exposure pattern; it does not by itself identify the mechanism producing that pattern. This distinction leads to testable expectations. Progressively slower release should reduce exposure chiefly when drug is shifted into a region or time period with lower effective uptake. If regional absorption remains preserved, slower release alone should not consistently produce exposure loss. Similarly, a claim of dose dumping should be supported by independent evidence of accelerated release or loss of dosage-form integrity; an isolated increase in peak concentration is insufficient. Finally, models intended to support development or bioequivalence should be challenged across the formulation, physiological, and patient conditions most likely to separate competing mechanisms rather than validated only against a single average profile. Physiological within-subject variability [31], biopredictive dissolution [32], mechanistic BE modeling [33], and context-specific PBBM qualification [34] provide complementary tools for that purpose.

Conclusion

Modified-release technology controls drug liberation, but systemic exposure remains the outcome of a larger interacting system. Release mechanism, dosage-form integrity, food state, gastrointestinal transit and fluids, regional absorptive capacity, metabolism, recirculation, and patient physiology can preserve, weaken, or occasionally defeat the intended relationship between formulation design and pharmacokinetics. None of these factors implies that MR exposure is inherently unstable. The stronger conclusion is that predictability must be demonstrated over the conditions that materially interact with the product's release mechanism. Mechanistic testing is most informative when it distinguishes structural dosage-form failure from normal physiological variation, regional absorption limitation, and downstream disposition. Under that evidence-based interpretation, modified release can provide predictable exposure—but the predictability belongs to the validated product–physiology context, not to the formulation label alone.

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