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RELEASE PROFILES DO NOT EQUAL THERAPEUTIC PERFORMANCE IN CONTROLLED, RESPONSIVE, AND LONG-ACTING DRUG-DELIVERY SYSTEMS

Johan Mertens[1]*, Sylvie Dubois[2], Pieter De Smet[3], Lukas Wouters[4]

1. ***Department of Drug Delivery and Therapeutic Performance, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium.***
2. ***Department of Release Profiles and Controlled Delivery, Faculty of Pharmacy, University of Lille, Lille, France.***
3. ***Department of Responsive and Long-Acting Drug-Delivery Systems, Faculty of Pharmacy, Wageningen University, Wageningen, Netherlands.***
4. ***Department of Beyond-Release Therapeutic Modeling, Faculty of Pharmacy, University of Antwerp, Antwerp, Belgium.***

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ABSTRACT

Controlled, responsive, and long-acting drug-delivery systems are commonly evaluated through cumulative release curves, release-rate constants, burst fractions, or apparent duration of liberation. These measurements are indispensable for formulation characterization, yet they do not independently establish local exposure, systemic pharmacokinetics, biological response, therapeutic durability, safety, or clinical usefulness. This article develops an original drug-release theory to address the unresolved tendency to treat release performance as a surrogate for therapeutic performance. The proposed Release-to-Performance Coupling Theory organizes delivery-system behavior into linked but non-equivalent domains: assay-conditioned drug liberation, evolving depot state, material transformation, tissue transport, local and systemic exposure, biological response, and context-specific therapeutic performance. It further identifies physiological context and uncertainty as cross-cutting modifiers of every transition. The theory distinguishes analytical validity from biological relevance, correlation from mechanism, simulated exposure from prospective usefulness, and sustained drug presence from sustained therapeutic benefit. It also explains why formulations with similar cumulative release profiles may produce different exposure and response trajectories, whereas formulations with dissimilar in-vitro profiles may occasionally converge in vivo through compensating transport or disposition processes. The proposed construct is intended to guide mechanistic evaluation, model development, evidence integration, and formulation design rather than to function as a validated predictive model or regulatory decision rule. Its applicability is conditional on delivery platform, administration site, drug properties, disease state, biological trigger, and intended decision. Reframing release as one component of a multiscale performance chain may improve the design of biorelevant tests, computational models, responsive systems, and translation strategies while reducing unsupported claims based on cumulative release curves alone.

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Introduction

Long-acting and controlled-delivery formulations are designed to modify when, where, and for how long an active compound becomes available, but their pharmaceutical value depends on substantially more than the persistence of drug liberation. Clinical translation requires alignment among drug properties, formulation architecture, administration procedure, manufacturability, product characterization, pharmacokinetics, tolerability, patient use, and the therapeutic objective. Complex injectable products further demonstrate that nominal compositional similarity or a comparable release curve may be insufficient to establish equivalent in-vivo behavior, while clinically established biodegradable depots show that apparently related products can depend on different materials, microstructures, degradation pathways, and manufacturing histories [1–3].

Corresponding Author: Johan Mertens; Department of Drug Delivery and Therapeutic Performance, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium. E-mail: johan.mertens@ugent.be.

The scientific problem is therefore not whether release kinetics matter; they clearly do. The problem is whether release kinetics are being assigned interpretive authority beyond what the measurement can support.

The problem becomes more consequential when the term *release performance* is used across fundamentally different delivery architectures. Polymeric implants, in-situ forming depots, microspheres, suspensions, inserts, wafers, and related long-acting systems do not necessarily share a common rate-controlling process. Drug liberation may depend on dissolution, diffusion, solvent exchange, swelling, pore formation, erosion, polymer degradation, chemical cleavage, drug crystallinity, particle transformation, or combinations that change during treatment [4]. A cumulative curve compresses these processes into an amount-versus-time representation. It does not preserve all information about spatial heterogeneity, depot morphology, molecular transformation, tissue interaction, or the biological fate of the liberated compound.

The historical development of drug-delivery systems has progressively expanded from simple temporal control toward systems intended to achieve site specificity, biological responsiveness, improved usability, altered biodistribution, or extended pharmacological action [5]. This expansion has created an evidentiary mismatch. Release assays remain among the most accessible and reproducible formulation measurements, whereas direct characterization of depot evolution, tissue exposure, local pharmacodynamics, and long-term biological response is more difficult. Consequently, the most measurable variable can become the dominant variable in development narratives, computational models, and comparative claims. This dominance is methodologically unsafe when the measured endpoint is separated from therapeutic performance by several unobserved or weakly validated processes.

The objective of this article is to propose a theory for organizing those processes without treating them as automatically coupled. The proposed Release-to-Performance Coupling Theory distinguishes seven linked domains: nominal release profile, evolving depot state, material transformation, tissue transport, local and systemic exposure, biological response, and therapeutic performance. Physiological context and uncertainty modify every transition. Within computational pharmaceutical science, this distinction is particularly important because a model that predicts a release curve accurately may still be unsuitable for predicting exposure or therapeutic response if its training target does not represent those outcomes. The theory therefore reframes release kinetics as an evidence-bearing input to a larger multiscale argument, not as a standalone proof of pharmaceutical usefulness.

Why Release Kinetics Cannot Stand in for Therapeutic Performance

A release profile is an operational measurement produced by a formulation, an apparatus, a medium, a sampling scheme, and a set of analytical assumptions. Its interpretation is therefore conditional on both the product and the method. Studies of long-acting microspheres have shown that in-vitro–in-vivo relationships require formulation-specific evidence, that manufacturing and testing conditions can materially alter the observed release behavior, and that spectroscopic or solid-state characterization may be necessary to explain what an apparent dissolution profile represents [6–8]. These findings do not diminish the value of release testing. Instead, they define its proper epistemic role: a release curve can describe drug liberation under specified conditions, discriminate some product differences, and contribute to mechanistic or predictive models, but it cannot independently identify the complete chain leading to therapeutic performance.

The first distinction required by the theory is between analytical release validity and biological relevance. Analytical validity concerns whether a method measures drug liberation reproducibly, maintains chemical stability, achieves adequate recovery, and detects consequential formulation differences. A method developed for long-acting injectable suspensions illustrates the importance of selecting conditions capable of distinguishing changes in formulation behavior rather than merely generating a smooth or convenient cumulative curve [9]. Biological relevance asks a different question: whether the conditions, mechanisms, and timescales represented by the assay correspond sufficiently to those governing the administered product. A method can be precise but biologically uninformative, just as a physiologically elaborate method can be irreproducible or insufficiently discriminatory. Neither property should be inferred from the other.

The second distinction is between release correlation and therapeutic explanation. A formulation-specific in-vitro–in-vivo correlation may connect an in-vitro profile to an estimated in-vivo input or absorption process under defined conditions [10]. Such a relationship can support formulation comparison, model development, or study planning, but it remains several steps removed from therapeutic performance. Systemic exposure is additionally shaped by distribution, binding, metabolism, clearance, patient characteristics, and dosing history. Local performance may depend on concentrations that are not represented by plasma measurements. Biological response may exhibit thresholds, delays, tolerance, irreversible effects, disease adaptation, or toxicity at sites distinct from the intended target. Therefore, even a credible release–absorption relationship does not by itself establish efficacy, safety, clinical durability, or therapeutic equivalence.

The proposed theory consequently treats the cumulative release curve as a partial observable rather than a complete performance descriptor. Two systems may display similar cumulative profiles while differing in burst localization, depot geometry, particle transformation, tissue binding, active-moiety formation, local clearance, or inflammatory response. Conversely, dissimilar in-vitro profiles may yield more similar systemic exposures if downstream absorption or disposition processes compensate for their differences. These possibilities are not universal predictions; they are theoretically plausible divergence and convergence pathways that must be examined for each product and context. Release kinetics can support a therapeutic-performance claim only when the necessary coupling evidence is supplied and its uncertainty is stated. **Table 1** organizes the evidence, constructs, and interpretation boundaries needed to develop why release kinetics cannot stand in for therapeutic performance within the article's central argument.

Table 1. Evidence domains, core questions, scientific requirements, and interpretation boundaries for why release kinetics cannot stand in for therapeutic performance

Construct or evidence domain	Core question	Scientific basis	Role in the article	Failure or overclaiming risk	Boundary statement
Nominal release profile	What quantity is released, under which test conditions, and with what analytical reliability?	Apparatus, medium, sampling, recovery, stability, sink conditions, and assay precision	Defines the observable entry layer of the theory	Treating an assay-conditioned curve as an intrinsic and context-free product property	The profile describes liberation under specified conditions and does not independently establish in-vivo release
Discriminatory analytical validity	Can the method detect formulation or process changes that are scientifically consequential?	Controlled variation of particle, polymer, drug-state, manufacturing, or method attributes	Determines whether the assay can support formulation comparison	Equating repeatability with sensitivity or relevance	A reproducible method may still fail to distinguish meaningful product differences
Mechanistic interpretation	Which processes generate the observed profile?	Dissolution, diffusion, swelling, degradation, erosion, phase change, cleavage, and solid-state analysis	Connects curve shape to plausible release-controlling processes	Assigning mechanism from curve shape alone	Mechanistic claims require orthogonal measurements or perturbation evidence
Evolving depot state	Does the administered formulation retain the same structure represented in the test?	Depot formation, hydration, porosity, geometry, crystallinity, aggregation, and residual-product analysis	Introduces the depot as a dynamic mediator	Assuming the preadministration formulation remains physically unchanged in vivo	The relevant release-controlling structure may emerge only after administration
Local tissue transport	How does liberated drug move, bind, transform, or clear near the administration site?	Diffusion, convection, lymphatic uptake, vascular uptake, extracellular-matrix interaction, and cellular sequestration	Separates liberation from absorption and local exposure	Assuming all released drug becomes immediately bioavailable	Drug leaving the formulation may remain locally bound, transformed, cleared, or spatially restricted
Local and systemic exposure	Does formulation output produce the intended concentration–time pattern at the relevant site?	Local pharmacokinetics, plasma pharmacokinetics, biodistribution, deconvolution, and mechanistic modeling	Defines the exposure layer between release and response	Using plasma exposure as a universal surrogate for target-site exposure	Local and systemic exposure may diverge and must be matched to the therapeutic question
Biological response	Does exposure generate the intended pharmacological effect without unacceptable harm?	Pharmacodynamics, biomarkers, tissue response, toxicity, tolerance, and disease progression	Connects exposure to therapeutic consequences	Treating prolonged exposure as prolonged benefit	Exposure is necessary for many effects but does not alone establish therapeutic value
Therapeutic performance	Does the system provide context-specific efficacy, safety, durability, usability, and reversibility?	Integrated formulation, exposure, response, patient, and clinical evidence	Defines the terminal evaluative construct	Reducing multidimensional performance to a single release measure	Therapeutic performance is decision- and context-specific and cannot be inferred from release kinetics alone
Coupling evidence	Is each transition from release to performance directly supported, modeled, or experimentally tested?	IVIVC, IVIVE, physiologically based modeling, imaging, local PK, exposure–response analysis, and prospective validation	Qualifies the strength of the central claim	Treating one successful correlation as universally transferable	Coupling evidence is formulation-, route-, population-, and purpose-specific
Uncertainty and transportability	How reliable are measurements, models, assumptions, and cross-context extrapolations?	Sensitivity analysis, external testing, variability assessment, model comparison, and scenario analysis	Prevents overinterpretation of apparently precise results	Confusing model precision with calibrated uncertainty	Confidence in one layer does not automatically transfer to downstream layers

Depot Formation, Transport, Degradation, and Biological Response

The release-to-performance chain begins changing as soon as a formulation is administered. A depot is not merely a passive reservoir from which drug exits according to a pre-existing mathematical function. It may spread, drain, contract, swell, separate into phases, exchange solvent, recruit fluid, interact with proteins, or become redistributed through tissue planes. Investigation of an intramuscular oil depot demonstrated that its in-vivo fate contributes directly to drug absorption, emphasizing that drainage and physical evolution can affect systemic input independently of the nominal release characteristics of the original formulation [11]. The theory therefore defines depot formation as the emergence of the actual post-administration material state and depot evolution as its subsequent spatial, chemical, and structural trajectory.

Material degradation must likewise be separated from drug release rather than treated as its automatic equivalent. In biodegradable implants, additives can modify hydration, polymer mobility, pore formation, and degradation while accelerating or slowing drug liberation through mechanisms that are not directionally identical [12]. Polymer molecular-weight loss, bulk erosion, surface erosion, mass loss, and active-drug appearance are related observations, but they do not measure the same event. A formulation may degrade without immediately releasing all associated drug, or drug may diffuse substantially before

extensive polymer mass loss occurs. The proposed theory consequently represents material transformation and drug liberation as interacting state variables whose coupling may change over the dosing interval.

For in-situ forming systems, the conditions under which the depot is created can determine the microstructure that later governs transport. Solvent exchange, phase inversion, precipitation rate, water penetration, drug partitioning, and early pore formation may generate heterogeneous structures that are absent before administration. Experimental work on in-situ forming implants has shown that implant formation influences subsequent release kinetics, supporting the inclusion of a formation-history term within any mechanistic account of performance [13]. This term is not proposed as a single numerical parameter. It denotes the set of administration-dependent and environment-dependent processes through which an injectable liquid, suspension, or precursor becomes the operative in-vivo depot.

The dominant release mechanism may also change over time. In-vivo examination of risperidone-forming depots indicates that diffusion, polymer degradation, erosion, and structural alteration can contribute at different stages rather than operating as one stationary process [14]. Longitudinal computed-tomography characterization further shows that implant geometry and internal structure can evolve in ways that are associated with drug-release behavior [15]. These observations support a core proposition of the theory: the object that controls release at a later time may not be materially equivalent to the object administered initially or represented in a conventional assay. Biological response adds another feedback layer because inflammation, immune-cell recruitment, vascular changes, extracellular-matrix remodeling, or local toxicity may alter transport and depot transformation while also being consequences of exposure. The depot–tissue system should therefore be represented as a coupled and evolving pharmaceutical microenvironment, with causality and directionality assigned only where experimental evidence supports them.

Connecting Release Profiles to Local and Systemic Exposure

The first downstream quantity that gives release kinetics pharmacological meaning is exposure, but exposure must be specified by location, chemical species, population, and time. Drug leaving a depot may generate concentrations within the administration site, adjacent tissues, lymphatic fluid, plasma, target organs, or off-target organs, and these concentration trajectories need not change proportionally. Physiologically based pharmacokinetic modeling of long-acting antiretroviral administration illustrates how depot input assumptions must be translated through age-dependent physiology, distribution, metabolism, and clearance before dosing suitability can be explored [16]. The theoretical implication is that a release profile becomes an exposure hypothesis only after it is embedded within an explicit absorption and disposition structure.

Local tissue transport is a particularly important source of separation between release and systemic pharmacokinetics. After subcutaneous or intramuscular administration, liberated molecules may diffuse through extracellular matrix, bind to tissue components, aggregate, undergo enzymatic transformation, enter lymphatic vessels, cross vascular endothelium, or be taken up by resident and recruited cells. Reviews of biorelevant subcutaneous test systems emphasize that matrix composition, fluid turnover, lymphatic transport, protein association, local inflammation, and formulation-specific interactions can influence absorption [17]. These processes may delay systemic appearance, maintain local concentrations after formulation release, or remove drug from the measurable soluble fraction without producing immediate systemic exposure.

Mechanistic models can help organize these transitions when their structural assumptions remain visible. A physiologically based model developed for intramuscular long-acting antiretroviral drugs incorporated injection-site processes into a whole-body pharmacokinetic representation, demonstrating how local depot behavior can be linked to circulating concentrations without treating release and plasma input as identical quantities [18]. Within the proposed theory, such models occupy a translation layer between formulation measurements and systemic exposure. Their value depends not only on goodness of fit but also on whether the model represents plausible local mechanisms, whether parameters are identifiable, and whether predictions remain calibrated outside the formulations and populations used for development.

Biorelevant in-vitro systems and mechanistic in-vitro–in-vivo extrapolation provide complementary routes for strengthening this translation layer. A subcutaneous test designed for insulin formulations showed that a physiologically informed environment may improve correspondence between in-vitro release and expected in-vivo behavior for a defined product class [19]. Mechanistic extrapolation approaches have similarly combined formulation behavior, tissue processes, and pharmacokinetic modeling to support comparison of long-acting injectables [20]. Neither strategy establishes therapeutic equivalence or clinical benefit alone. Their appropriate role is to test whether specified release-to-exposure relationships are plausible, reproducible, and sufficiently transportable for the intended decision. The theory therefore requires local and systemic exposure to be modeled as distinct but interacting outputs, with explicit uncertainty at the release–transport, transport–absorption, and absorption–disposition interfaces.

Responsive and Long-Acting Systems under Changing Physiological Conditions

Responsive systems make the release–performance distinction especially important because their operating conditions are supplied partly by biology rather than solely by formulation design. Enzyme-responsive carriers depend on the abundance, accessibility, and catalytic activity of the selected enzyme; inflammatory delivery systems may respond to reactive species, proteases, acidity, or other mediators that fluctuate with disease activity; and pH-responsive materials operate only when local acidity falls within the range required to alter ionization, swelling, cleavage, or permeability [21–23]. A response observed under a fixed laboratory trigger therefore demonstrates material responsiveness under that condition, not therapeutic responsiveness across the heterogeneous and time-varying states encountered in vivo.

In infection-responsive systems, the relevant trigger may vary by pathogen, strain, anatomical site, biofilm structure, treatment stage, and prior antimicrobial exposure. Enzyme-triggered antimicrobial platforms illustrate how bacterial enzymes can be used to activate release, yet trigger access may be restricted by extracellular matrices, spatial segregation, low organism burden, or off-target expression in host tissues [24]. The nominal responsiveness of a carrier must consequently be separated into at least four questions: whether the trigger exists, whether it reaches the responsive element, whether activation occurs at a therapeutically appropriate rate, and whether the resulting exposure improves the intended biological outcome without unacceptable release elsewhere.

Long-acting and responsive functions may also conflict. Extending depot residence can preserve a formulation through periods in which disease-associated triggers increase, decrease, or migrate spatially. Conversely, a system designed for rapid activation may lose the temporal stability required for prolonged dosing. Broader analyses of bioresponsive delivery systems show that translation depends on reliable coupling among biological signal, material transformation, payload liberation, and downstream pharmacology [25]. In the proposed theory, responsiveness is therefore not a standalone material attribute. It is a context-dependent relationship between a changing biological input and a delivery-system response, bounded by trigger specificity, trigger magnitude, temporal persistence, accessibility, off-state leakage, and the consequences of incorrect activation.

This reasoning changes how responsive and long-acting systems should be modeled. A single trigger concentration, constant pH, or static enzyme activity should be treated as a scenario rather than as a complete representation of the physiological environment. Models should allow trigger states, perfusion, inflammation, matrix density, immune-cell activity, and disease burden to change during treatment. They should also distinguish *material activation* from *drug release*, *drug release* from *local exposure*, and *local exposure* from *biological response*. The proposed synthesis does not assert that every system requires a fully dynamic multiscale model. It asserts that claims of therapeutic responsiveness must be proportional to the number and quality of coupling transitions that have been tested, especially when the biological trigger is heterogeneous or clinically unstable.

Evaluation Criteria beyond Cumulative Release Curves

Evaluation should begin with analytical adequacy but should not end there. A release method must show that it can detect changes in attributes reasonably expected to alter product behavior, including particle characteristics, drug loading, suspension properties, polymer composition, depot formation, or manufacturing history. Work on long-acting injectable suspensions demonstrates that formulation parameters can produce distinguishable release behavior and therefore provides a basis for testing method sensitivity [26]. Within the proposed theory, this capability is termed analytical discrimination. It is necessary for product development, but it does not show that the discriminated differences will change exposure or therapeutic response.

Accelerated release testing requires an additional criterion: preservation of the mechanism relevant to the intended extrapolation. Increasing temperature, changing pH, adding surfactants, or modifying hydrodynamics may shorten assay duration while also changing polymer mobility, degradation, drug solubility, particle transformation, or the dominant release process. Evidence that polymer source and temperature can affect both microsphere release and in-vitro–in-vivo relationships demonstrates why acceleration cannot be validated through temporal compression alone [27]. An accelerated method should therefore be assessed for rank-order preservation, mechanism concordance, drug and excipient stability, structural similarity, and the decision for which the acceleration is intended.

Mechanistic evaluation should further determine whether alternative processes can explain apparently similar curves. Reactive dissolution models provide one example of separating chemical transformation and dissolution contributions that may otherwise be hidden within cumulative release data [28]. Similar reasoning can be extended to degradation, erosion, diffusion, phase inversion, crystallinity changes, or active-moiety formation. The goal is not to replace every empirical assay with a complex mathematical model. It is to ensure that model structure and complementary measurements are sufficient for the claim being made. A mechanistic interpretation remains conditional when several parameter combinations, unmeasured depot states, or different biological processes can reproduce the same observation.

The proposed evaluation architecture therefore contains seven connected domains: analytical validity, mechanistic discrimination, depot-state fidelity, tissue-context relevance, local and systemic exposure linkage, exposure–response linkage, and uncertainty-aware decision relevance. Contemporary analysis of PLGA-based long-acting injectables emphasizes that material attributes, manufacturing processes, product structure, degradation, and release must be interpreted together rather than as isolated development variables [29]. Examination of IVIVC development further shows that the reliability of a correlation depends on the meaning and quality of both the in-vitro measurement and the estimated in-vivo input [30]. **Figure 1** presents the release-to-exposure translation bridge, showing how the article's key components and boundaries are connected within evaluation criteria beyond cumulative release curves.

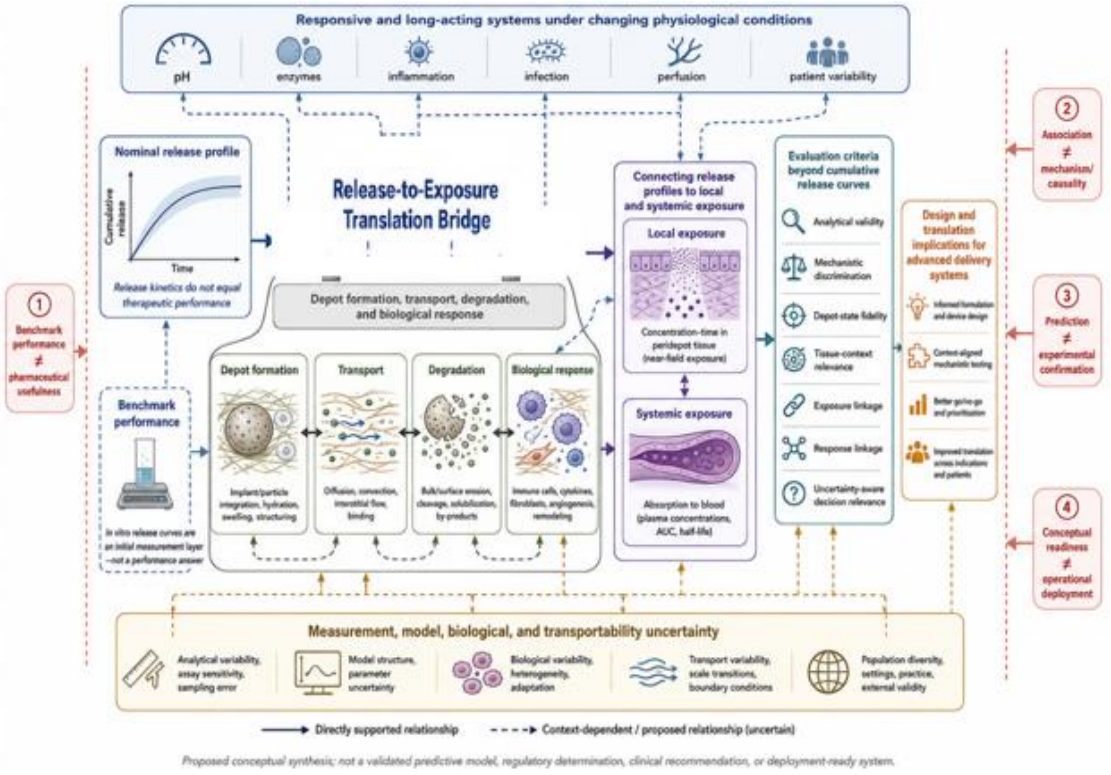

Figure 1. Release-to-Exposure Translation Bridge.

The figure is an original conceptual synthesis that organizes the article's central contribution across release kinetics cannot stand in for therapeutic performance, depot formation, transport, degradation, and biological response, depot formation, biological response, connecting release profiles to local and systemic exposure, responsive and long-acting systems under changing physiological conditions. Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, regulatory determination, clinical recommendation, or deployment-ready system.

Design and Translation Implications for Advanced Delivery Systems

The first design implication is that formulation attributes should be selected according to the coupling transition they are expected to control. Polymer composition, molecular-weight distribution, particle structure, drug state, porosity, residual solvent, excipient functionality, and degradation behavior should not be characterized merely because they are measurable. They should be connected to hypotheses about depot formation, liberation, tissue transport, exposure, or response. Analytical reviews of long-acting PLGA microspheres emphasize the importance of linking excipient and product characterization to improved understanding of product behavior [31]. Under the proposed theory, a critical quality attribute becomes therapeutically meaningful only when a defensible pathway connects it to a consequential downstream state.

The second implication is organizational. Long-acting product development cannot be divided cleanly into isolated formulation, analytical, modeling, manufacturing, and clinical workstreams. A peer-reviewed synthesis from a multidisciplinary workshop on aqueous long-acting suspensions highlighted the need to integrate formulation science, manufacturing, dissolution testing, pharmacokinetic modeling, and clinical considerations [32]. The Release-to-Performance Coupling Theory provides a proposed common structure for this integration: each workstream should specify which transition it measures, predicts, or constrains, which assumptions it passes to the next layer, and which uncertainties remain unresolved.

The third implication concerns systems in which the released chemical species is not yet the active therapeutic entity. Long-acting prodrug strategies may involve dissolution of a prodrug, cleavage of a linker or promoiety, redistribution of an intermediate, and formation of the pharmacologically active compound [33]. In such cases, a release curve for the prodrug cannot be interpreted as an active-drug exposure profile unless conversion kinetics and location are established. Similar caution applies to carriers that release complexes, precursors, nucleic-acid constructs, or species requiring intracellular activation. The theory therefore adds chemical and biological transformation as an explicit layer whenever the identity or activity of the released entity changes before target engagement.

The final implication is that delivery architecture should be matched to disease, route, therapeutic window, intended duration, reversibility needs, and the consequences of under- or overexposure. Reviews of long-acting parenteral systems for chronic diseases show that platform choice is inseparable from drug properties and treatment context [34]. In anticancer delivery, prolonged local retention or systemic exposure must additionally be balanced against heterogeneous tumor biology, off-target toxicity, and changes in disease state during treatment [35]. A release profile can inform these decisions, but it cannot resolve

them independently. **Table 2** organizes the evidence, constructs, and interpretation boundaries needed to develop design and translation implications for advanced delivery systems within the article's central argument.

Table 2. Evaluation, implementation, and research priorities arising from Release Profiles Do Not Equal Therapeutic Performance in Controlled, Responsive, and Long-Acting

Component or layer	Inputs	Core function	Expected output	Uncertainty or limitation	Validation requirement
Analytical release layer	Apparatus, medium, sampling design, recovery, stability, formulation attributes	Measures assay-conditioned drug liberation	Reproducible and discriminatory release profile	Method may alter the mechanism or omit biological constraints	Robustness, recovery, stability, and controlled-variation studies
Depot-state layer	Administration conditions, imaging, material properties, morphology, hydration, degradation	Represents formation and structural evolution after administration	Time-resolved depot-state description	Depot may be spatially heterogeneous or incompletely observable	Longitudinal imaging and residual-depot characterization
Material-transformation layer	Dissolution, erosion, degradation, cleavage, crystallinity, swelling	Distinguishes processes governing liberation and active-species formation	Mechanistically interpretable transformation trajectory	Several mechanisms may produce similar cumulative curves	Orthogonal analytical measurements and perturbation studies
Tissue-transport layer	Matrix properties, perfusion, lymphatics, binding, immune interactions, local metabolism	Translates depot output into local absorption and retention	Local input and transport representation	Human tissue conditions are difficult to reproduce or measure	Biorelevant models linked to in-vivo tissue observations
Local-exposure layer	Tissue concentrations, spatial gradients, target-site residence, local clearance	Quantifies drug availability near the administration or action site	Local concentration–time profile	Sparse sampling and invasive measurement	Prospective local-pharmacokinetic or imaging studies
Systemic-exposure layer	Absorption input, distribution, metabolism, clearance, population physiology	Translates depot output into circulating and organ exposure	Population-specific systemic exposure predictions	Model-form and parameter uncertainty	External pharmacokinetic validation and scenario testing
Biological-response layer	Target engagement, biomarkers, pharmacodynamics, immune response, toxicity	Relates exposure to desired and adverse consequences	Context-specific response hypothesis	Association may not identify mechanism or causality	Time-aligned exposure–response and intervention studies
Responsive-context layer	pH, enzymes, inflammation, infection, perfusion, disease burden	Represents changing biological activation conditions	Trigger-specific activation and release scenarios	Trigger distributions may vary spatially and temporally	Longitudinal in-vivo trigger mapping and off-target assessment
Therapeutic-performance layer	Efficacy, safety, durability, reversibility, usability, adherence context	Integrates pharmaceutical and clinical consequences	Bounded statement of intended performance	Multidimensional outcomes cannot be reduced to one metric	Prospective evaluation in the defined context of use
Uncertainty layer	Measurement error, parameter uncertainty, structural alternatives, biological variability	Propagates uncertainty across coupling transitions	Calibrated intervals and decision-relevant scenarios	Unknown mechanisms may not be captured numerically	Sensitivity analysis, external challenges, and model comparison
Implementation layer	Defined decision, evidence thresholds, responsible experts, traceable assumptions	Aligns evidence generation with development decisions	Staged and auditable evidence package	May be mistaken for an accepted regulatory framework	Prospective application and independent evaluation
Research-priority layer	Identified gaps, failed predictions, contradictory evidence, platform boundaries	Directs studies toward unresolved coupling transitions	Platform-specific validation agenda	Research priorities may not transfer across routes or indications	Multiplatform testing with prespecified hypotheses

Figure 2 presents the evidence, validation, and translation boundary observatory for release profiles do not equal therapeutic performance, showing how the article's key components and boundaries are connected within design and translation implications for advanced delivery systems.

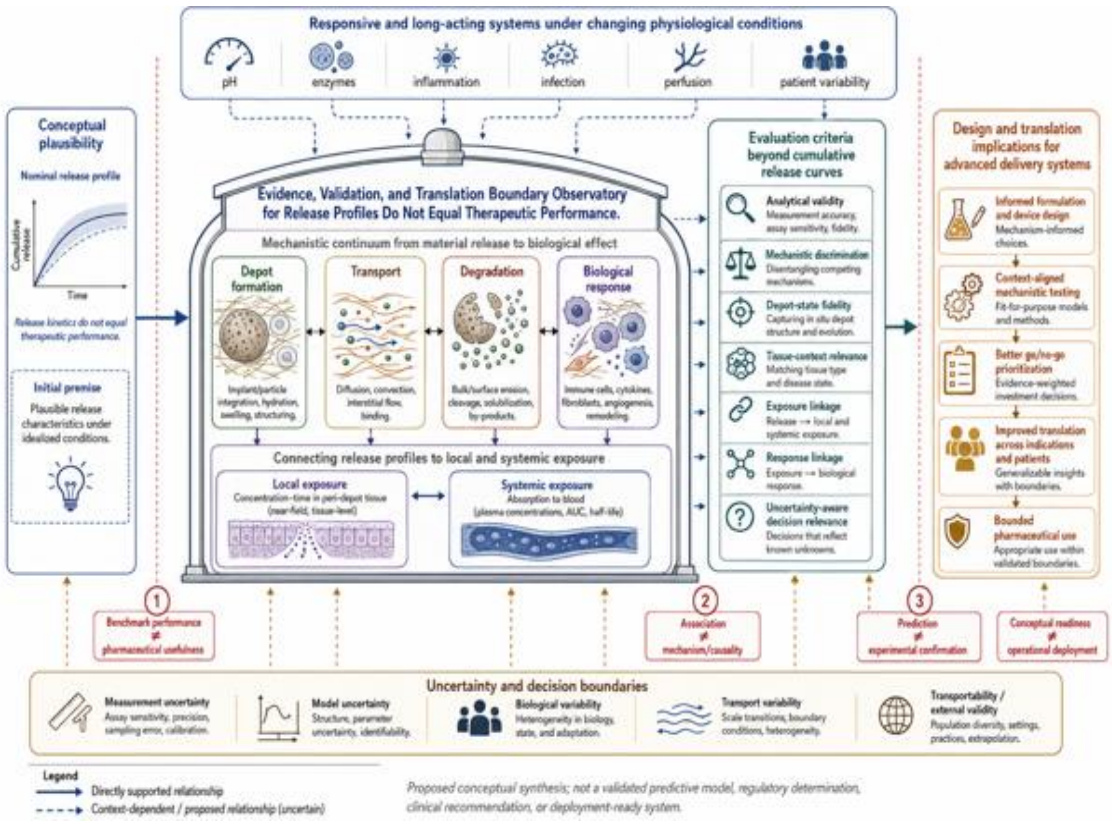

Figure 2. Evidence, Validation, and Translation Boundaries.

The figure is an original conceptual synthesis that shows how claims move from conceptual plausibility through evaluation, uncertainty assessment, and bounded pharmaceutical use. Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, regulatory determination, clinical recommendation, or deployment-ready system.

Limitations and Boundary Conditions

The Release-to-Performance Coupling Theory is a conceptual synthesis and has not been prospectively validated as a unified predictive framework. Its components are supported unevenly across delivery platforms: PLGA microspheres, in-situ implants, oil depots, suspensions, responsive carriers, prodrugs, and local delivery systems differ in both evidence density and governing mechanisms. The proposed sequence should not be interpreted as requiring every system to pass through an identical physical pathway. Some formulations do not form a discrete depot, some act mainly through local exposure, and some release an inactive precursor that requires later conversion. The theory is therefore modular and conditional rather than universal.

The evidence base also contains methodological limitations. Many studies are product-specific, preclinical, retrospective, or developed within narrow formulation families. In-vitro–in-vivo correlations may depend on deconvolution assumptions, pharmacokinetic models may be nonidentifiable, and biorelevant assays may reproduce selected tissue features while omitting vascular, immune, mechanical, or disease-related complexity. Imaging may reveal depot morphology without fully identifying molecular release mechanisms, while plasma pharmacokinetics may remain insensitive to spatially localized exposure. These limitations mean that greater experimental or computational complexity should not automatically be interpreted as greater predictive validity.

Misuse can occur if the theory is converted into a checklist that assigns readiness from the presence of model components rather than from their validation. A mechanistic diagram does not establish causality; a model fit does not establish prospective prediction; a predicted exposure profile does not establish therapeutic benefit; and an integrated evidence package does not establish regulatory acceptability. The proposed construct cannot determine clinical dose, product equivalence, safety, efficacy, or approval status. Its legitimate use is to identify which assumptions separate release measurement from therapeutic claims and to guide proportionate evidence generation for a specified formulation, population, route, and decision.

Research Agenda and Implementation Priorities

The first research priority is prospective testing of coupling hypotheses rather than retrospective explanation of known performance. Studies should predefine how a change in formulation or administration is expected to alter depot structure, release mechanism, local transport, systemic exposure, or response, and then measure several adjacent layers within the same experiment. Longitudinal imaging, residual-depot analysis, local concentration measurements, plasma pharmacokinetics, and relevant biological responses should be temporally aligned where feasible. Deliberately perturbed formulations are especially

valuable because they test whether a proposed model can predict the consequences of changes in polymer source, particle state, implant formation, trigger threshold, or administration conditions.

A second priority is development of interoperable data and modeling infrastructure. Release datasets should retain method conditions, mass balance, stability information, material characterization, manufacturing history, and uncertainty rather than reporting cumulative percentages alone. Depot-imaging data, local pharmacokinetics, systemic pharmacokinetics, tissue-response measurements, and disease-context variables should use traceable time stamps and common product identifiers. Computational models should expose their context of use, state variables, parameter sources, identifiability constraints, calibration procedures, and external-validation status. Such infrastructure would support comparison of alternative mechanisms without implying that a single universal model is appropriate.

Implementation should proceed in stages. The first stage should use the theory as a qualitative evidence map during formulation design and method development. The second should test selected coupling transitions with orthogonal experiments and mechanistic models. The third should evaluate prospective prediction across changed formulations, populations, physiological contexts, or administration conditions. Only after such testing should the construct be considered for decision-specific qualification. Reporting should clearly separate observed measurements, inferred mechanisms, simulated quantities, prospective predictions, experimentally confirmed effects, and clinically demonstrated outcomes. This staged approach preserves the theory's intended role as a research and development framework while preventing premature operational or regulatory interpretation.

Conclusion

Release kinetics are essential descriptors of controlled, responsive, and long-acting delivery systems, but they are not equivalent to therapeutic performance. The proposed Release-to-Performance Coupling Theory reframes drug liberation as the beginning of a multiscale evidence chain involving depot formation and evolution, material transformation, tissue transport, local and systemic exposure, biological response, physiological context, and uncertainty. Its principal contribution is not a new universal metric but a disciplined separation of quantities that are frequently conflated. A release curve can support pharmaceutical decisions when its analytical meaning is established and when the relevant downstream coupling relationships are demonstrated for the intended product and context. It cannot independently establish efficacy, safety, clinical durability, product equivalence, or translational readiness. Future progress will depend on longitudinal depot characterization, biorelevant transport models, local pharmacokinetics, mechanistic exposure translation, context-sensitive evaluation of responsive systems, prospective perturbation studies, and explicit uncertainty reporting. By replacing release-centered inference with coupling-centered evidence, advanced delivery research may produce claims that are more mechanistically interpretable, experimentally testable, and appropriately bounded.

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