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Oral Formulation Design Should Optimize Temporal Exposure Rather Than Dissolution Alone

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ABSTRACT

Dissolution remains indispensable to oral formulation development, but its interpretation becomes incomplete when the quantity dissolved is treated as a sufficient surrogate for the drug exposure that can actually be generated from a dosage form. Oral absorption occurs within a moving physiological system in which gastric emptying, intestinal transit, changing luminal composition, formulation-state transformations, supersaturation, precipitation, re-solubilization, permeability, food, and patient physiology alter both the amount and the timing of drug available for uptake. A formulation that dissolves rapidly under one experimental condition may therefore produce no exposure advantage if release occurs before an absorptive opportunity, if dissolved drug becomes nonabsorbable, if precipitation precedes uptake, or if physiological variability shifts the sequence of formulation and gastrointestinal states. This Perspective argues for a time-resolved formulation-design objective centered on the trajectory of exposure-relevant drug availability rather than dissolution magnitude alone. Evidence from biorelevant dissolution, dissolution-permeation systems, dynamic gastrointestinal models, formulation-state studies, food-effect research, and physiologically based modeling is integrated while preserving molecule-, product-, dose-, physiological-, and model-specific boundaries. The resulting synthesis treats dissolution as one necessary process within a temporally coupled formulation-gastrointestinal-absorption system.

Keywords: Oral drug absorption, Biorelevant dissolution, Gastrointestinal transit, Supersaturation, Dissolution-permeation, Food effect

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INTRODUCTION

Dissolution testing occupies a central position in oral dosage-form development because release into a molecularly or colloidally available state is commonly necessary before gastrointestinal absorption can occur. Its usefulness, however, depends on the question being asked. Clinically relevant dissolution approaches increasingly connect in vitro release behavior to pharmacokinetic consequences, while biorelevant dissolution and physiologically based pharmacokinetic modeling provide ways to translate formulation performance into expected absorption behavior [1, 2]. The inferential error arises when dissolution ceases to be treated as one exposure-determining process and instead becomes the formulation-design endpoint itself.

Translational modeling has reinforced the need to connect dissolution with the physiological and pharmacokinetic processes that intervene between dosage-form release and systemic exposure [3]. Contemporary oral-absorption research has similarly highlighted precipitation, non-sink behavior, colloidal states, permeability, and absorptive

removal as factors capable of altering the meaning of a measured dissolved concentration [4]. A formulation may therefore increase apparent dissolution without increasing the fraction of drug that remains absorbable at the relevant intestinal location or for the relevant duration.

This distinction becomes more important because the gastrointestinal tract is not a reproducible dissolution vessel. Regional luminal environments, motility, food, dosage-form state, age, disease, anatomy, and other physiological variables can alter the sequence through which a formulation passes before absorption [5, 6]. The central problem is consequently temporal as well as quantitative. The clinically meaningful question is not simply how much drug dissolves, but whether an adequate exposure-relevant drug state exists at the right location, for long enough, under the physiological conditions encountered by the intended population.

This Perspective therefore develops a proposed time-resolved formulation-design interpretation. It does not replace dissolution testing or claim that every oral product requires elaborate dynamic modeling. Instead, it argues that formulation decisions should distinguish the measured dissolution profile from the evolving sequence of luminal drug states and from the eventual systemic exposure profile. That distinction is developed through dissolution-surrogate limitations, gastrointestinal transit, time-dependent solubilization, permeability, precipitation, food and physiological variability, and subsequent exposure-centered validation.

Dissolution as an incomplete surrogate

Conventional dissolution experiments necessarily simplify the gastrointestinal environment. Even fed-state methods require explicit choices about media composition, hydrodynamics, mechanical forces, fluid volumes, and transit assumptions, and no single in vitro configuration reproduces the entire postprandial gastrointestinal process [7]. This limitation does not make such methods unsuitable. It means that their predictive interpretation should remain tied to the mechanism and product for which the method was designed.

Biopredictive dissolution methods also differ across laboratories and development programs. Recent harmonization work illustrates that physiologically motivated test systems may vary substantially in apparatus, media, transfer conditions, and other parameters even when they share the goal of improving clinical relevance [8]. A more physiologically complex experiment is therefore not automatically more predictive. Methodological complexity becomes useful only when it captures a process that materially controls the relevant exposure outcome. Available gastrointestinal fluid volume provides a clear example of why apparently simple dissolution measurements can become misleading. For selected salt-form drugs, incorporating a clinically relevant dose-to-fluid-volume relationship into bicarbonate-buffer dissolution improved correspondence with estimated human absorption compared with conventional conditions [9]. The implication is not that one fluid volume should replace another universal standard. Rather, dissolution behavior can change because the drug dose, available solvent volume, local buffer chemistry, and dosage-form transformation interact.

Accordingly, dissolution should be interpreted as a state-dependent measurement. The concentration or fraction dissolved at a given experimental time reflects the imposed fluid composition, volume, mixing, sink condition, and removal processes. When those conditions differ from the physiological sequence experienced in vivo, the same numerical dissolution endpoint may represent a different exposure opportunity. The appropriate design question is therefore whether the assay captures the product-specific process limiting absorption, not whether it generates the largest or fastest dissolution value.

Gastric and intestinal transit

Oral drug absorption unfolds across anatomically and physicochemically distinct gastrointestinal regions. Luminal composition, pH, fluid availability, permeability, transport processes, and residence time vary along the gastrointestinal tract, meaning that drug released at different locations may encounter different probabilities of remaining soluble and crossing the intestinal membrane [10]. Transit therefore does more than move a formulation downstream: it controls the chronological sequence of environments in which release, dissolution, precipitation, and absorption occur.

These relationships become more uncertain when physiological assumptions derived from healthy adults are transferred to special populations. Pediatric and elderly physiology, disease, gastrointestinal surgery, and other population-specific changes can modify luminal conditions, transit, drug release, and absorption, although the evidence strength and magnitude of these effects differ substantially among populations and drugs [11]. Temporal formulation design should therefore avoid converting population variability into a single generic correction factor. Food further changes transit kinetics. Modeling of mixed meals has shown that gastric-emptying behavior can vary with meal characteristics including caloric content and fat composition [12]. A dosage form that remains in

the stomach during a delayed fed-state interval may experience a substantially different dissolution history before entering the intestine than the same product administered under fasted conditions. For acid-sensitive drugs, weak bases, enteric systems, or formulations whose hydrated state evolves during gastric residence, this history can influence subsequent intestinal behavior.

Postprandial gastrointestinal fluid properties themselves also vary over time rather than switching instantaneously from a single “fasted” to a single “fed” state. Dynamic representation of these changes has improved quantitative prediction for studied oral dosage forms [13]. The resulting design implication is that transit and solubilization should not be considered separate clocks. Gastric emptying determines when the formulation reaches the intestine, while evolving intestinal conditions determine what happens to the released drug after arrival.

A time-resolved design framework therefore treats regional residence as an exposure opportunity rather than merely a physiological nuisance parameter. Rapid release is potentially advantageous only when the released state persists until absorption can occur. Delayed release can be beneficial when it aligns drug availability with a favorable region, but detrimental when it moves release beyond a limited absorptive region. Neither conclusion can be inferred from dissolution rate alone.

Time-dependent solubilization

Solubilization is often discussed as though the formulation enters a medium, generates dissolved drug, and can then be ranked by the resulting concentration. Sequential gastrointestinal conditions complicate this interpretation. In amorphous solid dispersions containing the weakly basic drug delamanid, changing gastric pH before intestinal transfer altered subsequent release behavior, and surface crystallization contributed to impaired release for some enteric-polymer systems [14]. The intestinal outcome was therefore partly determined by what had already happened to the formulation in the stomach.

Different enabling strategies can likewise generate distinct temporal states rather than interchangeable increases in apparent solubility. Comparative evaluation of particle-size reduction, salt formation, and amorphous formulation for a weak-base candidate demonstrated formulation-dependent biopharmaceutical behavior [15]. Such comparisons argue against selecting an enabling technology solely because it produces the highest early dissolution value under one assay condition.

The coupling becomes still clearer when absorptive removal is introduced. In an artificial gut/absorption simulator, physiological-rate absorption changed the dissolution behavior, bound-drug distribution, precipitation, and even the performance ranking of ketoconazole amorphous solid dispersions relative to nonsink dissolution conditions [16]. Absorption can therefore alter the luminal concentration trajectory that dissolution experiments attempt to measure. Dissolution and uptake are not always separable sequential events; they may act as coupled processes.

Hydrated formulation structure is another time-dependent determinant. Phase-diagram and morphological analysis of amorphous solid dispersions has shown that water-induced phase behavior and drug loading can alter the morphology through which release occurs, including transitions associated with impaired release above a formulation-specific limit of congruency [17]. The relevant formulation state is consequently not exhausted by the dry dosage-form label. What matters after administration is how the system transforms upon hydration and whether the resulting phases continue to provide drug in an absorbable state.

The distinction among precursor state, transformation, drug availability, and interruption of the sequence is difficult to preserve in prose alone. **Table 1** therefore organizes time-dependent solubilization as a sequence-aware formulation problem rather than as a static comparison of technologies.

Table 1. Sequence-dependent solubilization states that can separate apparent dissolution improvement from sustained absorptive availability

Weak-base system exposed to changing gastric conditions Particle-size-reduced crystalline formulation Salt-based enabling formulation Amorphous or amorphous-dispersion formulation				
Formulation case emerging from the solubilization sequence	Weak-base system exposed to changing gastric conditions	Particle-size-reduced crystalline formulation	Salt-based enabling formulation	Amorphous or amorphous-dispersion formulation

Precursor state before the critical transition	Drug remains embedded in, released from, or associated with the original dosage-form matrix	High surface-area crystalline particles	Ionized or metastable high-energy solid state	High-energy drug dispersed within a polymeric matrix
Transformation event during gastrointestinal processing	Gastric hydration, ionization and subsequent transfer to higher intestinal pH	Wetting and dissolution increase as gastrointestinal fluid contacts exposed surfaces	Rapid dissolution followed by environmental pH and common-ion changes	Hydration, polymer dissolution or swelling, phase separation and drug liberation
Drug phase or availability after the transition	Transiently dissolved, supersaturated, crystallizing, or incompletely released drug	Molecularly dissolved drug coexisting with residual crystals	Elevated dissolved concentration that may become supersaturated relative to the free form	Molecular drug, drug-rich phases, colloidal species and/or supersaturated solution
Time dependence relevant to design	Intestinal performance depends partly on the earlier gastric history	Benefit persists only while dissolution can replenish drug removed by absorption or dilution	Advantage can be early and transient rather than maintained throughout intestinal residence	Release may change as the hydrated matrix reorganizes
Event that can interrupt or reverse the intended exposure trajectory	Surface crystallization, loss of supersaturation or altered matrix release during transfer	Insufficient local solubility, precipitation, rapid transit or depletion of absorptive opportunity	Conversion to less soluble free form or precipitation before sufficient uptake	Drug-rich phase persistence, crystallization, phase disconnection or loss of congruent release

Permeability and absorptive windows

The distinction between dissolved drug and absorbable drug becomes decisive at the intestinal membrane. Solubilization enhancement can alter thermodynamic activity, colloidal partitioning, unstirred-water-layer transport, and free-drug concentration in ways that prevent a simple proportional relationship between apparent solubility and membrane flux. In a coamorphous telmisartan–amlodipine system, improvements in solubility and oral absorption were accompanied by permeability behavior that depended strongly on hydrodynamic and unstirred-water-layer conditions [18]. The relevant lesson is not that solubility enhancement compromises permeability, but that the two quantities cannot always be optimized independently.

Dissolution–permeation studies reinforce this point. Across ten investigated products, flux-based evaluation provided better food-effect discrimination than dissolution measurements alone and captured negative food-effect behavior that a dissolved-amount interpretation could miss [19]. These results remain product- and method-specific, yet they demonstrate how a formulation may generate substantial dissolved drug while the amount capable of crossing a membrane changes in another direction.

The concept of an absorptive window should therefore be interpreted broadly. It can include a true regional limitation in permeability or transporter expression, but it can also arise functionally from the overlap among drug availability, intestinal residence, membrane transfer, and systemic input. A formulation that creates a concentration maximum before appreciable intestinal absorption begins may waste part of that solubilization advantage. Conversely, a slower or spatially targeted release profile may produce adequate exposure even when its conventional dissolution curve appears less aggressive.

A time-resolved formulation objective consequently asks whether release and solubilization coincide with the period in which drug can be effectively removed from the lumen. This emphasizes flux opportunity rather than dissolved concentration alone. It also provides a mechanistic reason why formulations that look different *in vitro* can sometimes converge clinically, while formulations with similar dissolution profiles may diverge when permeability or regional residence becomes limiting.

Precipitation and re-solubilization

Supersaturating formulations explicitly demonstrate why temporal state transitions matter. After a weak base moves from gastric to intestinal pH, or after an enabling formulation generates concentrations above equilibrium solubility, precipitation may compete directly with absorption. Population-balance modeling of gastrointestinal pH-shift precipitation has shown that nucleation and particle-growth kinetics can reproduce time-dependent

precipitation profiles for selected weakly soluble compounds [20]. Treating precipitation as an instantaneous equilibrium correction would erase precisely the interval during which absorption may occur.

However, longer supersaturation is not automatically better. For dipyridamole and ketoconazole in a preclinical investigation, the degree of supersaturation, rather than its duration, was more closely associated with systemic exposure under the studied high-permeability conditions [21]. This is an important boundary to the proposed temporal argument. Optimizing temporal exposure does not mean mechanically extending every dissolved or supersaturated state. It means matching the rate and duration of drug availability to the competing rates of precipitation, transit, and absorption.

Re-solubilization adds another layer. Precipitated material is not necessarily permanently lost from the absorption process, particularly if downstream changes in bile components, fluid volume, pH, or local concentration again favor dissolution. Conversely, a precipitate that can re-dissolve in principle may contribute little clinically if intestinal transit carries it beyond an effective absorption region before sufficient re-solubilization occurs.

The design variable is therefore the sequence of accessible states: release, dissolution, supersaturation, precipitation, possible re-solubilization, and absorptive removal. Different formulations may pass through the same states at different rates and may consequently generate different systemic input even when a conventional endpoint dissolution value is similar.

Food and physiological variability

Food effects expose the limitations of single-condition dissolution particularly clearly because food simultaneously changes multiple gastrointestinal variables. Meal ingestion can modify gastric emptying, luminal fluid composition, bile secretion, pH, viscosity, hydrodynamics, drug solubilization, dosage-form disintegration, intestinal transit, and sometimes permeability-related processes. Contemporary food-effect assessment therefore favors mechanism-led selection of in vitro and modeling tools rather than assuming that one fed-state dissolution response is sufficient for every product [22].

The same exposure pattern can also arise from different underlying mechanisms. In an investigation linking biorelevant fed-state dissolution with population pharmacokinetics for rivaroxaban, permeability-related effects were implicated more strongly than gastric motility as an explanation for the investigated low-exposure behavior [23]. This illustrates why formulation intervention should follow mechanistic diagnosis. If permeability rather than dissolution or gastric release is limiting, accelerating dissolution may have little ability to correct the clinical problem.

Dynamic gastrointestinal experiments provide another view of this interaction. Immediate- and sustained-release metformin products displayed different release and bioaccessibility trajectories when fasted and fed conditions were recreated in a dynamic gastrointestinal system [24]. Such experiments do not constitute human pharmacokinetic proof, but they reveal process information that is lost when fed and fasted states are represented by isolated static media.

Translation becomes stronger when dynamic gastrointestinal outputs are explicitly connected to pharmacokinetics. For cinnarizine, diclofenac potassium, and paracetamol products, a dynamic gastrointestinal model linked with pharmacokinetic convolution reproduced the direction of both positive and negative food effects in the studied cases [25]. The limited product set prevents universal predictive claims, but the contrasting food-effect directions are important: physiological realism is useful because food does not act through one monotonic mechanism.

Even solubility-limited absorption must be interpreted conditionally. A recent simplified PBPK analysis found that solubility-limited absorption could help discriminate positive food effects for selected BCS II/IV drugs within defined mechanistic boundaries, including the absence of dominating intestinal metabolism or efflux [26]. Thus, a variable can be highly informative without being universally controlling.

For formulation design, physiological variability should consequently be treated as a family of perturbations applied to the time-dependent exposure sequence. A robust product is not necessarily the one with the least variable dissolution curve under every laboratory condition. It is one for which plausible changes in gastric residence, fluid composition, solubilization, precipitation, permeability, and transit do not push systemic input outside the intended exposure range.

Table 2 organizes these perturbations as failure modes because identical-looking dissolution changes can demand different formulation responses.

Table 2. Failure-mode triage for distinguishing food- and physiology-driven exposure changes from superficially similar dissolution behavior

Likely physiological or formulation origin	Observable signature that would raise suspicion	Competing explanation that should remain open	Corrective or discriminating test	Residual design consequence after the immediate mechanism is addressed
Misleading or adverse pattern requiring diagnosis Higher fed-state dissolved concentration without proportional exposure gain				
Bile-mediated solubilization increases total dissolved or colloid-associated drug while free-drug flux remains constrained	Dissolution rises more strongly than membrane flux or PK	Delayed gastric emptying changes the timing rather than the magnitude of input	Coupled dissolution–permeation assessment with fasted/fed media	Avoid treating total dissolved concentration as the sole formulation endpoint
Misleading or adverse pattern requiring diagnosis Delayed exposure despite apparently adequate eventual dissolution				
Prolonged gastric residence, delayed dosage-form emptying or slow transition to the effective intestinal region	Similar final dissolved fraction but shifted release/absorption timing	Matrix hydration or food–dosage-form interaction may independently slow release	Dynamic gastric-to-intestinal transfer test with meal-dependent residence	Evaluate timing of intestinal delivery rather than only final extent dissolved
Misleading or adverse pattern requiring diagnosis Reduced exposure with no major loss of measured dissolution				
Permeability or free-drug availability becomes limiting	Comparable luminal dissolution with lower absorptive flux or clinical exposure	Unmodeled metabolism, transporter effects or altered intestinal residence	Dissolution–permeation testing plus mechanism-appropriate PBPK sensitivity analysis	Formulation solubility enhancement alone may not correct the exposure deficit
Misleading or adverse pattern requiring diagnosis Large product sensitivity to fed/fasted physiological changes				
Formulation transformation depends on pH, bile environment, fluid volume or hydrodynamics	Release trajectory diverges after sequential state changes rather than at the initial dissolution step	Analytical method itself may exaggerate sensitivity	Dynamic multistage GI testing using product-relevant physiological ranges	Prioritize robustness of state transitions across plausible physiological conditions
Misleading or adverse pattern requiring diagnosis Positive food effect attributed entirely to greater solubility				
Solubility-limited absorption may dominate for an appropriate compound	Model sensitivity and fed-state solubility changes move predicted exposure coherently	Gastric emptying, precipitation, permeability, metabolism or efflux may contribute	Mechanism-informed PBBM/PBPK analysis with alternative hypotheses retained	Use solubility-focused formulation changes only when competing limitations are excluded sufficiently
Misleading or adverse pattern requiring diagnosis Unexpected low exposure in a subgroup despite acceptable product dissolution				
Patient-specific physiology changes transit, luminal conditions, permeability or interacting processes	Clinical PK variation exceeds what the qualified dissolution model predicts	Adherence, comedication, disease state or other nonformulation factors	Population-informed mechanistic modeling and targeted clinical covariate assessment	Define the population boundary within which the formulation model remains credible

Note: Failure modes and diagnostic sequencing constitute a proposed synthesis. They are not validated clinical decision rules and do not assign numerical thresholds or causal certainty.

The combined evidence developed to this point requires a representation that retains temporal ordering while showing that physiological variability can divert a formulation into different states. **Figure 1** therefore maps formulation and gastrointestinal states as a field with explicit uncertainty corridors rather than as a deterministic dissolution-to-exposure pipeline.

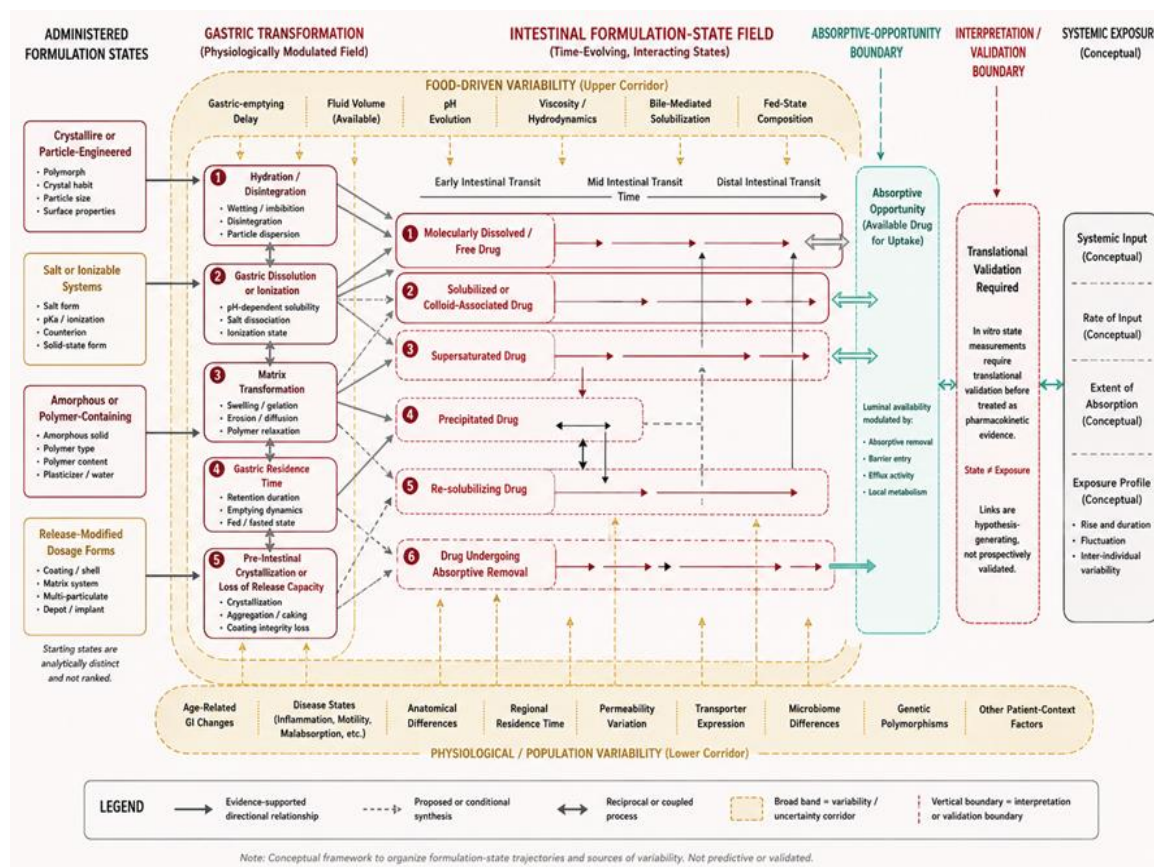


Figure 1. Physiological perturbations redirect oral formulations through alternative exposure-relevant states before absorption

Temporal exposure profiles

The formulation-design endpoint proposed here is not the maximum fraction dissolved at a selected sampling time, but the time-resolved profile of drug that remains capable of contributing to systemic input. This distinction matters because systemic exposure can be relatively insensitive to substantial dissolution variation when other processes buffer those differences. In a virtual bioequivalence analysis of naproxen, relatively broad dissolution behavior remained compatible with acceptable pharmacokinetic performance within the modeled product-specific safe space [27]. The result should not be generalized to compounds with different half-lives, permeability, absorption regions, or therapeutic constraints. It nevertheless demonstrates that dissolution differences acquire clinical meaning only after they are propagated through the rest of the absorption and pharmacokinetic system. A temporal exposure profile therefore requires several clocks to be considered simultaneously: dosage-form transformation, drug release, development or loss of supersaturation, precipitation, possible re-solubilization, intestinal transit, membrane transfer, and systemic disposition. Earlier evidence shows why these clocks cannot be collapsed into one curve. Gastric history can alter subsequent intestinal release [14]; absorptive removal can modify luminal dissolution and precipitation [16]; increased apparent solubility can interact nonlinearly with permeability [18]; and precipitation evolves kinetically after environmental change [20]. Even supersaturation duration is not universally the decisive quantity, because its importance depends on the relative rates of uptake and precipitation [21].

The proposed temporal exposure profile should consequently be interpreted as an exposure-oriented representation rather than as a new measurable physicochemical property. Depending on the drug and dosage form, it may be approximated using sequential dissolution, dissolution-permeation testing, dynamic gastrointestinal systems, mechanistic modeling, or combinations of these approaches. The necessary level of complexity should be determined by the suspected rate-limiting processes. For a robust, rapidly permeable drug,

conventional dissolution may already provide sufficient discrimination. For a formulation whose performance depends on gastric history, transient supersaturation, permeability, or food-sensitive state transitions, an endpoint dissolution comparison may discard clinically important timing information.

A time-resolved formulation design framework

The evidence synthesized above supports a proposed time-resolved formulation design framework in which formulation optimization proceeds through a sequence of mechanistic questions rather than through a universal objective of accelerating dissolution.

First, the dominant exposure limitation should be identified. This may involve insufficient release, low equilibrium solubility, rapid precipitation, inadequate absorptive flux, unfavorable regional delivery, or excessive sensitivity to food or patient physiology. Second, the formulation states connecting administration to absorption should be mapped in their physiological order. Third, the timing of those states should be compared with gastric and intestinal transit and with the period during which membrane uptake can occur. Fourth, plausible fed-state and population perturbations should be applied to determine whether a formulation advantage persists or disappears. Finally, the resulting luminal behavior should be translated to pharmacokinetic consequences rather than interpreted as a clinical endpoint directly.

Physiologically based biopharmaceutics modeling is particularly suitable as one integration layer because it can combine formulation characteristics, dissolution behavior, gastrointestinal physiology, absorption, and systemic pharmacokinetics within a common quantitative structure [28]. Its role in the proposed framework is not to replace experimentation. It is to test whether mechanistic assumptions about formulation behavior are sufficient to reproduce exposure across relevant conditions and to identify which assumptions require stronger experimental support.

This framework therefore changes the formulation question from “Which product dissolves fastest?” to “Which formulation generates an adequate and sufficiently robust exposure-producing sequence under the physiological conditions that matter for the intended use?” The difference is subtle for products whose absorption is strongly dissolution limited and physiologically stable, but potentially decisive when formulation and gastrointestinal processes operate on comparable timescales.

Validation using biorelevant and PK evidence

A time-resolved design claim becomes useful only when its individual process assumptions can be challenged experimentally and its integrated predictions can be confronted with pharmacokinetic observations. Validation should therefore proceed across levels rather than relying on agreement at one stage.

At the *in vitro* level, the selected system should reproduce the process believed to control exposure: sequential pH change, physiologically plausible fluid volumes, precipitation, absorptive removal, fed-state transitions, or another product-specific mechanism. Increasing apparatus complexity without demonstrating sensitivity to the relevant mechanism adds little confidence. Where competing explanations exist, experiments should be designed to discriminate among them rather than simply reproduce an observed dissolution profile.

At the translational level, the central question is whether the formulation-state model predicts the timing and extent of systemic input across relevant physiological conditions. A recent vericiguat PBBM application integrated solubility, dissolution, luminal physiology, and PBPK components and reproduced observed pharmacokinetic behavior across fasted, fed, and proton-pump-inhibitor conditions in the investigated case [29]. Such cross-state agreement is more informative than calibration to one physiological condition, although a successful single-drug application cannot validate the proposed framework generally.

Validation should also remain proportional to decision risk. When conventional dissolution is demonstrably sensitive to clinically meaningful formulation differences, more elaborate testing may be unnecessary. Conversely, when dissolution profiles cannot explain observed food effects, formulation differences, or population variability, additional dynamic or mechanistic evidence becomes justified. The purpose of the framework is therefore not maximal experimental complexity but mechanistic sufficiency: enough information to establish that the measured formulation behavior can plausibly account for the exposure outcome being used to guide development.

CONCLUSION

Oral formulation performance is produced by a sequence of interacting states rather than by dissolution in isolation. Drug release, gastrointestinal transit, solubilization, supersaturation, precipitation, re-solubilization,

permeability, food, and patient physiology determine whether dissolved drug exists at the appropriate location and time to contribute to systemic exposure.

The proposed time-resolved formulation design perspective therefore treats dissolution as an essential measurement embedded within a larger exposure-generating process. It does not prescribe one assay, one model, or one optimal release pattern. Instead, it requires formulation decisions to identify the dominant exposure limitation, preserve the temporal order of relevant gastrointestinal transformations, test robustness to physiological variability, and validate luminal behavior against pharmacokinetic evidence when clinical interpretation is intended.

For some oral products, conventional dissolution may remain an adequate development surrogate. For others, optimizing dissolution magnitude without considering timing can favor a formulation state that is transient, poorly absorbed, physiologically fragile, or clinically irrelevant. The appropriate design target is therefore not dissolution maximization itself, but an exposure-producing temporal trajectory whose complexity is matched to the drug, dosage form, physiological context, and development decision.

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