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Long-Acting Injectables Need Joint Control of Depot Formation, Drug Escape, and Tissue Response

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ABSTRACT

Long-acting injectable drug products are commonly interpreted through their nominal release-controlling material, particle attributes, or in vitro release profile. Such descriptions are useful but incomplete because the administered product does not remain in its pre-injection state. In situ forming systems undergo solvent exchange, phase separation, and structural consolidation; polymeric microspheres hydrate, reorganize, degrade, and erode; crystalline suspensions dissolve within a changing extracellular and cellular environment. Meanwhile, the surrounding tissue supplies fluid, buffering capacity, proteins, extracellular matrix, inflammatory cells, and potentially a foreign-body response that can modify the microenvironment through which drug must escape. This Mechanistic Perspective argues that long-acting injectable performance should therefore be interpreted through three coupled domains: formation and transformation of the depot, escape of drug from that evolving depot, and biological response of the local tissue. Evidence from phase-inverting implants, PLGA microspheres, crystalline suspensions, imaging studies, dissolution methodologies, cellular experiments, and mechanistic modeling indicates that control can be conditional and time dependent rather than attributable to a single invariant rate-limiting step. The perspective develops the basis for a proposed Depot–Escape–Tissue Coupling Model in which formulation attributes determine an initial state but subsequent release depends on reciprocal changes in matrix structure, drug physical state, fluid access, cellular interaction, and tissue response. The model is intended as a hypothesis-organizing and formulation-design framework rather than an empirically validated universal mechanism. Its value lies in identifying which state variables must be measured, challenged, and translated before an apparently stable release profile can be treated as mechanistically understood.

Keywords: *Long-acting injectables, PLGA depots, In situ forming implants, Drug dissolution, Depot microstructure, Foreign-body response*

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INTRODUCTION

Long-acting injectables are often developed and compared as though product performance can ultimately be assigned to a manageable set of formulation variables: polymer molecular characteristics for degradable depots, particle size and crystal form for suspensions, or an in vitro release curve for the finished product. Yet contemporary development experience shows that these variables do not operate independently. PLGA-based systems remain difficult to design mechanistically because nominal polymer descriptors can conceal structural

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variation, while long-acting suspensions present their own unresolved relationships among crystalline drug properties, manufacturing, release testing, and in vivo behavior [1, 2]. A sustained profile can therefore be reproducible without its controlling mechanism being fully resolved.

The central problem is that an injectable depot is not a passive reservoir. Administration initiates a physical and biological perturbation. Liquid precursor formulations may exchange solvent with tissue fluid and undergo phase inversion. Polymeric particles hydrate and change porosity while polymer chains cleave and soluble degradation products accumulate. Crystalline drug particles experience local dissolution conditions that may differ from standard bulk dissolution media. Simultaneously, cells can infiltrate or surround the depot, internalize particulate drug, and modify the local diffusional environment. These processes occur at different spatial and temporal scales and need not preserve the same ordering across products.

This perspective therefore separates three questions that are frequently merged. First, what depot actually forms after administration? Second, through what physical process does drug escape from the state that exists at a particular time? Third, how does the receiving tissue alter that state or the path by which drug reaches the circulation or local target? The proposed synthesis is that formulation attributes establish initial conditions but do not permanently specify the controlling step. Control may migrate as the depot solidifies, hydrates, reorganizes, degrades, becomes more porous, experiences changes in drug physical state, or interacts with local cells.

The resulting Depot–Escape–Tissue Coupling Model, developed later in this article, is explicitly proposed rather than presented as a validated universal mechanism. Its purpose is to organize mechanistic questions that should be resolved product by product and to prevent an in vitro release profile from being interpreted as self-explanatory. This distinction is particularly important for translation: agreement between an assay and an in vivo profile may reflect preservation of the relevant mechanism, compensating errors, or only a restricted formulation range. A useful mechanistic framework must therefore preserve uncertainty as well as mechanism.

Formation of the injection depot

The first mechanistic event in a long-acting injectable is not prolonged release but creation of the post-injection state from which release will occur. For some systems, this state is preformed before administration, as in microspheres and crystalline suspensions. For in situ forming implants, however, injection initiates a dynamic transformation whose kinetics and resulting structure depend on formulation composition. Experimental work with PLGA in situ forming implants demonstrates that polymer attributes and active pharmaceutical ingredient characteristics interact rather than producing a fixed hierarchy of effects, while solvent selection can modify injectability, phase behavior, morphology, early burst, and subsequent diffusion pathways [3, 4]. The same nominal dosage-form category can therefore produce materially different depots after contact with an aqueous biological environment.

Solvent exchange is especially important in phase-inverting implants. Water entering a polymer solution reduces polymer solubility while solvent leaves the injected mass, causing precipitation and progressive formation of a polymer-rich structure. The rate at which this occurs affects whether the implant develops a dense outer region, interconnected pores, internal liquid domains, or a more rapidly consolidated morphology. These structural outcomes matter because they establish the paths through which dissolved drug, undissolved drug, solvent, water, and polymer degradation products subsequently move.

The depot should consequently be defined as a time-dependent material state rather than the geometric volume administered through the needle. Computed-tomography studies of in situ forming implants have demonstrated that internal structure and drug distribution can be followed as the implant develops and changes, directly illustrating that the post-injection depot is not structurally static [5]. Such observations are important because formulation development often relies on pre-injection characterization and terminal measurements even when the intermediate state may be the one governing release.

The underlying phase-inversion mechanism is well established for solvent-exchange systems: non-solvent entry and solvent exit destabilize the polymer solution, produce polymer-rich and polymer-poor domains, and eventually generate a solid or semisolid implant [6]. What is not established is that one phase-inversion trajectory applies to all long-acting injectables. Crystalline suspensions begin from a different physical architecture, and preformed microspheres introduce a particulate polymer matrix rather than a liquid precursor. Accordingly, "depot formation" should be interpreted broadly as establishment of the post-administration release environment while retaining platform-specific mechanisms.

This distinction also prevents an important inferential error. A formulation can be compositionally well characterized before administration but still produce an inadequately characterized depot after administration.

Polymer concentration, solvent miscibility, API solubility, injection geometry, local fluid access, and early precipitation may interact to determine the structure that actually exists in tissue. These variables should therefore be considered formation variables rather than merely manufacturing or administration details.

Solidification and phase behaviour

Solidification is sometimes described as though faster consolidation should straightforwardly suppress burst and prolong release. The evidence is more conditional. In situ forming PLGA systems using different solvent environments show that phase behavior can reduce early escape while simultaneously creating morphologies that facilitate later transport. Alternative solvent studies likewise demonstrate that water ingress, solvent loss, polymer precipitation, and whether drug begins dissolved or dispersed can produce different combinations of burst, lag, and subsequent release [7]. The relevant quantity is therefore not "solidification speed" in isolation but the trajectory through which polymer-rich, solvent-rich, aqueous, and drug-containing regions reorganize.

This has two implications. First, early burst and later sustained release should not automatically be treated as manifestations of the same controlling process. A rapidly precipitating outer layer may initially restrict drug movement while internal solvent exchange later creates pores or shortened diffusion paths. Conversely, slower transformation may permit substantial early diffusion before a more stable matrix is established. The controlling pathway may therefore change even within the same implant.

Second, phase behavior should ideally be observed longitudinally rather than reconstructed entirely from endpoint samples. Spatially offset Raman spectroscopy has been applied to monitor in situ implant formation through tissue while drug release was measured independently, demonstrating the feasibility of following formation and escape together rather than treating them as separate experiments [8]. The method does not itself establish human predictiveness, but it illustrates an analytical principle that is important for long-acting products: time-resolved measurements are needed whenever release depends on a changing material state.

Phase behavior also determines what "drug loading" means after administration. Drug may remain molecularly dispersed, precipitate as the solvent environment changes, partition into polymer-rich regions, or persist as suspended crystalline domains. These states can coexist spatially. A single bulk assay conducted before injection cannot reveal how much of the administered dose occupies each state after phase separation. Mechanistic interpretation should therefore preserve a distinction between the nominal formulation composition and the distribution of material states within the formed depot.

Drug diffusion and dissolution

Once a depot has formed, drug escape is often described using diffusion, dissolution, degradation, or erosion. These mechanisms are analytically separable, but they can overlap and change in relative importance. In a rabbit study of risperidone in situ forming PLGA depots, polymer degradation and release were followed together, and release for most tested formulations was interpreted as strongly degradation associated while bulk erosion-related measurements changed on different time scales [9]. The study is important not because it identifies degradation as a universal LAI mechanism, but because it demonstrates why molecular degradation, mass loss, morphology, and drug release should not be treated as interchangeable measurements.

For a dissolved drug, diffusion requires an accessible aqueous or solvent-containing path and a concentration gradient. For a crystalline suspension, dissolution precedes molecular diffusion away from the crystal surface. In a polymeric depot, both processes may occur while the matrix itself is changing. A release profile is consequently an integrated observation generated by several possible resistances. Without supporting measurements, the profile cannot specify which resistance dominated at a given time.

The testing environment further complicates interpretation. Novel dissolution approaches for long-acting injectables have shown that apparatus configuration and hydrodynamic conditions can materially influence the discrimination obtained between products or formulations [10]. This is not merely an analytical nuisance. If the in vitro environment changes boundary-layer thickness, sink conditions, particle retention, agitation, solvent exchange, or removal of degradation products, then the assay can change the relative importance of the same processes that are being interpreted mechanistically.

Drug physical state provides another control point. Incorporation of mPEG-PLGA has been shown to alter progesterone crystallinity and release behavior within PLGA microspheres, demonstrating that changes in matrix hydration and drug-state evolution can occur together [11]. More recent work with meloxicam microspheres deliberately compared different states of drug incorporation and found that microcrystalline, particulate, and more molecularly distributed drug states produced different release and degradation behavior in the studied intra-

articular system [12]. Such findings argue against assuming that polymer transformation acts upon an invariant API state.

For formulation design, "escape" is therefore best treated as a mechanistic flux rather than a synonym for cumulative percentage released. The relevant questions are what fraction of drug is molecularly mobile, what dissolution step is required, which paths connect drug to external fluid, whether those paths change with hydration or degradation, and whether the surrounding tissue provides the same boundary conditions as the assay. These questions become especially important once the matrix itself begins to transform.

Polymer or matrix transformation

Polymeric long-acting systems are commonly specified using molecular weight, lactide-to-glycolide ratio, and end-group chemistry. These properties are important, but they do not exhaust the structural variables that determine matrix transformation. Comparative work with PLGA raw materials has shown that nominally similar polymers can display different degradation and release behavior and, importantly, that not every apparent material difference produces a distinct performance profile [13]. Polymer source is therefore neither irrelevant nor determinative by itself. The mechanistically relevant issue is which underlying structural differences alter hydration, chain cleavage, pore formation, drug mobility, and erosion in the actual formulation.

Matrix microstructure is the intermediate scale at which such material properties become spatially organized. Three-dimensional focused-ion-beam scanning electron microscopy coupled with image analysis has enabled quantification of polymer, pore, and API distributions within PLGA microspheres, and image-derived microstructures have been used to model release for the analyzed formulations [14]. This type of analysis exposes a limitation of bulk-average descriptors: two particles can share comparable overall composition while differing in pore connectivity, drug-domain geometry, or local path length.

Polymer characterization itself may also require architecture-specific methods. Earlier work on injectable PLGA systems showed that conventional molecular-weight, composition, and end-group measurements can leave release-relevant heterogeneity unresolved [15]. This concern is particularly clear for branched glucose-initiated PLGA, for which branch-sensitive characterization is required to describe structures that cannot be adequately represented as simple linear chains [16]. The implication is not that routine polymer measurements are uninformative, but that the analytical resolution should match the structural complexity of the material being controlled.

These observations support a cross-scale interpretation of matrix transformation. Polymer chemistry establishes a distribution of molecular structures; processing organizes those structures with drug and pores into a particulate or implant architecture; hydration and degradation then change that architecture; and the resulting geometry modifies diffusion, dissolution, local acidity, and erosion. Transfer from one scale to the next is conditional rather than automatic. A molecular attribute matters clinically only if it changes a downstream state sufficiently to alter release or exposure under the relevant biological conditions.

A cross-scale view is particularly useful because it prevents formulation development from searching for direct correlations where intermediate states are missing. **Table 1** therefore maps the transformations that can intervene between polymer or matrix attributes and release behavior while retaining an explicit boundary between measurable depot changes and in vivo transfer.

Table 1. Cross-scale interpretation of matrix transformation when nominal material attributes do not uniquely specify long-acting release

Manuscript-derived transformation event	Depot-scale state that should be interrogated	Biorelevant readout	Consequence for drug escape	Mechanistic failure that can produce misleading interpretation	Formulation lever	Patient or tissue variability that can modify transfer	IVIV transfer test	Endpoint within the proposed joint-control logic
Hydration of a preformed polymer matrix	Spatial water access and swelling rather than bulk water uptake alone	Internal aqueous connectivity and local mobility	Creates or enlarges paths for dissolution and diffusion	Similar bulk hydration conceals different pore connectivity	Polymer architecture, porosity, particle structure	Local fluid turnover and interstitial	Challenge release under conditions that preserve matrix	Determine whether escape is controlled by access to mobile

						composition	hydration mechanism	aqueous pathways
Early chain cleavage before visible erosion	Molecular-weight loss within an apparently intact depot	Polymer degradation trajectory with morphology retained	Can increase mobility before measurable mass loss	Weight loss is used as a surrogate for molecular degradation	Polymer molecular structure and end-group environment	Local water access and buffering	Compare molecular degradation with release rather than mass loss alone	Separate degradation-associated escape from macroscopic erosion
Development or opening of pores	Evolving pore number, size, connectivity, and path length	Three-dimensional microstructure	Alters diffusional resistance and accessibility of drug domains	Bulk composition is assumed to define transport geometry	Processing conditions and matrix architecture	Tissue pressure, fluid access, local swelling	Preserve pore-generating mechanism during accelerated testing	Identify when microstructure becomes the effective transport controller
Redistribution or recrystallization of API	Local molecular, particulate, or crystalline drug state	Spatially resolved solid-state measurement	Changes whether dissolution is required before diffusion	Polymer effects are inferred while API state is assumed invariant	Drug loading method, polymer–drug interaction, hydrophilicity	Local solvent quality, water activity, pH	Verify that in-vitro drug-state evolution resembles the biorelevant state	Distinguish matrix-controlled from drug-state-controlled escape
Polymer-rich and polymer-poor domain evolution in phase-inverting systems	Time-dependent internal phase organization	Solvent loss, water ingress, phase morphology	Can suppress early escape yet later shorten transport paths	Early burst alone is treated as evidence of overall release control	Solvent system, polymer concentration, API solubility	Rate and geometry of local fluid contact	Reproduce formation before comparing later release	Preserve formation history as an input to subsequent escape
Advanced degradation and erosion	Loss of structural continuity and release of soluble polymer fragments	Mass loss, morphology, degradation products	May accelerate escape or expose remaining drug domains	Erosion, degradation and release are treated as one process	Polymer composition and architecture	Clearance and local accumulation of acidic products	Assess whether accelerated conditions retain the same degradation regime	Determine whether the dominant control point has migrated during depot life

Matrix transformation is consequently best understood as a sequence of state changes whose relevance must be demonstrated at the next scale rather than presumed. **Figure 1** represents this argument as a time-resolved state field rather than a linear degradation pathway.

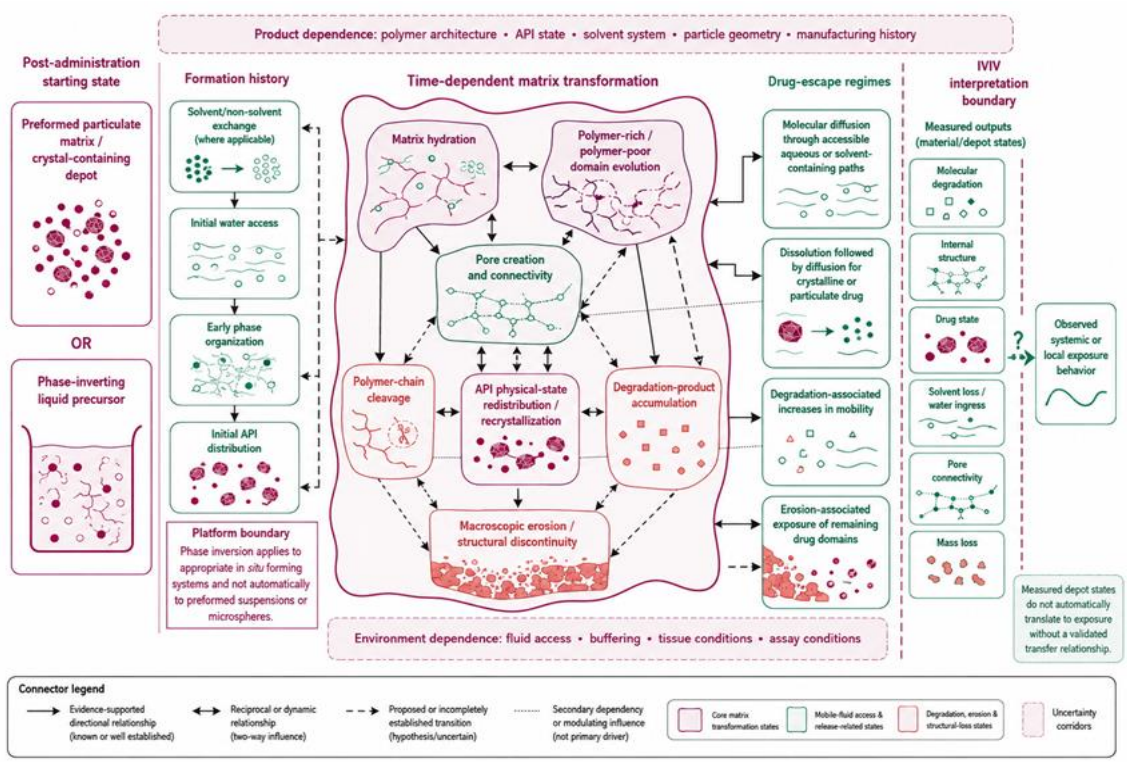


Figure 1. Time-varying matrix states redistribute control over drug escape before macroscopic depot disappearance

Local fluid and cellular infiltration

A depot placed in tissue immediately encounters an aqueous and cellular environment that is absent from many simplified release assays. Fluid enters pores and interparticle spaces, dissolves drug, transports polymer degradation products, changes local pH, and determines the sink conditions experienced by drug near the depot boundary. Yet extracellular fluid is only one component of this environment. Cells may accumulate around the depot or, for sufficiently small particulate systems, interact directly with drug particles.

This distinction is especially important for crystalline long-acting suspensions. Macrophage experiments using aripiprazole lauroxil and paliperidone palmitate demonstrated particle internalization and intracellular handling, with dissolution influenced by cellular abundance and particle characteristics [17]. The same study did not detect a measurable inflammatory cytokine response under the tested conditions, an important null observation because it separates particle uptake from an assumption that cellular interaction must necessarily produce overt inflammation.

Cellular infiltration can therefore change the effective dissolution environment without functioning simply as an inflammatory penalty. A drug crystal within a macrophage encounters a compartment different from bulk extracellular fluid, while particles remaining extracellularly experience another dissolution boundary. The proportions occupying these states are likely to depend on particle size, surface properties, local cell recruitment, injection history, and product-specific tissue response. Current evidence does not establish their quantitative contribution to human exposure for all LAIs, so cellular handling should be represented as a possible mechanistic pathway rather than an obligatory rate controller.

The same reasoning applies to fluid penetration of polymer matrices. Water entry is required for many hydrolytic degradation and dissolution processes, but the spatial distribution of water can be heterogeneous. Regions near the depot surface may experience rapid exchange, whereas internal domains can retain degradation products or develop different solvent and pH conditions. Consequently, "fluid access" should not be reduced to the presence of water in the surrounding tissue. Its relevant form is transport through the actual geometry of the depot.

These processes can be organized more clearly as transitions than as a list of biological factors. **Table 2** therefore treats local fluid and cellular infiltration as alternative or parallel state changes whose downstream consequences depend on the formulation state encountered.

Table 2. Sequence-aware ledger of fluid and cellular transitions that can redirect drug escape from an established injectable depot

Precursor depot state	Transition trigger	Observable state change	Physiological condition that governs the transition	Consequence for depot or drug behavior	Condition that can interrupt, limit, or reverse the sequence
Hydrophobic or incompletely hydrated polymer domain	Contact with interstitial fluid	Progressive wetting and formation of internal aqueous regions	Local water availability, matrix permeability, osmotic and compositional environment	Enables polymer hydrolysis, drug dissolution, and movement through newly accessible paths	Dense structure, low connected porosity, poor wetting, or rapid closure of transport paths
Porous or degrading polymer matrix	Continued fluid exchange	Redistribution or removal of soluble degradation products	Fluid turnover and buffering around the depot	Changes local chemical conditions and can modify degradation or drug stability	Restricted exchange or accumulation within poorly connected internal domains
Extracellular crystalline drug particle	Local dissolution environment	Molecular drug generated at the particle surface	Solubility, local saturation state, fluid renewal, boundary-layer conditions	Supplies dissolved drug for diffusion away from the depot	Poor sink conditions, low intrinsic solubility, agglomeration, or reduced accessible surface
Extracellular particulate prodrug accessible to phagocytic cells	Macrophage contact and uptake	Intracellular localization of particulate material	Local cellular abundance, particle dimensions, surface characteristics	Creates a second dissolution and, where relevant, metabolic-conversion environment distinct from extracellular fluid	Limited recruitment, particle characteristics incompatible with efficient uptake, or sequestration outside active cellular compartments
Matrix or particle surface interacting with proteins and extracellular structures	Adsorption, adhesion, or local tissue contact	Altered interfacial composition and effective transport boundary	Route-specific extracellular matrix composition and local tissue chemistry	May change residence, fluid access, cellular recognition, or local retention	Different administration site, surface chemistry, or biological composition
Persistent depot with repeated fluid and cellular contact	Ongoing local biological recognition	Accumulation of cells and organization of a tissue–depot interface	Duration, material chemistry, particulate burden, route, and host response	Establishes the conditions under which a foreign-body response may modify transport	Resolution, weak biological recognition, or formulation/tissue conditions that do not sustain the response

The sequence is not obligatory. A particle can remain predominantly extracellular; a polymer depot may hydrate with little cellular penetration; and measurable cellular interaction need not produce a strong inflammatory response. The analytical requirement is therefore to identify which transition actually occurs for the product rather than assigning a standard tissue narrative to every long-acting injectable.

Foreign-body response

Persistent drug depots sit at an interface between pharmaceutical material and host tissue. The resulting foreign-body response is often discussed primarily as a tolerability issue, but it may also have mechanistic relevance to drug transport. In one mechanistic modeling analysis of intramuscular aripiprazole lauroxil, representation of an inflammatory-cell layer around the depot was incorporated to investigate how injection-site tissue response could influence drug movement and systemic pharmacokinetics [18]. This evidence supports biological plausibility for a tissue-associated transport barrier, but it remains model-based and should not be interpreted as direct histological proof that an identical layer controls absorption in every patient or product.

The broader biological literature around persistent drug-delivery devices reinforces the principle that tissue response is modifiable rather than a fixed background variable. Local inhibition of the NLRP3 inflammasome around a long-lived subcutaneous antiretroviral implant reduced inflammatory and fibrotic features in a rodent system while maintaining drug activity [19]. Because that study involved a nanofluidic implant rather than an injectable PLGA or crystalline depot, it cannot directly establish the same mechanism or intervention for conventional LAIs. It does, however, demonstrate an important boundary condition for mechanistic thinking: host response can be actively changed, and therefore a tissue layer surrounding a drug depot should not automatically be treated as invariant.

Formulation characteristics may also influence the tissue interface directly. Surface-modified cationic PLGA microparticles designed for intra-articular delivery interacted with glycosaminoglycan-rich synovial components and produced route-specific changes in local retention and inflammatory readouts [20]. Again, these findings cannot be transferred quantitatively to intramuscular or subcutaneous LAIs, but they show that tissue interaction is partly a formulation property rather than solely a patient property.

Foreign-body response should therefore be separated into at least two questions. The first is biological: what cells, extracellular structures, and signaling states accumulate around or within the depot? The second is pharmaceutical: does that response change water access, diffusional path length, particle uptake, local pH, degradation-product clearance, or another variable that actually influences drug escape? Histological evidence of inflammation does not by itself prove an effect on release, just as an altered pharmacokinetic profile does not by itself prove that fibrosis caused the change.

This distinction becomes central to the proposed coupling model. If tissue response changes the physical or chemical environment experienced by the depot, then biological reaction can feed back into material transformation. If it changes the path that dissolved drug must traverse, then the tissue becomes part of the effective release resistance. If neither occurs to a meaningful extent, tissue reaction may remain primarily a tolerability phenomenon rather than a release controller. The mechanistic task is not to assume one of these possibilities but to discriminate among them using measurements capable of connecting tissue state to depot state and drug flux.

Feedback between tissue reaction and release

The local tissue environment can influence release through more than a diffusional barrier outside the depot. It can also alter the depot internally. In exenatide-loaded PLGA microspheres, the microclimate pH measured in vivo differed from that produced by conventional concentrated in vitro conditions, and those differences were associated with pH-sensitive peptide degradation [21]. This finding is especially important because hydrolytic polymer degradation is often treated as an intrinsic material property even though water exchange, buffering, and removal of acidic degradation products depend on the surrounding environment.

Tissue-to-depot feedback can therefore occur through several distinct routes. Fluid access can determine hydration and removal of soluble degradation products; cellular interaction can alter the fate of particulate drug; and an organized tissue layer surrounding the depot may change the effective path between dissolved drug and systemic circulation. These mechanisms are supported by different evidence classes and should not be combined into a single established causal chain. Instead, they indicate that tissue state can become a boundary condition for processes otherwise assigned exclusively to the formulation.

Reciprocity follows from the same logic. Depot chemistry and particle characteristics can influence local biological recognition, while the resulting biological environment can alter fluid access, cellular handling, or transport. The direction and magnitude of this feedback are product, route, and time dependent. Tissue response should therefore be modeled neither as an inevitable release barrier nor as biologically irrelevant background. Its mechanistic importance has to be demonstrated by connecting measurable tissue changes to measurable changes in depot state or drug flux.

A depot–escape–tissue coupling model

The evidence developed across the preceding sections supports a proposed Depot–Escape–Tissue Coupling Model. The model divides long-acting injectable behavior into three analytically distinct but interacting domains. The depot domain comprises the material state produced after administration and its subsequent evolution, including hydration, phase organization, API state, pore development, polymer degradation, and erosion. The escape domain comprises the processes by which drug becomes mobile and leaves that evolving structure, including dissolution, diffusion, degradation-associated mobility, erosion-mediated exposure of drug domains, and cellular handling where relevant. The tissue domain comprises local fluid conditions, extracellular structures, recruited or resident cells, inflammatory organization, and other biological states capable of modifying the first two domains.

The model does not assign a universal sequence to these processes. Instead, it proposes that the effective control point can migrate over time. Early release from a phase-inverting implant may depend strongly on solvent exchange and structural consolidation, whereas later behavior may depend more heavily on polymer degradation, connected porosity, or residual drug state. A crystalline suspension may begin with extracellular dissolution as the dominant process but subsequently acquire a meaningful cellular component if particles are internalized.

Likewise, tissue organization around a persistent depot may become increasingly relevant even when it contributed little immediately after injection.

A central consequence is that apparently similar release profiles can arise from different combinations of controlling processes. Conversely, formulation variants with similar initial attributes may diverge after administration if they form different microstructures, experience different drug-state transitions, or interact differently with the receiving tissue. The model therefore treats agreement between a formulation property and pharmacokinetic behavior as insufficient evidence of mechanism unless the intermediate state connecting them has also been demonstrated.

Table 3 converts this principle into an evidence-reconciliation problem. Its purpose is not to rank mechanisms but to specify what can and cannot be inferred when formulation, depot, in vitro release, tissue, and exposure observations agree or disagree.

Table 3. Reconciling concordant and discordant evidence within the proposed Depot–Escape–Tissue Coupling Model

Observed evidence pattern	Time dependence that must be considered	Biorelevant observation needed	Release or exposure interpretation that is justified	Interpretation that is not justified	Plausible failure mechanism	Formulation or experimental lever	Discriminating evidence required
Similar pre-injection composition but different release	Divergence may arise during formation or later transformation	Internal structure, API state, hydration, degradation trajectory	Post-administration state differs despite nominal compositional similarity	Composition alone is the demonstrated cause of exposure difference	Hidden polymer architecture, phase history, pore geometry, or API redistribution	Polymer source, solvent system, processing, drug loading method	Time-resolved depot characterization linked to release
Similar in vitro release but different in vivo exposure	Tissue contribution may emerge only after administration	Depot-site fluid, tissue, cellular, or structural state	The in vitro system may omit a biologically relevant transport or transformation condition	The formulation necessarily behaves differently intrinsically	Tissue barrier, altered microenvironment, cellular uptake, route-specific conditions	Biorelevant media, tissue-relevant apparatus, mechanistic model structure	Matched in vitro and in vivo measurements of the suspected controlling state
Different in vitro release but similar in vivo exposure	Different mechanisms may converge over the observed interval	Release mechanism under both conditions	In vitro discrimination does not automatically imply clinically meaningful divergence	The more rapidly releasing in vitro formulation must produce greater exposure	Compensating tissue transport, altered dissolution, changing control point	Apparatus hydrodynamics, temperature, sink conditions	IVIV analysis preserving formulation-specific release mechanisms
Early burst differs while later release converges	Early and late control points may be different	Formation kinetics and later matrix state	Early formation or surface-access differences may dominate burst	One mechanism controls the entire release period	Solvent exchange, surface-associated drug, subsequent pore/degradation convergence	Solvent, polymer concentration, particle or implant architecture	Separate early-formation and later-transformation measurements
Tissue response differs but systemic exposure is similar	Tissue effects may be transient, non-rate-limiting, or compensated	Drug flux across the tissue–depot interface	Tissue biology may differ without controlling overall exposure	Any histological difference must alter pharmacokinetics	Redundant transport pathways or excess diffusional capacity	Surface properties, route, local inflammatory environment	Direct relationship between tissue state, local drug flux, and systemic input
Exposure diverges without a clear	An unmeasured state may control only	Higher-resolution microstructure, local	Existing measurements are insufficient to	Absence of difference in routine CQAs proves	Unresolved drug state, microclimate, pore connectivity,	Analytical resolution and sampling schedule	Orthogonal measurements capable of distinguishing

difference in standard depot measurements	part of depot life	chemistry, cellular handling, or tissue interface	identify the controlling mechanism	mechanistic equivalence	biological transport	competing mechanisms

The proposed model is summarized visually in **Figure 2**. Its central feature is not a single release pathway but an adaptive control field in which the relative importance of depot, escape, and tissue variables can change during the residence time of the injectable product.

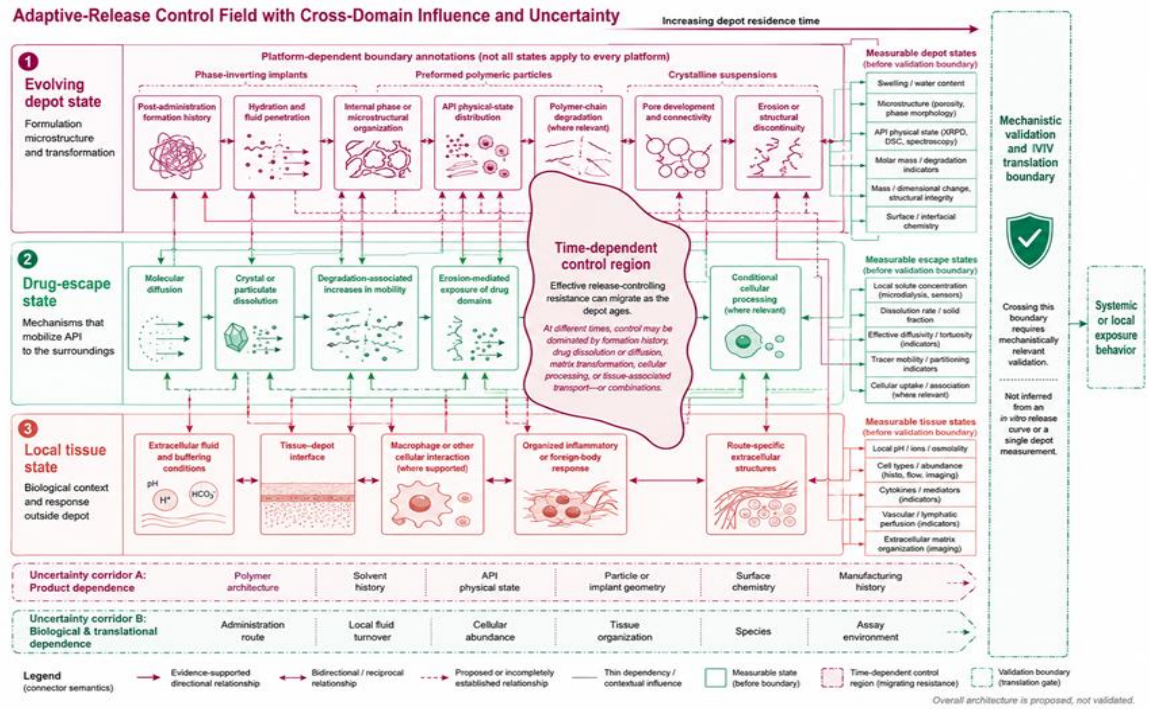


Figure 2. Release control migrates across depot, drug-escape, and tissue states during long-acting injectable residence

In vitro–in vivo translation

Translation requires more than reproducing the shape of an in vivo curve. In risperidone PLGA microspheres, IVIV relationships improved when formulations retained comparable release mechanisms and when the in vitro environment better reflected the physiological temperature of the animal model [22]. Suspension studies likewise demonstrate that meaningful IVIV relationships can be developed when formulation variants differ through controlled, performance-relevant attributes rather than unrelated compositional changes [23].

Across the PLGA literature, this principle is broader than any single apparatus or mathematical transformation. A review of long-acting injectable IVIVC studies concluded that mechanistic preservation is essential when accelerated release methods are used and that simple alignment of fraction released with fraction absorbed can be insufficient [22-24]. Translation should therefore test whether the in vitro system preserves the controlling state, not merely whether two cumulative curves can be fitted.

Emerging computational approaches may help organize this problem. A physiology-based machine-learning framework combining formulation variables, molecular interaction information, and pharmacokinetic or pharmacodynamic modeling has demonstrated proof-of-concept optimization in a preclinical long-acting injectable setting [25]. Such results justify integrated modeling as a development tool, but they do not establish prospective predictive superiority across products or patients.

Product-specific optimization remains necessary. For risperidone in situ forming implants, modifying in vitro release conditions improved correspondence with in vivo behavior by addressing attributes contributing to the original mismatch [26]. In aripiprazole microsuspensions, flow-through testing provided greater discrimination of particle-related formulation differences than the paddle method in the investigated system and supported an IVIV relationship in rats [27]. Neither result establishes a universally superior apparatus. Together, they show that the release method should be selected to expose the mechanism and CQA most likely to matter for the product.

Within the proposed coupling model, an IVIV failure is therefore diagnostically useful. It may indicate an inappropriate hydrodynamic condition, incorrect formation history, missing matrix transformation, altered drug state, species-specific physiology, or a tissue contribution absent from the assay. A mechanistically useful IVIV strategy should be able to discriminate among these explanations rather than treating empirical correlation as the final objective.

Formulation design rules

Joint control changes the order of formulation development. The first question should not be which polymer, solvent, particle size, or apparatus is "best," but which state is expected to constrain drug escape over the clinically relevant interval. That hypothesis then determines which formulation variable should be manipulated and which intermediate state must be measured.

Three practical rules follow. First, control the post-administration state rather than the pre-injection composition alone. Polymer architecture, solvent exchange, API physical state, particle geometry, and processing history matter to the extent that they alter the depot that actually develops in tissue. Second, measure mechanism-specific state variables alongside release. Molecular-weight loss should not substitute automatically for erosion; bulk hydration should not substitute for connected aqueous pathways; and cumulative release should not substitute for dissolution, diffusion, or cellular processing when those mechanisms are competing explanations.

Third, qualify translation by perturbing the suspected control point. A useful release method should discriminate formulations known to differ in a mechanistically relevant attribute and should remain consistent with the formation, dissolution, or degradation regime expected in vivo. Where tissue interaction is suspected, development may require complementary cell, tissue, imaging, or mechanistic-model evidence rather than attempting to force the complete biological environment into one dissolution vessel.

Manufacturing belongs inside this control strategy. Continuous antisolvent crystallization has demonstrated that particle size distribution, solid state, downstream processing, scale-up, and long-term physical stability of a crystalline LAI suspension can be controlled within an integrated process [28]. Such process control does not establish clinical equivalence, but it shows that release-relevant particle states can be engineered upstream rather than evaluated only after final product manufacture.

The broader design objective is thus not to discover a universal release equation for long-acting injectables. It is to construct a product-specific causal hypothesis linking formulation inputs to post-administration states, drug-escape mechanisms, tissue conditions, and exposure, and then to design measurements capable of falsifying that hypothesis. The proposed Depot–Escape–Tissue Coupling Model provides the organizational structure for that task while leaving the controlling mechanism to be established experimentally for each product.

CONCLUSION

Long-acting injectable performance emerges after administration, not at the moment the formulation leaves the manufacturing line. The resulting depot changes physically and chemically while drug dissolves or diffuses, polymer or matrix structure evolves, and the surrounding tissue supplies fluid, cells, extracellular interfaces, and potentially an organized foreign-body response. None of these domains should automatically be assigned permanent control over release.

The central argument of this perspective is therefore that depot formation, drug escape, and tissue response should be investigated jointly while remaining analytically separable. The proposed Depot–Escape–Tissue Coupling Model treats the controlling resistance as potentially time dependent and product specific, provides a framework for interpreting discordant in vitro and in vivo observations, and identifies intermediate states that must be measured before formulation–exposure relationships can be called mechanistic.

This framework is not an empirically validated universal model. Its value is methodological: it replaces the search for a single nominal release-controlling attribute with a falsifiable sequence of questions about what depot forms, how drug becomes mobile, how the depot and tissue alter one another, and whether an in vitro system preserves the relevant conditions. Long-acting injectable development becomes more mechanistically informative when control is assigned only after these competing explanations have been distinguished.

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