



Original Article

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Lipid-Based Formulations Under Variable Gastrointestinal Physiology

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ABSTRACT

Lipid-based formulations are commonly evaluated as systems that improve the apparent solubility of poorly water-soluble drugs, yet their performance is generated within a gastrointestinal environment that changes continuously after administration. Digestion, bile salt and phospholipid availability, meal composition, luminal pH, gastric emptying, intestinal transit, drug precipitation, absorptive removal, and epithelial lipid processing can alter both the formulation and the physiological environment against which it is tested. Consequently, the concentration of drug recovered in an aqueous or colloidal phase is not necessarily equivalent to the concentration thermodynamically available for membrane transport, and precipitation observed during digestion is not necessarily equivalent to loss of absorption. This critical review examines lipid formulation classes as dynamic states rather than static vehicles and evaluates how digestive transformation, colloidal restructuring, physiological variability, supersaturation, and absorptive processes change the interpretation of formulation performance. Particular attention is given to bile salt and phospholipid variability, fed–fasted transitions, pH and transit, and the time relationship between precipitation and absorption. The review develops a proposed physiology-conditioned formulation-state interpretation in which formulation performance is judged across sequential luminal and absorptive states, with explicit validation boundaries between solubilization, free drug, permeability, and systemic exposure. This interpretation does not replace established formulation classifications or claim prospective prediction. Instead, it identifies where apparently favorable *in vitro* behavior may fail to transfer because the physiological condition, measurement compartment, time scale, or absorptive sink has changed.

Keywords: Lipid-based drug delivery, Gastrointestinal physiology, Lipolysis, Bile salts, Supersaturation, Drug precipitation

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INTRODUCTION

Lipid-based formulations (LBFs) are intended to overcome oral delivery constraints that arise when dissolution, solubilization, or maintenance of a drug in a membrane-accessible state limits absorption. Their experimental evaluation, however, often imposes much greater physiological uniformity than exists in the gastrointestinal tract. Gastric and intestinal fluid volumes, pH, bile secretion, motility, transit, food-associated secretions, luminal composition, and absorptive conditions vary between individuals and within the same individual over time, and these changes can modify oral drug absorption and pharmacokinetics [1]. For an LBF, such variation is unusually

important because gastrointestinal processing does not merely expose a finished formulation to a new medium: dispersion and digestion progressively reconstruct the colloidal environment carrying the drug.

This distinction becomes particularly important for supersaturating systems. Supersaturation can arise through different formulation strategies, including delivery of drug above its equilibrium solubility and approaches designed to generate supersaturation during gastrointestinal processing. These strategies differ in their mechanistic basis, maturity, susceptibility to precipitation, and dependence on digestive events [2]. Treating them as a single category defined only by increased apparent solubilization can therefore obscure the state in which drug actually reaches the absorptive surface.

The experimental model can add another layer of interpretation. Lipolysis outcomes vary with enzyme source and activity, formulation composition, medium composition, digestion conditions, sampling strategy, and the way drug is assigned among aqueous, colloidal, and precipitated fractions [3]. Thus, a favorable result under one digestive condition cannot automatically be read as a formulation-intrinsic property. The central argument developed here is that LBF performance should instead be interpreted as conditioned by physiological state and measurement scale. The proposed synthesis separates four questions that are often compressed into one: whether the formulation generates a favorable luminal drug state, whether that state persists during gastrointestinal transformation, whether drug remains available for membrane transport, and whether the resulting behavior transfers across relevant physiological conditions. These questions become increasingly distinct as digestion proceeds.

Lipid formulation classes and mechanisms

Conventional classification of LBFs remains useful because lipid, surfactant and cosolvent content strongly influence dispersion, digestibility and drug carrying capacity. Nevertheless, nominal class alone cannot specify the mechanism responsible for improved exposure. In a fenofibrate system, for example, novel oil-like cinnamoyl amino acid octanol ester material used in a self-microemulsifying formulation increased oral bioavailability relative to tested comparators, while the experiments did not support increased intestinal permeability or P-glycoprotein inhibition as the explanation [4]. The example illustrates that drug-vehicle affinity and maintenance of a favorable solubilized state can change formulation behavior without invoking a permeability-enhancing mechanism.

Digestibility further prevents the dosage form from being treated as a static container. Pancreatic lipase can transform lipid excipients and lipid-based carriers during gastrointestinal residence, changing the material available for colloidal assembly, drug partitioning and release [5]. Digestion may therefore be advantageous when it produces colloidal species that sustain drug in solution, but detrimental when the disappearance of the original solvent environment removes drug carrying capacity. The direction cannot be assigned from the presence of digestible lipid alone.

Supersaturating hybrid systems add another possibility: the formulation can be designed not simply to carry dissolved drug but to control the state reached after dispersion or digestion. A supersaturating lipid-based solid dispersion of atazanavir produced enhanced solubilization and supersaturation in the digestive aqueous phase under the investigated in vitro conditions [6]. Such findings support the feasibility of engineering post-dispersion drug state, but they do not establish that higher digestive-phase supersaturation will invariably improve systemic exposure. The clinically relevant consequence depends on whether supersaturation persists long enough, whether precipitation competes with absorption, and whether the fraction remaining solubilized is sufficiently available for membrane transport.

Accordingly, the mechanistic distinction used throughout this review is not “lipid formulation versus non-lipid formulation,” but stored formulation state versus gastrointestinally transformed state. The former describes what is administered; the latter determines what the intestine encounters.

MATERIALS AND METHODS

This article was conducted as a critical narrative review designed to evaluate how gastrointestinal physiological variability influences the interpretation of lipid-based formulation performance. The objective was not to estimate pooled effect sizes or perform quantitative meta-analysis, but to critically examine mechanistic evidence, methodological limitations, and translational boundaries across formulation, digestion, absorption, and exposure assessment.

A structured literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and Embase to identify relevant studies published from January 2010 to December 2025. Search terms were developed around four major concept domains: (1) lipid-based formulations and oral drug delivery; (2) gastrointestinal transformation, digestion, bile salts, phospholipids, and simulated intestinal fluids; (3) supersaturation, precipitation, permeability, lymphatic transport, and absorption models; and (4) in vitro–in vivo translation and biopharmaceutical evaluation. Additional studies were identified through backward citation searching of relevant articles and forward citation tracking of key methodological papers.

Eligible studies included original research articles, mechanistic investigations, advanced in vitro model studies, computational studies, and authoritative reviews that provided evidence relevant to the relationship between lipid formulation behavior and physiological conditions. Studies were considered relevant when they investigated at least one of the following: gastrointestinal transformation of lipid formulations, changes in drug solubilization or supersaturation during digestion, effects of bile and phospholipid composition, absorptive sink effects, epithelial transport, lymphatic delivery, or approaches for improving in vitro–in vivo interpretation.

Studies were excluded when they focused exclusively on formulation preparation without mechanistic evaluation, reported only routine physicochemical characterization without physiological relevance, or lacked sufficient information to interpret the relationship between formulation state and biological outcome.

Study selection and evidence synthesis were performed iteratively by evaluating each article according to four predefined interpretive domains: (1) formulation-state generation, including dispersion, digestion, and colloidal restructuring; (2) physiological-condition dependence, including food state, bile composition, pH, transit, and intestinal variability; (3) absorptive-state relevance, including free drug availability, permeability, and lymphatic processes; and (4) translational validity, including the extent to which experimental models support in vivo interpretation.

Because the purpose of this review was conceptual integration rather than quantitative comparison, formal risk-of-bias scoring was not applied. Instead, methodological quality was critically assessed according to experimental design appropriateness, physiological relevance of the model system, alignment between measured endpoints and biological inference, and whether conclusions were supported across multiple experimental scales.

The evidence was synthesized narratively to identify recurring interpretation errors, unresolved validation boundaries, and conditions under which apparently favorable formulation outcomes may fail to translate. The resulting physiology-conditioned formulation-state interpretation was developed from this synthesis as a conceptual framework intended to organize existing evidence rather than function as a validated predictive model.

Digestion and Colloidal Transformation

Digestion converts the original formulation into a changing mixture of lipid digestion products, bile-associated colloids, residual excipients and drug. Experimental and molecular-dynamics work on a type I formulation demonstrated that post-digestion phase behavior and colloidal organization affect the capacity of the system to solubilize danazol [7]. This supports a view of digestion as a compositional transition rather than simply a reduction in intact triglyceride concentration. The relevant drug environment may move among oil-rich domains, mixed colloids, aqueous species and precipitated material as digestion progresses.

Drug physicochemistry determines how strongly those transitions affect precipitation. Comparative lipolysis experiments across multiple drugs and formulations showed that molecular properties, ionization behavior and formulation context influenced both supersaturation and the nature of precipitated material [8]. A weak base encountering changing pH and lipid digestion products therefore cannot be assumed to behave like a neutral compound with the same nominal equilibrium solubility. Conversely, identifying precipitation in one formulation does not establish an intrinsic tendency to precipitate under all digestive conditions.

A major interpretive problem arises when digestion is studied without simultaneous removal of absorbable drug. Coupling lipolysis to a Caco-2 permeation compartment altered luminal drug concentrations and supersaturation relative to conventional digestion experiments because permeation acted as an absorptive sink [9]. The importance of this observation is conceptual as well as methodological: absorption is capable of changing the luminal state whose stability is being measured. Precipitation and absorption are therefore competing processes rather than obligatorily sequential events.

Adding physiological complexity does not guarantee better prediction. A biphasic lipolysis method incorporating gastric-to-intestinal transition and an organic absorption sink improved agreement with in vivo behavior in three of four evaluated literature datasets, while conventional pH-stat lipolysis performed better for one dataset [10]. The discordant case is important because it argues against ranking models simply by their number of physiological features. A more complex model may improve prediction when its added process is relevant to the formulation,

yet distort interpretation when sink properties, dispersibility or phase partitioning no longer represent the dominant *in vivo* limitation.

The same caution applies to the measurement of “solubilized drug.” With saquinavir-containing LBFs, digestion changed free drug concentration, thermodynamic activity and permeability in ways that were not explained by total solubilized concentration alone [11]. Micellar or colloidal retention can preserve a large apparent aqueous drug pool while simultaneously reducing the freely available concentration driving membrane transfer. Consequently, a formulation can perform well in a solubilization assay but less well at the absorptive boundary. Temporal resolution is equally important. Real-time analytical lipolysis has been developed to follow drug concentration during digestion rather than reconstructing the process exclusively from discrete end points. In a fenofibrate system, a Palatase-based method combined with inline ultraviolet analysis generated digestion behavior comparable with the conventional pancreatin-based approach under the tested conditions [12]. This does not make the alternative enzyme universally interchangeable with pancreatin, but it demonstrates why dynamic measurements are valuable: the most informative state may be transient and disappear before an end-point sample is collected.

Taken together, these studies support a proposed digestive-state distinction among total drug carried by the evolving colloidal system, drug remaining molecularly available for transfer, drug leaving the lumen through an absorptive sink, and drug becoming kinetically or physically unavailable through precipitation. None of these quantities should be treated automatically as a surrogate for another.

Bile salt and phospholipid variability

Bile salts and phospholipids are often represented experimentally as fixed constituents of simulated intestinal media, but their pharmaceutical role depends on how they participate in dynamically assembled intestinal colloids. Molecular-dynamics studies, simulations informed by fed-state human intestinal fluid, and direct measurements of human intestinal fluids collectively demonstrate that bile-associated structure, lipid composition and the solubilizing environment are composition-sensitive rather than invariant [13–15]. The implication for LBFs is that gastrointestinal fluid should not be regarded as a passive dilution phase. It is an active component of the drug-carrying system formed after dispersion and digestion.

Fed-state simulations further show that model construction itself matters. The initial molecular distribution and representation of glyceride components can alter predicted colloidal structures and drug solubilization [14]. Such sensitivity is not merely a computational inconvenience: it reflects the fact that experimentally aspirated intestinal fluid contains ensembles of colloidal species whose composition changes after food and lipid processing. Computationally reproducing one ensemble therefore does not prove that the same architecture exists throughout the postprandial intestine.

Human-fluid measurements provide a complementary boundary. Fractionation of fasted and fed human intestinal fluids showed that lipid-rich fractions contributed materially to solubilization for the tested lipophilic drugs, while the magnitude varied across compounds, fluid pools and prandial states [15]. Thus, increasing bile- or lipid-associated solubilizing capacity is not a formulation-independent variable. Drug partitioning into these structures remains compound specific.

The problem becomes more apparent when a single nominal simulated medium is used to represent a population. A multi-medium simulated intestinal-fluid system captured a broader range of literature-reported human intestinal solubility values than a single canonical medium [16]. This supports the use of physiological envelopes during formulation testing, although equilibrium-solubility coverage should not be mistaken for validation of LBF pharmacokinetics.

Meal state introduces additional temporal heterogeneity. Characterization of intestinal fluids after a solid meal showed changes in composition and solubilizing capacity over the postprandial sampling period and differences from fluids obtained after a liquid meal [17]. Consequently, “fed state” is not one fixed physicochemical condition. For an LBF administered with food, the formulation may encounter different endogenous and exogenous lipid environments depending on meal composition and the timing of gastric emptying and intestinal entry.

The central synthesis from this section is therefore proposed rather than empirically validated as a unified framework: bile salt and phospholipid variability should be treated as a cross-scale validation gate between a measured formulation state and the exposure interpretation assigned to it. A formulation that maintains drug in colloidal solution under one bile/lipid composition has demonstrated condition-specific stability, not physiological invariance.

Because the same apparent formulation outcome can acquire a different meaning as the bile/lipid environment, patient state, measurement compartment and transfer test change, the distinctions are more efficiently compared across scales than described sequentially in prose.

Table 1. When bile-associated colloidal variability changes the interpretation of lipid-formulation performance across physiological scales

Principal failure mechanism in interpretation... Design boundary	Formulation lever exposed by the event	Patient-condition variability Dosage-form state	IVIV transfer test needed	Article-specific endpoint
Manuscript-derived luminal event Drug remains dispersed as mixed colloids form after lipid digestion				
Principal failure mechanism in interpretation Total colloidal drug is read as membrane-available drug Design boundary Solubilization does not equal absorption	Lipid/surfactant composition and digestibility	Patient-condition variability that can change the event Bile/lipid composition and prandial state alter colloid capacity Dosage-form state being judged Gastrointestinally transformed LBF	Demonstrate that preserved colloidal drug also preserves free drug or flux	Whether the favorable luminal state survives the absorptive boundary
Manuscript-derived luminal event Drug loses carrying capacity as the original formulation solvent environment disappears				
Principal failure mechanism in interpretation Precipitation is attributed only to poor formulation design Design boundary A condition-specific precipitate is not a universal formulation property	Selection of lipid species, cosolvent and precipitation-control strategy	Patient-condition variability that can change the event Lower or compositionally different endogenous solubilizing capacity can increase vulnerability Dosage-form state being judged Digestion-depleted formulation	Reproduce the event across physiologically plausible media	Whether failure persists across relevant physiology
Manuscript-derived luminal event Lipid-rich postprandial fluid increases apparent drug solubilization				
Principal failure mechanism in interpretation Food-associated solubilization is assigned to the formulation itself Design boundary Fed-state enhancement is context dependent	Compatibility with endogenous/exogenous lipid colloids	Patient-condition variability that can change the event Meal composition and postprandial timing change available lipid domains Dosage-form state being judged Formulation plus meal-generated colloidal system	Separate formulation contribution from intestinal-fluid contribution	Whether apparent food benefit is formulation intrinsic or physiology dependent
Manuscript-derived luminal event Drug repartitions as postprandial composition changes over time				
Principal failure mechanism in interpretation A single fed-state sample is treated as representative of the whole absorption window Design boundary One postprandial time point cannot establish temporal robustness	Persistence of drug affinity during evolving digestion	Patient-condition variability that can change the event Gastric emptying and time since meal alter the encountered state Dosage-form state being judged Time-evolving intestinal dispersion	Time-resolved digestion/solubilization assessment	Whether drug remains available throughout the relevant absorption interval

Manuscript-derived luminal event Stable behavior is observed in one nominal simulated intestinal medium				
Principal failure mechanism in interpretation Nominal medium stability is generalized to patients	Robustness to bile/lipid composition rather than optimization to one medium	Patient-condition variability that can change the event Interindividual fluid composition varies	Stress-test a physiologically justified media envelope	Whether the formulation remains interpretable outside the calibration medium
Design boundary Proposed synthesis: transfer requires state robustness, not success at one nominal condition		Dosage-form state being judged Laboratory-conditioned LBF state		
Manuscript-derived luminal event A computational colloidal state explains measured solubilization				
Principal failure mechanism in interpretation Simulated structure is treated as established human mechanism	Molecular compatibility with predicted mixed assemblies	Patient-condition variability that can change the event Actual human-fluid composition may differ from modeled composition	Validate structural predictions against independent experimental readouts	Whether mechanism survives a scale-transfer test
Design boundary Model explanation and physiological validation remain separate		Dosage-form state being judged In silico reconstruction of transformed LBF		

The bile/phospholipid evidence also supports a visual distinction that prose and the table cannot fully represent: formulation state, physiological condition and exposure interpretation are connected through different validation boundaries rather than through one uninterrupted causal chain.

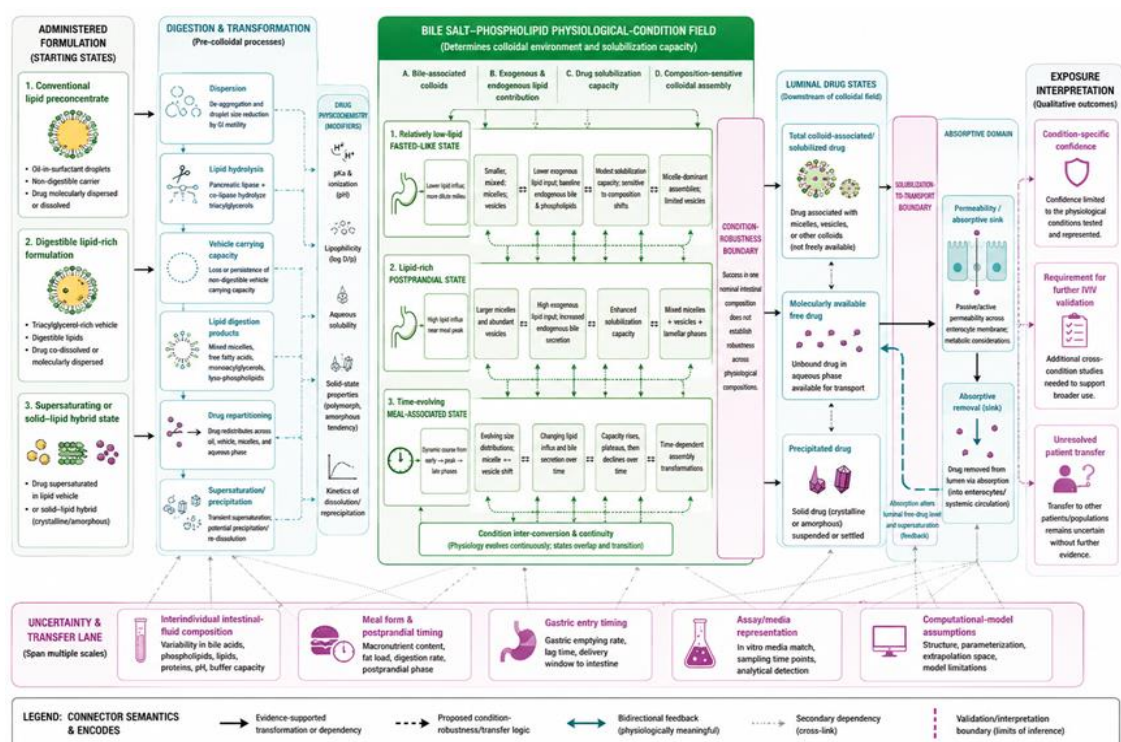


Figure 1. Bile-dependent colloidal states define where formulation performance ceases to transfer across gastrointestinal conditions

Fed–fasted differences

The fed–fasted distinction remains pharmacologically useful, but it becomes misleading when interpreted as a pair of fixed media compositions. Human intestinal-fluid measurements demonstrate variation in solubilizing

capacity among fasted and postprandial states, while solid-meal sampling indicates that the postprandial composition itself evolves with time [15, 17]. For LBFs, food can therefore influence more than the equilibrium solubility of the drug: it can alter gastric residence, the timing of formulation entry into the intestine, endogenous secretion, exogenous lipid availability, and the composition of the colloidal system into which formulation-derived material is incorporated.

Dynamic gastrointestinal modeling illustrates why this temporal dimension matters. The dynamic gastrointestinal model reproduced the direction of food effects for three tested immediate-release products with distinct clinical food-effect behavior [18]. Those products do not constitute validation of the model for LBFs, yet the result demonstrates that dynamic gastrointestinal conditions can recover product-specific behavior that would be difficult to represent with one static “fed” dissolution condition.

For LBF development, the consequence is not that every formulation requires a maximally elaborate food-effect experiment. Rather, food-state variables should be selected according to the mechanism being claimed. A formulation whose advantage depends strongly on intestinal lipid solubilization requires a different physiological stress test from one whose principal benefit derives from rapid dispersion before significant digestion. The proposed interpretation therefore treats fed–fasted status as a trajectory of gastrointestinal conditions, with meal form and time determining which part of that trajectory the formulation encounters.

Gastrointestinal pH and transit

Luminal pH and transit are often investigated as independent formulation variables, although their pharmaceutical effects occur in sequence. Gastric residence determines how long a formulation remains exposed to acidic conditions and whether dispersion or phase separation begins before intestinal entry. Gastric emptying then changes not only location but the surrounding fluid composition, enzyme environment and ionization conditions. Human variability in pH, fluid volume, motility and transit therefore affects the temporal order in which dissolution, supersaturation, digestion and absorption can occur [1].

This sequence is partly represented in models that incorporate a gastric-to-intestinal transition. The improved performance of biphasic lipolysis in several—but not all—evaluated datasets shows that reproducing the transition can add relevant information when gastric processing or absorptive removal is important [10]. The discordant dataset prevents the transition itself from being treated as a universally predictive feature.

Formulation composition may also alter the sequence rather than merely responding to it. In a ketoconazole study, a long-chain type II formulation changed early absorption behavior and apparent first-pass disposition relative to other tested conditions; accompanying experiments implicated changes in free drug availability and absorption timing rather than a simple increase in dissolved dose [19]. Because the evidence is preclinical and drug specific, it does not establish a general effect on human gastric emptying or metabolism. It does, however, reinforce an important boundary: gastrointestinal physiology affects formulation behavior, while the formulation may in turn alter the timing and pathway through which drug becomes available for absorption and metabolism.

Accordingly, pH and transit should not be reduced to isolated stress conditions when the principal formulation risk is sequence dependent. The relevant question is whether a drug remains in an absorption-compatible state as it crosses changing pH, composition and residence-time environments.

Drug precipitation during digestion

Precipitation is often treated as the point at which an LBF has failed. That interpretation is incomplete because precipitation and absorption occur on competing time scales. In a coupled digestion–intestinal absorption study with fenofibrate, transient supersaturation supported short-term absorption even when precipitation subsequently occurred; continued solubilization became more important as the absorption period increased [20]. Thus, the same amount of precipitated drug can have a different exposure consequence depending on when precipitation occurs relative to absorptive removal.

The formulation determinants of this relationship are also conditional. With type II cinnarizine formulations, lipid chain length, supersaturation and digestion affected oral exposure, but long-chain lipid was not consistently superior to medium-chain lipid across the evaluated comparisons [21]. A simple hierarchy such as “more digestible,” “more long-chain lipid,” or “more solubilization” is therefore difficult to defend without specifying the formulation state and experimental condition.

The measured phase can further change the apparent IVIV relationship. Evaluation of supersaturated type I formulations using pH-stat lipolysis showed that overall aqueous-phase measurements did not consistently reproduce prior in vivo ranking, whereas interpretation of specific colloidal or micellar fractions improved some

comparisons [22]. This finding identifies a validation boundary between where a drug is measured and what biological process the measurement is assumed to represent.

Dose loading presents another interpretive problem. Supersaturated type IIIb cinnarizine formulations produced higher non-dose-normalized exposure under tested conditions, but the advantage was attenuated when exposure was considered relative to administered dose, and precipitation inhibition did not produce a clear additional exposure benefit [23]. Consequently, an apparent pharmacokinetic advantage of a supersaturating formulation can reflect increased delivered dose as well as—or instead of—a proportionally improved absorptive state.

Type IV formulations illustrate why digestive dependence must remain formulation-class specific. In a corresponding cinnarizine study, supersaturation produced only limited overall exposure effects and lipase inhibition did not materially alter performance under the tested conditions [24]. Because type IV systems contain no conventional digestible lipid phase, importing mechanistic expectations from type II or type III systems would obscure rather than clarify the evidence.

The synthesis emerging from these experiments is a proposed sequence-aware interpretation of precipitation. The relevant state transition is not simply “solubilized → precipitated.” Instead, formulation dispersion or digestion first establishes a transient drug activity; absorption removes some drug; nucleation and precipitation remove another fraction; colloidal repartitioning may preserve or lower the free concentration; and these processes continue while the formulation moves through the intestine. The exposure consequence depends on their relative rates and durations.

A sequence-aware ledger is therefore needed to keep analytically distinct cases from being collapsed into one precipitation percentage or end-point concentration.

Table 2. Sequence conditions that determine when precipitation becomes an absorptive liability during lipid-formulation digestion

Supersaturation measured without an absorptive sink Short-lived supersaturation during rapid absorption Type II digestion with changing lipid chain environment Type I supersaturated system assessed by pH-stat lipolysis				
Precipitation-state case	Supersaturation measured without an absorptive sink	Short-lived supersaturation during rapid absorption	Type II digestion with changing lipid chain environment	Type I supersaturated system assessed by pH-stat lipolysis
Precursor formulation state	Digested formulation retaining dissolved drug above equilibrium	High-activity drug state after dispersion/digestion	Digestible lipid-rich formulation	Predissolved/supersaturated non-digestible lipid system
Transition trigger	Continued lipolysis and loss of carrying capacity	Supersaturation followed by nucleation	Lipolysis and colloidal restructuring	Dispersion and phase redistribution
Biorelevant observable	Luminal dissolved/colloidal concentration and precipitated fraction	Drug flux during the transient high-concentration interval	Exposure together with digestive sensitivity	Drug assigned to overall aqueous versus specific colloidal phases
Time dependence	Apparent supersaturation may persist longer when drug is not removed	Early minutes can differ from a longer absorption interval	Depends on formulation composition and digestion	Readout can change during the digestion protocol despite limited vehicle digestion
Downstream absorptive or release consequence	Can exaggerate the amount of drug remaining available to precipitate	Substantial early transport can occur before precipitation dominates	Chain length does not impose a universally favorable exposure direction	Aggregate aqueous drug may poorly represent the phase relevant to in vivo performance

Condition that interrupts, reverses or changes the sequence	Addition of an absorptive sink lowers luminal drug and changes competition with nucleation	Longer residence/absorption period increases dependence on maintained solubilization	Lipase inhibition or altered lipid composition changes the sequence	Phase-resolved interpretation changes apparent IVIV relationship
Article-specific interpretation endpoint	Whether precipitation measured in an isolated lumen is relevant to an absorbing intestine	Whether precipitation occurs before or after useful absorptive removal	Whether the formulation benefit is genuinely digestion dependent	Whether the assay compartment matches the biological inference
Supersaturated type IIIb formulation with increased drug loading Supersaturated type IV formulation				
Precipitation-state case	Supersaturated type IIIb formulation with increased drug loading	Supersaturated type IV formulation		
Precursor formulation state	Dispersible formulation carrying drug above equilibrium saturation	Surfactant/cosolvent-rich non-lipid-digestible state		
Transition trigger	Dilution, digestion and possible nucleation	Dispersion and precipitation rather than conventional triglyceride digestion		
Biorelevant observable	AUC/Cmax interpreted with and without dose normalization	Exposure under supersaturated and inhibitor conditions		
Time dependence	Exposure benefit may change when normalized to delivered dose	Digestive lipolysis has limited mechanistic leverage		
Downstream absorptive or release consequence	Raw exposure can increase without proportional increase in absorptive efficiency	Higher supersaturation need not produce a large exposure gain		
Condition that interrupts, reverses or changes the sequence	Dose normalization and precipitation-inhibitor comparison alter mechanistic interpretation	Lipase inhibition has little effect when conventional digestible lipid is absent		
Article-specific interpretation endpoint	Whether supersaturation itself, rather than additional dose, explains the apparent benefit	Whether a physiological perturbation is relevant to the actual formulation class		

Intestinal permeability and lymphatic transport

The absorptive boundary introduces a second major point at which apparently favorable LBF behavior can change meaning. A formulation may preserve a large amount of drug in a colloidal aqueous phase while simultaneously reducing the freely available fraction that drives membrane transfer. In a digestion–absorption comparison using cinnarizine, formulations that maintained more drug in a solubilized state did not necessarily generate the greatest absorptive flux; under the investigated conditions, differences in free-drug availability and membrane surface-area-to-volume representation changed the interpretation [25]. The result does not imply that solubilization is undesirable. Rather, it establishes that solubilization and membrane delivery are separate performance dimensions.

This distinction becomes more complex when intestinal lymphatic transport is considered. Highly lipophilic drugs and appropriately designed delivery systems may enter intestinal lipid-processing pathways and subsequently reach lymph rather than proceeding exclusively through portal absorption [26]. However, lipid administration alone is insufficient to establish meaningful lymphatic targeting. Drug physicochemistry, association with lipid-processing products, enterocyte handling, chylomicron formation, formulation composition and the quantity and nature of absorbed lipid all constrain the pathway.

Molecular design can deliberately increase engagement with this biology. Triglyceride-mimetic prodrugs of mycophenolic acid demonstrated that linker length and intestinal stability altered lymphatic transport and lymph-node exposure in a preclinical structure series [27]. This evidence is mechanistically informative but should not be generalized to conventional LBFs: the prodrug itself was designed to participate in triglyceride metabolic processing, whereas an unmodified drug dissolved in a lipid vehicle may have substantially different intracellular handling.

The lymphatic system is also not a passive conduit whose capacity is constant across patients or disease states. Intestinal lymphatic biology includes regulated lipid transport, immune interactions, vascular–lymphatic exchange and tissue-specific functions that can be altered in disease [28]. Consequently, formulation design directed toward lymphatic exposure introduces a patient-state dependency beyond luminal solubilization. The relevant biological boundary shifts from “can the drug remain solubilized?” to “can the drug or its designed derivative enter and persist within the cellular and lymphatic processes required for transport?”

Model choice determines how confidently that boundary can be studied. Primary human and murine intestinal epithelial models have been compared with Caco-2 cells for their ability to reproduce lipid-processing and lipoprotein-related functions relevant to lymphatic transport. Primary epithelial systems displayed features that were more physiologically representative for the investigated endpoints [29]. Nevertheless, even primary enteroids remain simplified relative to an intact intestine containing blood flow, lymph flow, immune cells, neural regulation and dynamic luminal digestion.

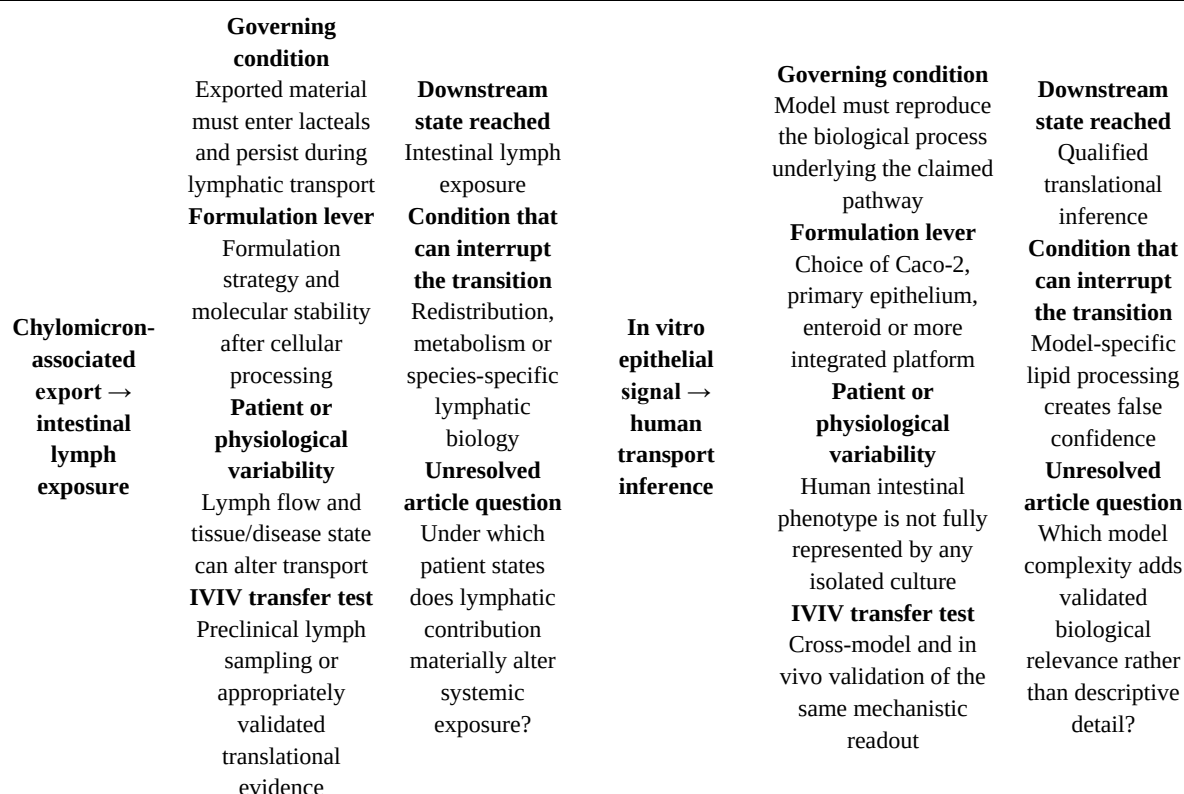
The synthesis proposed here therefore separates three absorptive states: colloid-associated drug that remains intraluminal, molecularly available drug capable of epithelial permeation, and drug entering lipid-processing pathways with potential access to intestinal lymph. Transition among these states depends on formulation properties and physiology and should not be inferred from total dissolved drug alone.

Because those transitions occur sequentially but can fail at different levels, their governing conditions and validation requirements are better represented as a transition ledger than as a conventional comparison table.

Table 3. Formulation-state transitions that separate luminal solubilization, epithelial transfer and intestinal lymphatic access

Formulation-state transition	Evidence structure	Boundary and consequence	Formulation-state transition	Evidence structure	Boundary and consequence
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Colloid-associated drug → molecularly available drug	Governing condition Drug must partition out of bile/lipid/surfactant assemblies into a membrane-accessible fraction Formulation lever Lipid species, surfactant level, cosolvent content and resulting colloidal affinity Patient or physiological variability Bile/lipid composition and intestinal dilution change colloid binding IVIV transfer test Measure free fraction or flux rather than total aqueous drug alone	Downstream state reached Membrane-accessible luminal drug Condition that can interrupt the transition Strong colloidal sequestration preserves apparent solubility while lowering activity Unresolved article question When does improved solubilization cease to improve absorptive driving force?	Molecularly available drug → epithelial permeation	Governing condition Free concentration must be sustained at the epithelial surface Formulation lever Supersaturation persistence and precipitation control Patient or physiological variability Transit, fluid volume and absorptive surface change time available for transfer IVIV transfer test Couple digestion to a physiologically justified permeation or absorption sink	Downstream state reached Enterocyte-accessible drug Condition that can interrupt the transition Precipitation, rapid dilution or inadequate absorptive area reduces transfer Unresolved article question Which in vitro sink best represents the clinically relevant absorption boundary?
Enterocyte uptake → intracellular lipid processing	Governing condition Drug or designed derivative must remain compatible with intracellular lipid-handling pathways Formulation lever Lipophilicity, molecular architecture and association with lipid products Patient or physiological variability Enterocyte lipid-processing activity and nutritional state vary IVIV transfer test Demonstrate intracellular processing rather than infer it from luminal lipid association	Downstream state reached Lipid-processing-associated intracellular state Condition that can interrupt the transition Rapid basolateral/portal transfer or metabolic loss bypasses lymphatic routing Unresolved article question Which molecular attributes distinguish simple absorption enhancement from true lymphatic engagement?	Intracellular lipid processing → chylomicron-associated export	Governing condition Material must enter assembly/export processes supporting intestinal lipoprotein secretion Formulation lever Long-chain lipid environment or metabolically designed prodrug features Patient or physiological variability Food state, lipid absorption and enterocyte phenotype influence lipoprotein output IVIV transfer test Measure relevant lipoprotein/chylomicron association using physiologically suitable epithelial models	Downstream state reached Lymph-compatible exported material Condition that can interrupt the transition Inadequate chylomicron assembly or poor molecular incorporation Unresolved article question How much model evidence is sufficient before claiming lymph-directed formulation behavior?



The absorptive evidence also requires a time-resolved visual architecture because luminal drug can repartition repeatedly while permeability and lipid processing remove different fractions through different pathways.

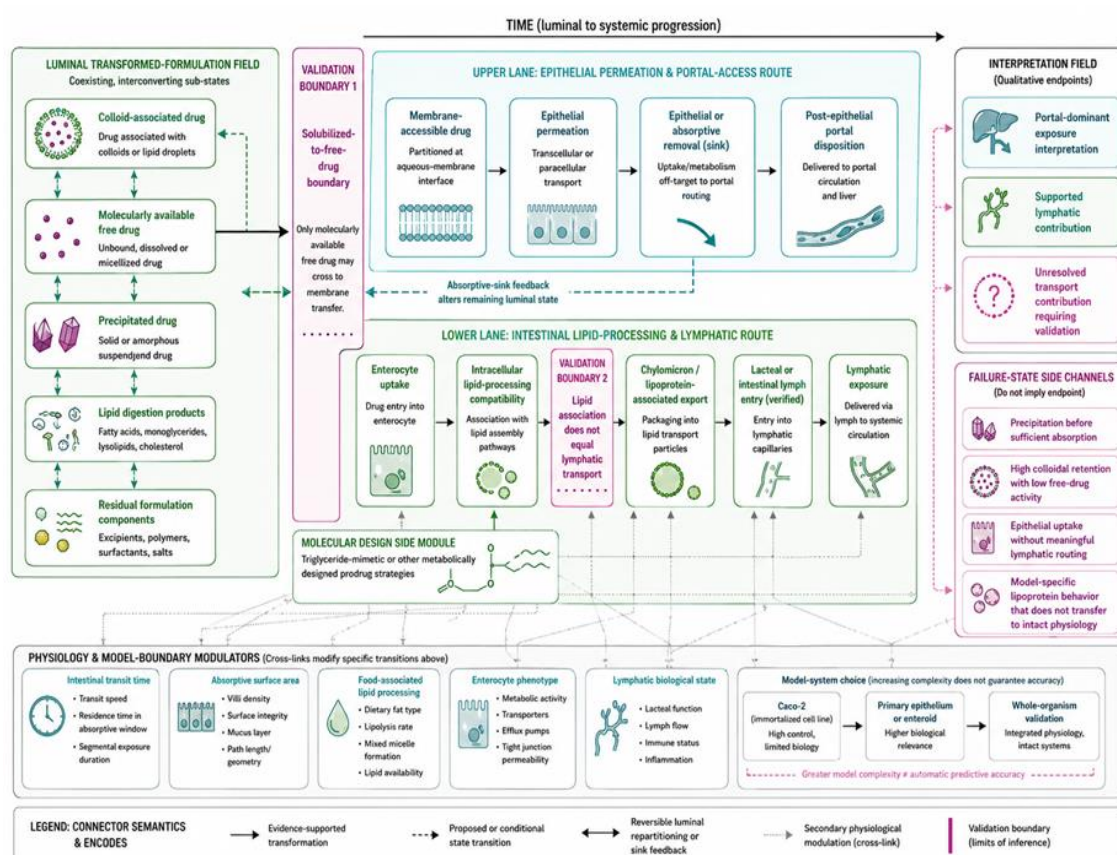


Figure 2. Free-drug escape and intestinal lipid processing determine whether luminal formulation success reaches portal or lymphatic exposure

Patient-specific physiological variability

Patient variability should not be added to LBF interpretation only at the final pharmacokinetic stage. Gastrointestinal conditions capable of modifying oral drug behavior vary between and within individuals [1]. Human intestinal-fluid experiments further show that lipid-associated solubilizing capacity differs across sampled conditions and compounds [15]. These observations suggest that the uncertainty affecting an LBF begins upstream, during the formation of the transformed luminal state.

A useful consequence is to distinguish physiological uncertainty from formulation failure. When performance changes across intestinal-fluid compositions, the formulation may be sensitive to a realistic biological variable rather than analytically unstable. Multi-medium intestinal-fluid systems have therefore been proposed to represent a wider physiological solubility range than a single nominal simulated medium [16]. Such approaches remain model representations rather than predictions of individual exposure.

Postprandial state introduces another source of within-person variation because meal form and sampling time change the intestinal environment encountered by the dosage form [17]. The relevant patient state is consequently dynamic: the same individual may expose a formulation to substantially different colloidal and transit conditions depending on meal, timing and gastric processing.

Formulation–patient interaction can also extend beyond luminal dissolution. Preclinical evidence indicates that LBF composition can change absorption timing and apparent first-pass behavior [19]. Intestinal lymphatic biology is likewise condition dependent and may vary with physiological or disease state [28]. These observations support, but do not validate prospectively, the article’s proposed view that patient-specific LBF performance emerges from a formulation × physiological-state interaction rather than from either component alone.

Current in vitro and in silico models

No single current model captures all relevant transitions from formulation dispersion through digestion, colloidal restructuring, free-drug generation, epithelial transport, lymphatic routing and human pharmacokinetics. Reviews of LBF IVIV relationships describe substantial progress in biorelevant lipolysis and coupled models, but human validation remains system specific rather than universally transferable [30].

Computational approaches can contribute at a different level. Molecular-dynamics simulations informed by experimentally characterized intestinal fluids can reveal interactions and colloidal structures that are difficult to resolve using bulk analytical measurements alone. Work comparing simulated and aspirated canine intestinal fluids showed that physiological bile conditions and interindividual composition affected predicted drug solubilization and that simplified simulated systems could reproduce selected experimental trends [31]. The species boundary remains critical: agreement in canine fluids or a computational representation cannot establish human formulation performance.

The appropriate question is therefore not which model is intrinsically “best,” but which inference each model has actually validated. Conventional lipolysis can test digestive-state changes; coupled permeation systems can assess how an absorptive sink alters those states; epithelial models can interrogate membrane or lipid-processing behavior; dynamic gastrointestinal models can represent changing luminal conditions; and in silico methods can explore mechanisms and parameter sensitivity. Confidence should increase only when the same claimed relationship survives the relevant scale-transfer test.

This review therefore proposes a modular validation hierarchy: formulation-state validity, physiological-condition validity, absorptive-readout validity and exposure-transfer validity should be assessed separately. Greater experimental complexity is useful only when the added component represents a process materially related to the formulation’s hypothesized advantage.

Design implications

The principal design implication is that LBF optimization should not terminate at maximum apparent solubilization. A high-solubilization state may be favorable, but its pharmaceutical value depends on whether it preserves sufficient free drug at the absorptive boundary [25]. Likewise, transient supersaturation can support meaningful early absorption even when later precipitation occurs [20]. Formulation selection should therefore consider the sequence and duration of states rather than ranking candidates by one end-point concentration.

Physiological stress testing should also be mechanism directed. When formulation performance depends strongly on mixed-colloid capacity, bile/lipid composition and postprandial state deserve deliberate variation [15]. When pH transition or gastric residence controls the generated supersaturation state, sequential rather than single-

compartment testing becomes more informative. When lymphatic delivery is claimed, cellular lipid processing and actual lymphatic transfer require evidence beyond luminal lipid association [26].

A second implication concerns negative evidence. Failure to reproduce an advantage under a changed bile composition, absorptive sink or dose-normalized comparison should not automatically be discarded as experimental noise. Such discordance can identify the boundary of the formulation mechanism. Conversely, adding physiological features to an assay should not be rewarded merely for making the experiment appear more realistic; the biphasic lipolysis literature demonstrates that greater mechanistic detail does not guarantee superior prediction for every formulation [10].

The proposed physiology-conditioned formulation-state interpretation therefore uses three questions as design gates. First, what drug state does the formulation create under the tested physiological condition? Second, does that state remain relevant after the next gastrointestinal or absorptive transition? Third, has the claimed advantage been validated at the scale to which it is being extrapolated? These gates deliberately separate formulation robustness from mechanistic plausibility and both from clinical predictivity.

For development programs, this approach favors an evidence chain rather than a single surrogate endpoint. Early screening may remain high throughput and reductionist. More advanced testing can then add only those physiological variables implicated by the candidate's mechanism: digestion, bile/lipid composition, food-state timing, pH transition, absorptive sink, epithelial lipid processing or lymphatic transport. The purpose is not maximal complexity but selective physiological fidelity.

CONCLUSION

Lipid-based formulations are transformed by the gastrointestinal tract rather than merely released into it. Their performance emerges from interactions among drug physicochemistry, dosage-form composition, digestion, bile-associated colloids, food state, pH and transit, precipitation, free-drug availability, epithelial transport and, for selected candidates, intestinal lymphatic processing.

The central interpretive error is to treat favorable behavior at one level as evidence of success at the next. Solubilization is not identical to thermodynamic availability, precipitation is not identical to absorption failure, epithelial uptake is not identical to lymphatic transport, and success in one simulated gastrointestinal condition is not evidence of physiological invariance.

The proposed physiology-conditioned formulation-state interpretation addresses this problem by separating luminal state generation, physiological robustness, absorptive transfer and exposure validation. It is a review-derived analytical architecture rather than a prospectively validated predictive model. Its value lies in making transfer boundaries explicit and in directing experimental complexity toward the physiological process that actually governs a formulation's proposed advantage.

Future progress will depend less on creating universally "biorelevant" assays than on matching each assay to a clearly defined inference. Formulations should be judged not only by the concentration of drug they can carry, but by whether the drug state they generate persists, transfers and remains interpretable across the gastrointestinal conditions in which oral absorption actually occurs.

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