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Supersaturation Is Useful Only When Precipitation Kinetics and Absorptive Flux Are Considered Together

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ABSTRACT

Supersaturating formulations are commonly judged by how high and how long dissolved drug concentrations remain above equilibrium solubility. That description is incomplete because the pharmaceutical value of supersaturation depends on competing rates: generation of the supersaturated state, redistribution into drug-rich or precipitated phases, and removal of molecularly available drug by absorption. Evidence from amorphous solid dispersions, cocrystals, lipid-based systems, biorelevant transfer models, and dissolution-permeation platforms shows that identical-looking concentration advantages can have different consequences when nucleation kinetics, gastrointestinal composition, phase state, permeability, and absorptive sink strength differ. A high apparent dissolved concentration may coexist with reduced thermodynamic activity, rapid precipitation, or poor membrane flux, whereas short-lived supersaturation may still support substantial absorption for highly permeable drugs. This Formulation Perspective therefore argues for interpreting supersaturation as a time-dependent mass-transfer problem rather than as a dissolution endpoint. The proposed supersaturation-precipitation-flux framework separates generation, phase loss or reservoir formation, and absorptive removal while retaining formulation, gastrointestinal, and assay boundary conditions. Its purpose is not to replace dissolution testing, but to identify when dissolution alone is insufficient for formulation ranking and when coupled kinetic and flux measurements are needed.

Keywords: Supersaturation, Precipitation kinetics, Amorphous solid dispersions, Gastrointestinal dissolution, Membrane flux, Biopharmaceutics

INTRODUCTION

Supersaturation is attractive because it temporarily creates dissolved concentrations above crystalline equilibrium solubility, potentially increasing the concentration gradient available for absorption. Yet a concentration-time curve measured in a closed donor compartment is not identical to absorptive opportunity. In an artificial gut/absorption simulator, introducing an absorptive pathway changed ketoconazole amorphous solid dispersion dissolution, speciation, and precipitation behavior, including formulation ranking under some conditions [1]. The sink was therefore not merely a downstream readout; it altered the state being measured.

The relative importance of supersaturation magnitude and persistence is likewise conditional. For dipyrindamole and ketoconazole, two highly permeable drugs examined under supersaturating conditions, the degree of supersaturation was more closely associated with exposure than prolonged maintenance, because absorption could occur rapidly relative to precipitation [2]. Conversely, formulation behavior can be misleading when dissolution

is interpreted without phase fate. A felodipine/PVPVA system with faster and higher apparent dissolution did not provide the superior bioavailability expected from that ranking; solid-state heterogeneity and the nature of the precipitated material changed the outcome [3]. Lipid-based fenofibrate experiments similarly showed that transient supersaturation could support early absorption, while longer absorptive periods increasingly depended on continued solubilization [4].

These observations motivate a narrower question than whether supersaturation is “good.” The relevant question is whether drug is generated into an absorbable state quickly enough, remains molecularly available or replenishable long enough, and is removed by the membrane before kinetically competing processes diminish that opportunity. The article therefore treats supersaturation as a coupled kinetic problem. Concentration, precipitation, drug-rich phase formation, gastrointestinal transformation, and membrane flux are kept analytically distinct, and the integrated architecture advanced later is explicitly proposed rather than presented as a prospectively validated predictor.

Generation of supersaturation

Supersaturation begins with a generation process whose rate and location depend on dosage-form chemistry. Cocrystals illustrate why the maximum concentration alone is insufficient. Their dissolution can create a supersaturated drug trajectory while coformer concentration, dose, and cocrystal solubility simultaneously alter the onset of precipitation; useful performance therefore depends on synchronization between drug release and loss from solution [5]. Generation should consequently be described as a kinetic input to a transient system, not simply as attainment of a supersaturation ratio.

Bulk measurements can also miss locally generated states. Modeling and microscopy of dissolving drug salts indicate that the unstirred layer adjacent to a particle can reach conditions favorable for liquid–liquid phase separation even when bulk measurements do not represent the same local composition [6]. The prediction was not exact for every compound, which is important: surface phase behavior is drug-specific and should not be generalized from pKa, solubility product, or nominal pH alone.

For amorphous solid dispersions, polymer ionization and gastrointestinal state further condition generation. Pretomanid dispersions containing an enteric polymer showed pH- and fed/fasted-dependent release and crystallization behavior, while standardized media did not reproduce all aspects of food-state performance [7]. Thus, the initial supersaturated state is already conditional on formulation architecture, local pH, dilution history, and medium composition before precipitation or absorption is considered.

Nucleation and precipitation kinetics

Once supersaturation is generated, its persistence depends on the pathway and timescale of phase loss. Posaconazole experiments showed that nucleation behavior changed with supersaturation and media composition, and that surfactants or pre-existing particles could alter precipitation kinetics [8]. A nominal concentration above solubility therefore describes thermodynamic driving force but not the time available before a competing solid phase becomes important.

The stochastic character of nucleation reinforces this distinction. A microarray approach applied to celecoxib captured distributions of precipitation behavior rather than a single deterministic time point [9]. Such variability matters for formulation comparison because a precipitation “endpoint” can conceal induction-time dispersion and assay sensitivity. It should not be converted directly into an *in vivo* precipitation rate without physiological validation.

Polymer effects add another layer. Hydroxypropyl cellulose grades differed in their ability to solubilize celecoxib and inhibit desupersaturation, demonstrating that these two functions need not rank together [10]. A polymer that raises apparent dissolved concentration is not therefore automatically the polymer that best delays precipitation. Polymer-mediated liquid–liquid phase separation also reflects both thermodynamic and kinetic influences: celecoxib phase boundaries and LLPS onset shifted with polymer identity and experimental conditions [11]. For formulation design, precipitation kinetics should therefore be represented as a conditional hazard governed by supersaturation, nucleation environment, excipient interactions, and available time, rather than as an inevitable consequence occurring at one fixed threshold.

Drug-rich phases and transient solubilization

Loss of a homogeneous molecular solution does not always mean immediate conversion to crystalline drug. Supersaturated systems may form drug-rich phases or colloidal reservoirs, but their biopharmaceutical meaning

depends on composition and exchange with the molecularly dissolved fraction. Quantitative NMR measurements of ibuprofen systems showed that polymer partitioning into drug-rich phases could lower the aqueous drug concentration and chemical potential [12]. A reservoir may therefore increase total drug retained in a dispersed state while not proportionally increasing the concentration that directly drives passive membrane transfer.

The same distinction appears with solubilizers. In ketoprofen systems, CTAB increased measured solubility, yet partitioning and phase behavior could reduce the maximum thermodynamic activity of the drug [13]. Apparent solubilization and absorptive driving force are therefore not interchangeable variables. Telaprevir amorphous solid dispersions further showed that polymer identity and drug loading determined whether LLPS occurred and influenced free-drug mass flow across a membrane system [14]. LLPS should not be treated as an intrinsically favorable formulation endpoint.

Nor does maintenance of supersaturation necessarily require sacrificing permeability. Selected probucol solid dispersions based on block-copolymer morphologies maintained supersaturation while retaining Caco-2 membrane permeation in the tested system [15]. The result is useful as a boundary case, not as proof of human absorption superiority. Together, these studies support separating at least three operational states in formulation interpretation: molecularly available drug, noncrystalline drug-rich or colloidal reservoirs capable of exchange with that pool, and precipitated crystalline material. Their relative importance is time-, composition-, and assay-dependent.

Gastrointestinal dilution and composition

The gastrointestinal environment transforms all of these states. Buffer chemistry is not a neutral background variable. Comparative testing showed that bicarbonate and phosphate systems could produce different dissolution and precipitation behavior even when nominal pH was similar, and the direction of the effect was compound-dependent [16]. This makes dilution history, buffer species, ionic environment, and local pH part of the mechanism being simulated rather than merely analytical settings.

Transfer models for ketoconazole, pazopanib, and lapatinib illustrate the translational consequence. Precipitation inhibition observed with HPMCAS in phosphate-based conditions did not translate into the expected pharmacokinetic benefit, whereas a bicarbonate-based transfer model better aligned with the tested in vivo behavior [17]. The result does not establish bicarbonate media as universally predictive; it shows that an apparently favorable supersaturation profile can be an artifact of an insufficiently physiological chemical environment.

Food state adds further coupled changes in dilution, bile components, lipids, and solubilization capacity. A supersaturable phospholipid dispersion of aprepitant showed that formulation composition and fed/fasted media altered supersaturation, dispersed-phase behavior, permeation, and subsequent preclinical performance [18]. The important analytical point is that gastrointestinal composition can simultaneously change generation, precipitation, reservoir formation, and the fraction available for membrane transfer. These effects should therefore be considered together rather than assigned to independent assay stages.

Because gastrointestinal composition can move the same formulation between materially different kinetic states, a design-space comparison is more informative than a single “biorelevant dissolution” label. **Table 1** separates the physiology-conditioned scenarios that determine whether a supersaturated state remains useful or becomes misleading.

Table 1. Gastrointestinal composition states that change the interpretation of supersaturation before absorption

Physiology-conditioned scenario	Starting dosage-form state	Composition or dilution condition	Dominant transformation event	Drug state that must be distinguished	Kinetic readout needed to judge usefulness	Non-negotiable interpretation boundary
Weak-base transfer from gastric to intestinal conditions	Dissolved or rapidly releasing supersaturating form	Abrupt pH increase with intestinal buffering	Supersaturation generation followed by nucleation or phase separation	Molecular drug versus newly formed noncrystalline or crystalline phase	Concentration-time trajectory together with precipitation onset	Bulk concentration alone cannot establish how long absorbable drug remains available
Bicarbonate-like	Supersaturating	Physiologically relevant buffer	Buffer-conditioned	Free drug, transient	Medium-sensitive	Matching nominal pH

intestinal buffering	formulation after transfer	species and capacity	dissolution and precipitation	reservoir, precipitate	precipitation kinetics	does not make phosphate and bicarbonate systems mechanistically equivalent
Phosphate-rich surrogate condition	Same nominal formulation and pH target	Higher nonphysiological buffer environment	Altered dissolution-layer and precipitation behavior	Apparent dissolved drug versus state likely to persist after physiological transfer	Comparison against a more physiological transfer condition	Favorable precipitation inhibition should not be assumed to translate in vivo
Fasted intestinal dilution	ASD, cocrystal, or dispersed formulation	Lower lipid/solubilization capacity and dynamic dilution	Rapid change in drug activity and reservoir stability	Molecular fraction versus colloidal/drug-rich fraction	Time-resolved supersaturation plus phase-state measurement	Total dispersed drug is not equivalent to membrane-driving drug
Fed-state dilution and solubilization	Formulation entering bile- and lipid-rich conditions	Increased solubilizing components with altered dilution history	Redistribution among molecular and solubilized reservoirs	Thermodynamically active drug versus solubilized drug	Supersaturation and permeation measured under the same nutritional condition	Increased apparent solubility does not guarantee increased flux
pH-responsive enteric ASD release	Polymer-controlled amorphous dispersion	Polymer ionization threshold combined with intestinal composition	Delayed or accelerated release followed by possible crystallization	Released molecular drug versus phase-separated drug	Release rate coupled to crystallization timing	Polymer performance cannot be separated from pH and food-state context

Note: The final column is a proposed synthesis of the evidence developed in the text. It specifies interpretation boundaries rather than a validated scoring system or universal decision rule.

The same reasoning is condensed visually in **Figure 1**. The gastrointestinal compartment is treated as an active transformation landscape that redistributes drug among molecular, reservoir, and precipitating states while establishing the conditions under which a downstream absorptive sink can become relevant.

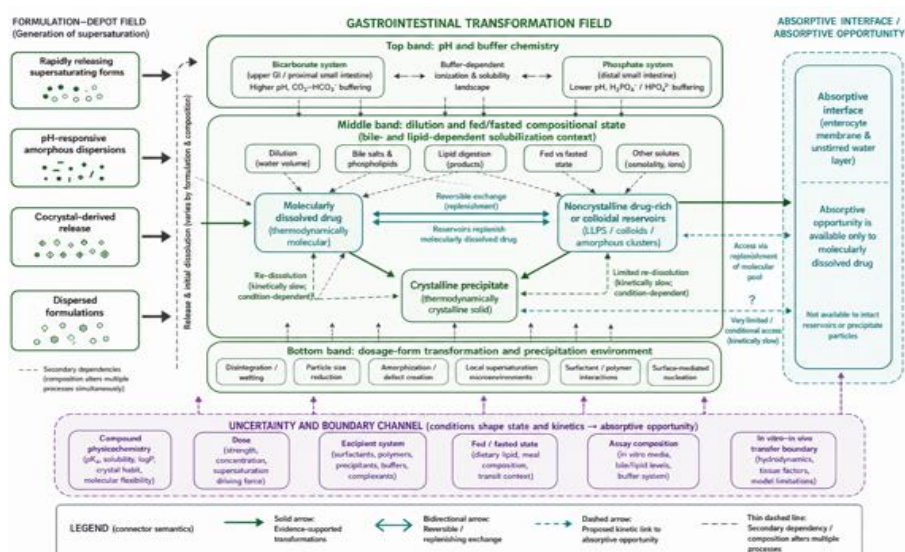


Figure 1. Gastrointestinal transformation determines which supersaturated drug states remain available for kinetic competition

Absorptive sink conditions

An absorptive sink changes the problem from passive observation of a donor compartment to dynamic removal of drug from it. Coupled dissolution–mass-transfer measurements of amorphous solid dispersions showed that adding an absorptive compartment could materially alter dissolution and phase behavior compared with closed testing [19]. This finding supports treating absorption as a kinetic competitor capable of modifying the concentration field that drives precipitation, not merely as a later pharmacokinetic consequence.

Colloidal or drug-rich particles can contribute indirectly by replenishing molecular drug as it is removed. Membrane-flux studies with atazanavir, lopinavir, and clotrimazole found size- and partition-dependent enhancement but also a flux plateau above amorphous solubility, consistent with passive transport remaining constrained by molecularly dissolved drug in the tested membrane system [20]. The result argues against assuming that intact colloidal particles constitute the principal passively absorbed species.

More integrated tools attempt to reproduce this feedback explicitly. The Dynamic Intestinal Absorption Model combined gastrointestinal transfer and permeation to differentiate pH-sensitive formulation behavior and support evaluation of a pH-modifying strategy for a weak-base compound [21]. Such systems are useful because they expose formulation sensitivity to dissolution–absorption coupling, but they remain compound- and model-dependent. They should be viewed as mechanistically richer test environments, not as universally validated surrogates for human exposure.

Coupling supersaturation to membrane flux

The decisive formulation variable is not total concentration alone but the concentration and activity of drug able to replenish the membrane-facing molecular pool over time. Excipient studies with atazanavir and ritonavir provide a direct counterexample to the assumption that greater apparent solubility necessarily improves transport: sodium dodecyl sulfate increased amorphous solubility yet reduced measured flux under the tested conditions [22]. The interpretation is not that solubilization is intrinsically harmful, but that solubilized drug, thermodynamic activity, particle state, and membrane-driving molecular drug can diverge.

Kinetic coupling also separates the rate of absorption from its eventual extent. Manipulating ketoconazole cocrystal dissolution altered supersaturation behavior and changed C_{max} and T_{max} in rats without a proportional change in total exposure [23]. A formulation can therefore reshape the temporal profile of absorptive opportunity without producing a corresponding change in exposure area.

These findings support a proposed formulation-level interpretation: supersaturation is useful when the rate of generating membrane-available drug and replenishing that pool is favorable relative to precipitation or sequestration within the relevant absorption window. This is not a claim that one measurable flux value can replace dissolution. Rather, concentration-time data should be interpreted alongside phase state and sink-conditioned mass transfer when formulation ranking is sensitive to precipitation, solubilization, or permeability. The practical consequence is a shift from asking how high supersaturation rises to asking how much kinetically accessible drug can reach the absorptive interface before competing transformations remove or sequester it.

Why dissolution alone misrepresents formulation performance

Dissolution remains indispensable for characterizing release, but its interpretation becomes fragile when concentration is treated as a sufficient surrogate for absorptive performance. Biopredictive work with dipyridamole has emphasized that dissolution profiles gain decision value when experimental conditions are physiologically relevant and the resulting profiles are interpreted together with biopharmaceutic modeling rather than as isolated concentration-time traces [24]. The limitation is not dissolution itself, but the assumption that concentration measured under one hydrodynamic and compositional condition uniquely determines absorptive performance.

Three kinds of mismatch are especially important in supersaturating systems. First, a closed dissolution compartment can overstate persistence because absorptive removal is absent; conversely, introducing a sink can reduce free-drug concentration sufficiently to delay precipitation or alter formulation ranking [1]. Second, the measured “dissolved” pool can contain drug whose thermodynamic activity differs from that of freely molecular drug, as demonstrated when solubilizer or drug-rich-phase partitioning changes concentration without equivalent changes in activity [13]. Third, apparently superior dissolution can coexist with unfavorable downstream phase behavior or lower bioavailability, as shown by the felodipine amorphous solid dispersion comparison [3]. These failure modes should not be collapsed into one correction factor.

A fourth mismatch arises when the medium itself creates the apparent advantage. In transfer experiments, precipitation inhibition seen under phosphate conditions did not yield the expected pharmacokinetic benefit, whereas the bicarbonate-based test better reflected the evaluated *in vivo* behavior [17]. Dissolution therefore has to be interpreted as the output of a particular chemical environment, not as an intrinsic property of the dosage form. A favorable curve may reflect useful release or a buffer-, surfactant-, or phase-state-dependent condition that will not persist after transfer.

The practical decision is consequently conditional. Conventional dissolution may be sufficient when formulations remain predominantly molecularly dispersed, precipitation is slow relative to transit and absorption, and excipient-mediated solubilization does not materially alter membrane-driving activity. It becomes increasingly incomplete when phase separation, rapid precipitation, pH-dependent transformation, strong colloidal solubilization, or permeability-dependent sink effects dominate. The decision states in **Table 2** separate what can legitimately be concluded from dissolution alone from situations in which additional phase-state, kinetic, or flux measurements are needed.

Table 2. Decision states for when dissolution can and cannot support formulation ranking in supersaturating systems

Decision state	Information available from dissolution	Time-dependent uncertainty that remains	Biorelevant readout needed	Permissible formulation decision	Observation that should trigger reassessment	Proposed supersaturation–precipitation–flux endpoint
Stable molecular release	Reproducible concentration–time profile with no evident phase transition	Whether sink removal materially changes the profile	Sink-coupled check when permeability or dose makes removal potentially important	Use dissolution as the primary comparative test if other boundaries remain matched	Different ranking after introduction of a sink	Dissolution may be sufficient only while generation and loss remain slower than the relevant absorptive perturbation
Rapidly precipitating supersaturation	High initial concentration followed by decline	Induction time and precipitation pathway	Time-resolved phase-state or precipitation measurement	Do not rank formulations from peak concentration alone	Similar peaks with different precipitation kinetics	Compare generated drug with the fraction remaining kinetically accessible before phase loss
Drug-rich or colloidal reservoir	High apparent dissolved or dispersed concentration	Rate of exchange with molecularly available drug	Free-drug/activity-sensitive measurement plus flux	Treat reservoir capacity separately from immediate absorptive driving force	Increased solubilization without increased flux	Evaluate reservoir replenishment relative to membrane removal
Strong excipient solubilization	Increased apparent or amorphous solubility	Whether thermodynamic activity is reduced	Permeation or mass-transfer measurement under matched composition	Avoid equating solubility gain with absorptive gain	Higher concentration accompanied by lower flux	Prefer membrane-available drug delivery rate over concentration alone
pH- or transfer-sensitive release	Favorable profile in one medium or stage	Whether behavior persists after GI transfer and dilution	Physiologically relevant transfer testing	Require matched gastric-to-intestinal conditions before ranking	Loss of advantage in a more physiological medium	Judge usefulness across the full transformation interval, not at one vessel condition
Absorptive-sink-sensitive formulation	Donor profile differs between closed and	Direction and magnitude of feedback from drug removal	Coupled dissolution–permeation experiment	Base ranking on the coupled state when the	Sink reverses or compresses	Compare generation, precipitation or sequestration, and

permeable systems	difference is material	formulation separation	absorptive removal on the same time base
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Note: The final column is a proposed decision logic, not a validated scoring system. It specifies which kinetic relationship should be interrogated rather than supplying universal thresholds.

An integrated supersaturation–precipitation–flux framework

A supersaturating formulation can be represented as a transient mass-transfer system with three competing processes: generation of supersaturation, loss or redistribution through precipitation and drug-rich phases, and absorptive removal. The first process determines how rapidly drug enters a nonequilibrium state; the second determines how that state is partitioned among molecular drug, reversible reservoirs, and less readily available solid phases; the third removes molecularly available drug and can feed back on both concentration and precipitation. Coupled dissolution–absorption experiments provide direct evidence that this feedback can occur [19].

The central contribution of this Perspective is a proposed supersaturation–precipitation–flux framework that places these processes on the same time axis. It does not define a new numerical index. Instead, it asks whether the rate of generating membrane-available drug exceeds the combined kinetic losses from precipitation or sequestration for long enough to exploit the relevant absorptive window. Under this formulation, a high peak may be useful when permeability is high and absorption is rapid, consistent with the dipyridamole and ketoconazole results [2]. The same peak may be less useful when precipitation precedes significant removal or when the measured concentration is dominated by a reservoir with low immediate activity.

The framework treats absorptive removal as capable of changing the upstream state rather than simply sampling it. When drug is removed from the molecular pool, a noncrystalline reservoir may replenish that pool, supersaturation may decrease, and nucleation pressure may change. Conversely, when replenishment is slow or precipitation captures drug rapidly, a high early concentration may have little persistence at the membrane interface. These relationships are proposed as organizing logic; their individual transitions arise from different experimental systems and do not establish one universal pathway.

The framework also separates total analytical concentration from biopharmaceutically active state. Polymer partition into a drug-rich phase can lower the aqueous molecular concentration even while drug remains noncrystalline [12], while colloidal particles may sustain flux primarily by replenishing molecular drug rather than by crossing the membrane intact [20]. These observations justify representing molecular drug, replenishable reservoirs, crystalline loss, and absorbed mass as different state variables whenever the assay can resolve them. They do not imply that every supersaturating formulation must populate every state.

A formulation comparison becomes most informative when these state transitions are measured under the same gastrointestinal and temporal conditions. If generation is rapid, precipitation slow, and absorptive removal efficient, supersaturation can be exploited without requiring long persistence. If generation is rapid but flux is weak, precipitation or reservoir sequestration can dominate before absorption. If a reservoir replenishes molecular drug efficiently, apparently modest free-drug concentrations may still sustain transport. Fed- or fasted-state changes can alter more than one branch simultaneously because composition modifies release, solubilization, phase behavior, and permeation conditions [18]. These regimes are proposed interpretive categories, not empirically validated classes. Their value is to identify which kinetic competition should be tested instead of allowing one dissolution metric to stand for the whole system.

The framework changes the unit of formulation interpretation. Rather than asking whether a product generates a predefined supersaturation magnitude, it asks whether the product maintains a favorable sequence of states over the relevant gastrointestinal interval. This sequence can differ between drugs and products even when their nominal supersaturation ratios are similar. Its future utility depends on demonstrating that the selected measurements improve formulation decisions prospectively; no such universal validation is assumed here.

Formulation design boundary conditions

The framework is necessarily bounded by drug physicochemistry, dose, dosage-form architecture, gastrointestinal state, permeability, and assay design. Pazopanib provides a clear phase-behavior example: pH, dose, amorphous solubility, and crystallization inhibition changed whether pH-induced supersaturation remained molecular, underwent liquid–liquid phase separation, or progressed toward crystallization [25]. A universal supersaturation threshold would therefore erase variables that determine the phase trajectory.

Permeability and absorptive timescale are equally important. For highly permeable drugs, substantial absorption can occur before prolonged supersaturation is required [2]. In contrast, when the absorption window extends or effective removal is slower, continuing solubilization may become more important, as observed for fenofibrate in the lipid-based formulation model [4]. These findings should not be combined into a single rule about optimal supersaturation duration; they define different kinetic regimes. Dose can further change the balance by altering both the amount entering the supersaturated state and the likelihood that phase boundaries are crossed.

Formulation excipients and gastrointestinal composition create additional transfer limits. Polymer grade can affect solubilization and precipitation inhibition differently [10], while bicarbonate and phosphate media can alter dissolution and precipitation in compound-dependent ways [16]. Likewise, excipients that increase apparent solubility can reduce flux under particular conditions [22]. Formulation ranking should therefore be regarded as conditional on the drug–excipient–medium combination rather than assumed to transfer unchanged across test systems, fed or fasted states, doses, or products.

Method choice should follow the dominant uncertainty rather than escalate automatically to the most complex apparatus. A molecularly dispersed formulation with slow precipitation may need little beyond appropriately biorelevant dissolution, whereas a rapidly phase-separating system may require orthogonal phase-state measurements. Strongly solubilized systems may require activity-sensitive or flux measurements, and pH-sensitive formulations may require gastric-to-intestinal transfer. This staged logic is proposed as a way to select informative experiments without implying that every supersaturating product requires the same test battery.

Prospective use of the proposed framework would ultimately require compound-specific measurements and validation. Advanced transfer/permeation platforms can support formulation-development questions [21], and physiologically informed dissolution coupled with biopharmaceutical modeling can improve interpretation [24]. Neither approach converts the framework into a universally validated predictor. Where decisions depend on exposure, suitable in vivo or clinical bridging remains necessary, with uncertainty retained for unrepresented physiological or gastrointestinal variability.

CONCLUSION

Supersaturation is pharmaceutically useful only when its kinetic fate is interpreted together with the opportunity for absorption. Peak dissolved concentration and duration above equilibrium solubility are incomplete descriptors because drug can redistribute among molecular, drug-rich, colloidal, and crystalline states while an absorptive sink removes the fraction capable of membrane transfer. Gastrointestinal pH, buffer composition, dilution, food state, dose, excipients, permeability, and dosage-form architecture determine which process dominates.

The proposed supersaturation–precipitation–flux framework therefore treats formulation performance as competition among generation, phase loss or reservoir formation, and absorptive removal on a common time base. It does not replace dissolution testing, prescribe universal thresholds, or assume that every supersaturating system follows the same phase trajectory. Its purpose is to identify when dissolution is an adequate comparative tool and when phase-state, precipitation-kinetic, activity-sensitive, or flux measurements are required.

The design objective is consequently not maximal supersaturation in isolation. It is preservation or replenishment of a kinetically accessible drug pool long enough for meaningful absorptive removal under the gastrointestinal conditions relevant to the product. Testing that proposition prospectively across compounds, dosage forms, physiological states, and translational levels remains necessary before the framework can be treated as predictive rather than interpretive.

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