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Formulation Challenges in Long-Acting Injectable Small Molecules: Emerging Strategies and Perspectives

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Abstract

Long-acting injectable (LAI) formulations represent a transformative approach in pharmacotherapy, particularly for conditions demanding sustained drug exposure over weeks to months. Although biologics have dominated this space historically, the adaptation of LAI technology to small molecules presents a distinct and complex set of challenges rooted in physicochemical properties, manufacturing scalability, and regulatory expectations. This review systematically addresses the principal formulation barriers encountered in developing LAI small-molecule products, including aqueous solubility limitations, polymorphic instability, particle engineering constraints, and the biological complexities of subcutaneous and intramuscular depots. We critically examine emerging strategies – nanosuspensions, in situ forming implants, lipid-based carriers, cyclodextrin complexation, and polymer – drug conjugates – against the backdrop of clinical relevance and translational feasibility. The roles of excipient selection, sterilization compatibility, and syringeability on depot performance are discussed in depth. Furthermore, pharmacokinetic modeling approaches that facilitate rational formulation design are evaluated. By synthesizing findings across therapeutic areas including psychiatry, infectious disease, oncology, and endocrinology, this review identifies recurring mechanistic patterns and proposes a practical framework for navigating the formulation decision tree in early-stage LAI development. The perspectives presented aim to inform both industrial formulators and academic researchers in accelerating the bench-to-bedside translation of next-generation LAI small-molecule products.

Keywords: Long-acting injectables, depot formulations, nanosuspensions, in situ forming systems, sustained release, small molecules, particle engineering, pharmacokinetics

INTRODUCTION

Medication non-adherence remains one of the most consequential – and underappreciated – drivers of suboptimal therapeutic outcomes across virtually every chronic disease category. Estimates suggest that adherence to oral regimens for conditions, such as schizophrenia, HIV, hypertension, and type 2 diabetes, rarely exceeds 50% beyond the first year of treatment, carrying profound consequences for both individual patients and broader public health systems [1]. Against this backdrop, the development of long-acting injectable formulations has attracted renewed scientific and commercial interest as a pharmacological strategy capable of decoupling dosing frequency from patient volition, thereby simplifying adherence while often reducing peak-to-trough plasma fluctuations.

The LAI market has historically been dominated by macromolecular entities – peptide hormones, monoclonal antibodies, and vaccine antigens – for which subcutaneous depots are often achievable

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through relatively straightforward concentration of aqueous solutions. Small molecules, by contrast, present a fundamentally different challenge: their physicochemical diversity, spanning lipophilicity, crystal habit, ionization state, and metabolic lability, renders a one-size-fits-all formulation approach untenable [2]. The transition from a daily oral tablet to a monthly or bimonthly intramuscular injection requires far more than a simple change in route of administration; it demands a reconceptualization of the drug product itself.

Historically, early LAI small-molecule products – particularly the haloperidol decanoate and fluphenazine decanoate depots introduced in the 1960s and 1970s – relied on oily vehicle technology, exploiting the slow diffusion of lipophilic prodrug esters from viscous sesame or coconut oil suspensions [3]. While effective, these systems carried limitations including injection site reactions, variable absorption, and an inability to rapidly reverse plasma levels in cases of adverse events. Contemporary formulation science has expanded the toolkit considerably, yet each emerging platform introduces its own set of translational hurdles [1]. provides a decision framework to guide formulation platform selection based on key drug physicochemical attributes (Figure 1).

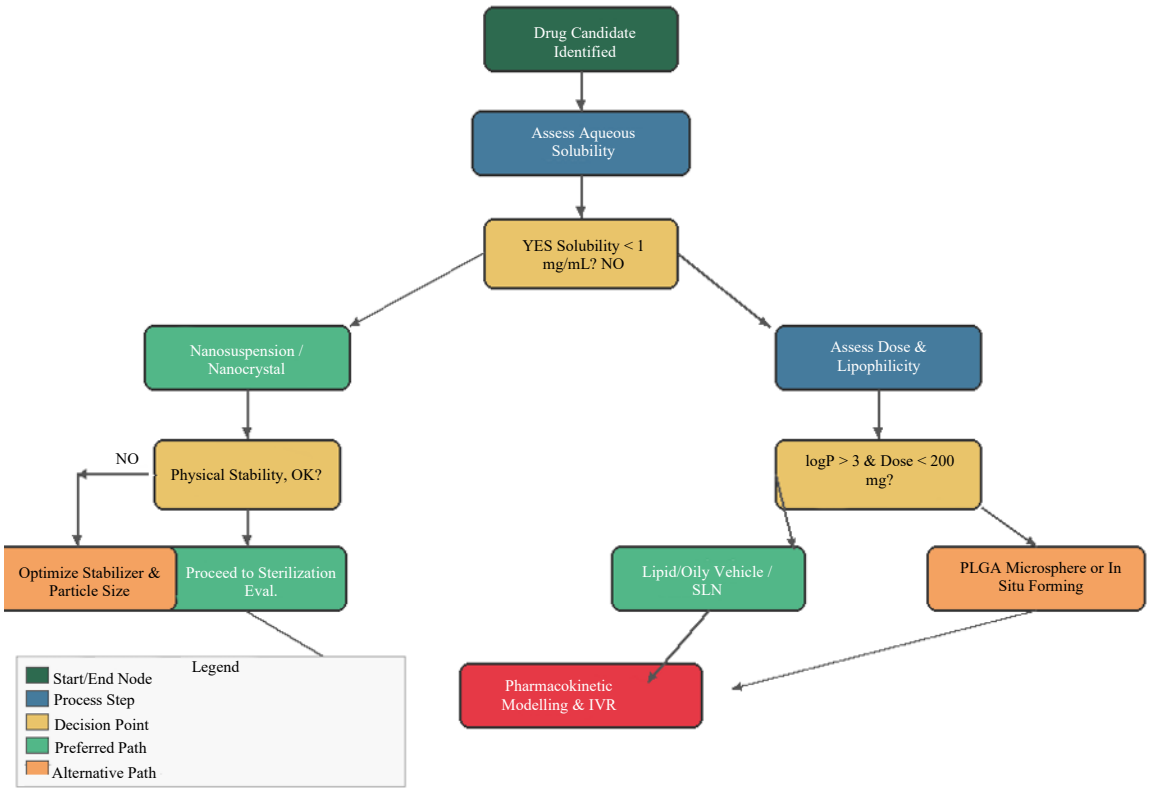

Figure 1. Formulation decision framework for LAI small molecules. The algorithm guides platform selection based on aqueous solubility, logP, dose requirements, and physical stability assessments. IVR = in vitro release; SLN = solid lipid nanoparticle; PLGA = poly (lactic-co-glycolic acid).

PHYSICOCHEMICAL AND BIOPHARMACEUTICAL CONSTRAINTS GOVERNING LAI DESIGN

Aqueous Solubility and Its Dual-Edged Implications

The conventional wisdom that low aqueous solubility is the enemy of drug delivery holds a particular irony in LAI development: many of the physicochemical characteristics that complicate oral bioavailability – high lipophilicity, poor water solubility, large crystalline lattice energy – can, under the right formulation conditions, be exploited to achieve the slow depot release necessary for long-acting performance [4]. A drug with an intrinsic solubility below 1 µg/mL in interstitial fluid may dissolve so slowly from a subcutaneous depot that therapeutically relevant plasma concentrations persist for weeks without any additional encapsulation strategy.

Nevertheless, solubility governs not only release rate but also the concentration achievable within an injectable volume. The maximum dose deliverable per injection is constrained by both solubility and the practically tolerable injection volume – typically 1–2 mL for subcutaneous routes and up to 5 mL for deep intramuscular injection into the gluteal muscle. Drugs requiring doses above approximately 300 mg per injection cannot realistically be delivered as dissolved solutions, necessitating suspensions or high-load depots [5]. This creates a design space where dissolution rate from a depot must be carefully calibrated: too rapid, and the system provides no duration advantage over oral dosing; too slow, and attainment of therapeutic plasma concentrations may be delayed to a clinically unacceptable degree.

Polymorphism, Crystallinity, and Physical Stability

Among the most insidious formulation challenges in LAI development is polymorphic transformation during manufacturing, storage, or following injection into biological tissue. Small-molecule drugs frequently exist in multiple crystalline forms that differ in solubility, dissolution rate, thermodynamic stability, and mechanical properties [6]. A high-energy polymorph selected for its faster dissolution rate in vitro may convert to a more stable, less soluble form during steam sterilization, lyophilization, or even upon prolonged storage as a nanosuspension – fundamentally altering the in vivo release profile without any detectable macroscopic change in the product.

The consequences of uncontrolled polymorphic conversion are not merely academic. The paliperidone palmitate case – now one of the most commercially successful LAI products globally – required extensive crystal engineering work to stabilize a specific particle size distribution and polymorph combination that would yield predictable monthly dosing intervals [7]. Differential scanning calorimetry, X-ray powder diffraction, and solid-state nuclear magnetic resonance collectively constitute the minimum analytical toolkit for characterizing polymorphic behavior, while solution-mediated transformation studies in physiologically relevant media provide the most translatable predictive data.

Depot Microenvironment and Tissue Dynamics

Following intramuscular or subcutaneous administration, a drug depot does not exist in a static environment. The tissue microenvironment at the injection site is a dynamic milieu characterized by fluctuating pH, variable perfusion, enzymatic activity, mechanical forces from muscle contraction, and an evolving inflammatory response to the injected material itself [8]. These factors can substantially alter drug release kinetics relative to predictions based solely on in vitro dissolution data, contributing to one of the most persistent challenges in LAI development: the poor in vitro–in vivo correlation (IVIVC) that complicates rational formulation optimization.

Subcutaneous tissue presents distinct challenges compared to intramuscular sites. The lower vascularity and lymphatic drainage capacity of subcutaneous fat means that absorption from subcutaneous depots is generally slower and more variable, particularly for hydrophilic molecules or particles below approximately 100 nm that may be taken up by lymphatic capillaries rather than blood microvessels [9]. Body composition – specifically the thickness and perfusion of the subcutaneous adipose layer – introduces meaningful inter-individual variability in absorption, which has clinical implications for dose prediction, particularly in obese or cachectic patient populations.

FORMULATION PLATFORMS: MECHANISMS, ADVANTAGES, AND LIMITATIONS

Nanosuspensions

Nanosuspensions – stabilized colloidal dispersions of pure drug particles typically in the 100–1000 nm range – represent the most clinically validated platform for LAI small molecules in the contemporary era [10]. The foundation of nanosuspension-based depot release lies in the Noyes–Whitney dissolution framework: particle size reduction dramatically increases specific surface area, and when combined with a drug of sufficiently low aqueous solubility, the dissolution rate from the depot can be tuned by controlling median particle size during manufacture. Smaller particles yield faster absorption; larger particles extend duration, as depicted schematically in Figure 2.

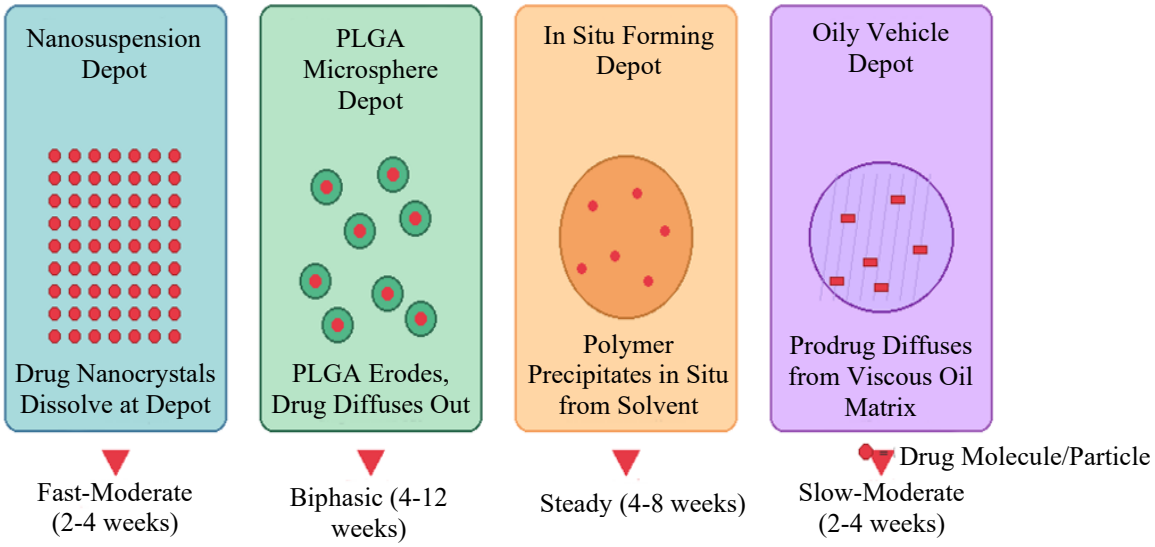

Figure 2. Schematic representation of drug release mechanisms from the four principal LAI depot platforms at the injection site. Red particles indicate drug molecules or nanocrystals; host matrices are depicted in platform-specific colors. Release rate estimates are approximate and dependent on formulation variables. SLN = solid lipid nanoparticle.

The stabilization of nanosuspensions against Ostwald ripening, aggregation, and sedimentation during shelf life requires judicious excipient selection. Polymeric stabilizers, such as hydroxypropyl methylcellulose, povidone, and poloxamers, adsorb onto crystal surfaces via steric and electrostatic mechanisms, maintaining colloidal stability over months to years [11]. However, these stabilizers must be carefully evaluated for their potential to alter the in vivo drug release profile through competitive desorption in biological fluids, and for their compatibility with both terminal sterilization and freeze-drying processes where applicable.

The clinical translation of nanosuspensions to LAI products has been most thoroughly realized in antipsychotic therapy. Aripiprazole monohydrate nanosuspension (Abilify Maintena), paliperidone palmitate nanosuspensions at one-month and three-month intervals (Invega Sustenna, Invega Trinza), and risperidone-loaded polymer microspheres (Risperdal Consta) collectively represent a proof of concept for the therapeutic durability achievable through particle engineering [12]. Nonetheless, each of these products required years of iterative optimization to achieve the particle size specifications, physical stability, and pharmacokinetic profiles demanded by regulatory agencies.

In Situ Forming Systems

In situ forming depot systems exploit the phase-transition behavior of specific polymer solutions to create a solid or semi-solid implant at the injection site following administration as a fluid. The most commercially established variant employs biodegradable poly(lactic-co-glycolic acid) (PLGA) dissolved in a water-miscible solvent such as N-methyl-2-pyrrolidone (NMP); upon contact with aqueous tissue fluids, solvent diffusion induces polymer precipitation around dissolved or dispersed drug, forming a depot matrix that erodes hydrolytically over time [13].

The kinetics of in situ depot formation are governed by the interplay between solvent diffusion, polymer phase inversion, and the concurrent drug partitioning between the precipitating polymer matrix and surrounding tissue. An initial burst release phase – attributable to drug near the depot surface that is liberated before polymer precipitation is complete – is a characteristic feature of NMP-based PLGA systems and remains a significant formulation challenge. Burst release can cause supratherapeutic plasma concentrations in the first 24–72 hours post-injection, raising tolerability concerns particularly for drugs with narrow therapeutic indices [14].

Strategies to attenuate burst release in in situ forming systems include increasing polymer concentration to accelerate phase inversion, incorporating hydrophobic excipients that slow water ingress, using higher molecular weight or end-capped PLGA grades to reduce the rate of matrix erosion, and encapsulating drug within an inner lipid layer prior to suspension in the polymer solution [15]. Thermosensitive hydrogel systems – principally poloxamer 407 and PLGA-PEG-PLGA triblock copolymers that are liquid at room temperature but gel at body temperature – offer an alternative in situ forming mechanism that avoids organic solvents entirely, potentially improving injection tolerability and reducing solvent-related toxicity concerns.

Lipid-Based Carriers

Lipid-based delivery systems for LAI applications encompass a spectrum from simple oily solutions and suspensions to more structurally complex liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid microspheres [16]. The oily vehicle approach – exemplified by testosterone undecanoate in castor oil and various antipsychotic decanoate esters in vegetable oils – relies on the inherently slow diffusion of hydrophobic drug molecules from a viscous lipophilic matrix into the surrounding aqueous interstitial fluid. Release rate is primarily modulated by the drug–oil partition coefficient, oil viscosity, and the surface area of the oil depot as it disperses post-injection.

Solid lipid nanoparticles and nanostructured lipid carriers offer greater versatility for drugs of moderate lipophilicity that would dissolve too rapidly in conventional oily vehicles. SLNs comprise a crystalline lipid matrix (typically glyceryl monostearate, tristearin, or Compritol) stabilized by emulsifiers, with drug distributed within or adsorbed onto the matrix. NLCs incorporate a blend of solid and liquid lipids, creating structural disorder within the matrix that increases drug payload capacity and reduces drug expulsion upon storage [17]. Both systems offer the potential for injectable sterilization by filtration when particle size is maintained below 200 nm, and they are composed of generally regarded as safe (GRAS) excipients, simplifying regulatory justification.

Polymer Microspheres and Microparticles

Biodegradable polymer microspheres – spherical particles in the 1–250 μm range composed principally of PLGA, polylactic acid (PLA), or polycaprolactone (PCL) – represent a mature and versatile LAI platform capable of sustaining drug release over days to months depending on polymer composition and particle architecture [18]. The Risperidone/PLGA microsphere product (Risperdal Consta) demonstrated that this approach could achieve biweekly intramuscular dosing for a major psychiatric indication, validating the platform commercially despite the complexity of the lyophilized powder-for-suspension presentation required for adequate shelf life.

Drug release from PLGA microspheres occurs through a combination of surface erosion, bulk hydrolysis-driven erosion, and drug diffusion through the polymer matrix – mechanisms whose relative contributions depend on polymer molecular weight, end-group chemistry, lactide-to-glycolide ratio, particle size, and drug loading [19]. Triphasic release profiles – an initial burst, a lag phase associated with water uptake prior to bulk erosion, and a terminal erosion-driven release phase – are commonly observed and may be pharmacokinetically undesirable. Formulation strategies to linearize release include blending PLGA grades of different molecular weights, incorporating pore-forming agents, and modulating drug–polymer compatibility through salt form selection.

Cyclodextrin Complexation

Cyclodextrin inclusion complexation, while primarily employed to enhance aqueous solubility for intravenous administration, has found selective application in LAI formulations where controlled release of the native drug from the complex dissociation equilibrium can provide a modestly prolonged pharmacokinetic profile [20]. Hydroxypropyl-β-cyclodextrin (HPβCD) forms non-covalent inclusion complexes with a range of small molecules whose hydrophobic moieties fit within the cyclodextrin cavity, increasing apparent solubility by several orders of magnitude. The equilibrium dissociation

constant of the complex in tissue interstitial fluid governs the free drug concentration and hence the driving force for absorption.

The utility of cyclodextrin complexation as a standalone LAI strategy is limited by the reversibility of complexation: in the dilute aqueous environment of interstitial fluid, rapid dissociation typically yields pharmacokinetic profiles only modestly extended relative to conventional formulations. However, hybrid approaches – incorporating cyclodextrin–drug complexes within PLGA microspheres or hydrogel matrices – may leverage both the solubilization benefit of cyclodextrins and the diffusion-controlled release of encapsulating matrices, expanding the accessible pharmacokinetic design space [21].

Prodrug and Salt Form Engineering

The conversion of a parent drug to a sparingly soluble ester prodrug or to a specific salt form with dramatically reduced aqueous solubility constitutes one of the oldest and most pharmacologically rational LAI strategies [22]. The haloperidol decanoate and fluphenazine decanoate paradigm established that fatty acid esterification at a hydroxyl group could reduce solubility sufficiently to enable sustained release from oily depots over several weeks, while enzymatic cleavage in plasma regenerates the active parent drug at a rate governed by prodrug concentration. The principal advantage of this approach is the inherent simplicity of the formulation relative to particulate systems; the principal risk is that the prodrug itself may possess pharmacological activity or toxicity distinct from the parent compound.

Contemporary prodrug strategies for LAI small molecules have moved beyond simple fatty acid esters toward more sophisticated approaches including phosphate prodrugs designed to precipitate at the injection site upon phosphatase-mediated hydrolysis, and polymer–drug conjugates in which the drug is covalently tethered to a biodegradable polymer backbone via hydrolytically or enzymatically labile linkers [23]. The latter approach, drawing conceptual inspiration from antibody–drug conjugate technology, theoretically enables precise pharmacokinetic tuning through linker chemistry selection, though the synthetic complexity and regulatory novelty of such entities present translational challenges.

MANUFACTURING, STERILIZATION, AND SCALE-UP CONSIDERATIONS

Injectable pharmaceutical products are among the most manufacturing-intensive dosage forms, subject to stringent sterility, particulate matter, and endotoxin requirements that impose constraints absent in oral formulation development [24]. The choice of sterilization method is particularly consequential for LAI small-molecule formulations: the physicochemical complexity of many depot systems renders terminal steam sterilization (autoclave, 121°C, 15 min) incompatible with product quality attributes. Thermal exposure at these conditions can drive polymorphic transformation in nanosuspensions, accelerate PLGA hydrolysis in microsphere systems, and degrade thermolabile excipients.

Aseptic processing – in which all components are sterilized separately before being combined under controlled conditions – is, therefore, the predominant sterilization strategy for complex LAI formulations. Filtration sterilization through 0.22 μm membranes is suitable for dissolved drug solutions and for nanosuspensions composed entirely of sub-200 nm particles but cannot be applied to microsphere suspensions or to formulations containing particles above the filter pore size. Gamma irradiation, while applicable to solid microsphere preparations, can induce free-radical mediated degradation of PLGA and may alter drug crystallinity in nanosuspensions, necessitating dose-response validation for each specific formulation [25].

Particle size control during nanosuspension manufacturing by high-pressure homogenization or wet media milling is among the most critical and challenging process parameters to maintain at commercial scale. Milling energy input, media size, drug and stabilizer concentrations, and processing temperature

collectively determine the achieved particle size distribution.11 Batch-to-batch reproducibility of particle size specifications – typically defined as D90, D50, and D10 values – directly determines the reproducibility of in vivo release and pharmacokinetic profiles, making process analytical technology (PAT) implementation essential for commercial LAI manufacturing. Dynamic light scattering, laser diffraction, and nanoparticle tracking analysis each offer complementary information on particle size distribution, with no single technique sufficient for complete characterization of the complex particle populations encountered in LAI nanosuspensions.

Syringeability and injectability – the ease of drawing product into a syringe and expelling it through a needle, respectively – are often underappreciated formulation quality attributes that become rate-limiting in late-stage development. High-viscosity oily vehicles, concentrated nanosuspensions, and microsphere suspensions all present potential challenges for reliable dose delivery through needles of gauge 19–23, which represent the practical range for depot injections in clinical practice [5]. Rheological characterization across the temperature range from refrigerated storage to body temperature is essential, as viscosity changes with temperature can significantly affect both syringeability and the depot formation geometry following injection.

Lyophilization (freeze-drying) is frequently employed for PLGA microsphere LAI products to achieve the long-term physical stability required for commercial shelf life. The freeze-drying process introduces its own set of formulation stresses – ice crystal formation, freeze concentration of solutes, and thermal transitions through the glass transition temperature of the polymer – each capable of altering microsphere morphology or drug distribution within the matrix [26]. Cryoprotectant selection (most commonly trehalose, sucrose, or mannitol) and lyophilization cycle optimization are, therefore, integral components of microsphere LAI formulation development rather than afterthoughts.

PHARMACOKINETIC MODELING IN LAI FORMULATION DEVELOPMENT

The development of LAI formulations is inherently pharmacokinetically driven: the target product profile specifies a desired plasma concentration–time curve, and formulation design is the means by which that curve is achieved. Pharmacokinetic modeling serves as the quantitative bridge between formulation variables and clinical outcomes, enabling rational design of dose, injection interval, and dose titration strategy [27].

Physiologically based pharmacokinetic (PBPK) models adapted for subcutaneous and intramuscular absorption incorporate mechanistic descriptions of drug dissolution at the depot, convective and diffusive transport through tissue, lymphatic uptake, and systemic distribution. These models, when parameterized with in vitro dissolution data and tissue-specific physiological parameters, can provide a priori predictions of pharmacokinetic profiles that complement – and in some cases may prospectively reduce the need for – extensive animal PK studies [28]. The accuracy of PBPK predictions for LAI formulations remains an active area of development, particularly for particle-based systems where the depot microenvironment evolves dynamically following injection.

Population pharmacokinetic modeling using non-linear mixed effects approaches (e.g., NONMEM, Monolix) is standard practice in the clinical development of LAI products and serves multiple functions: characterizing the sources and magnitude of pharmacokinetic variability across patient populations, identifying covariates, such as body mass index and injection site, that predict individual exposure, informing loading dose strategies to achieve rapid attainment of therapeutic steady state, and providing the quantitative basis for regulatory submissions [27]. The long dosing intervals inherent to LAI products – monthly to quarterly – extend the time required to achieve pharmacokinetic steady state, making loading dose optimization particularly important and PK modeling especially valuable in early clinical development.

Modeling and simulation approaches also play a pivotal role in late-stage regulatory submissions for LAI products. The FDA's Model-Informed Drug Development (MIDD) framework increasingly encourages sponsors to use population PK models to support labeling claims, including injection site

selection guidance (deltoid vs. gluteal), dose adjustment recommendations in special populations, and missed-dose management guidance [29]. The unique pharmacokinetic challenges posed by LAI products – where dose-normalized exposure may depend on injection site, patient body composition, and the physical state of the depot at the time of re-injection – make MIDD particularly well-suited to informing label language for these complex products.

THERAPEUTIC AREA PERSPECTIVES

Central Nervous System Disorders

Schizophrenia and related psychotic disorders represent the most clinically developed application domain for LAI small molecules, driven by the catastrophic consequences of medication non-adherence in this population – including relapse, hospitalization, and suicide [3]. The second-generation antipsychotic LAI portfolio, encompassing aripiprazole lauroxil (Aristada), aripiprazole monohydrate nanosuspension (Abilify Maintena), and the paliperidone palmitate series, has validated that monthly and even quarterly dosing is clinically achievable with nanosuspension and ester prodrug technologies. Despite this success, a substantial proportion of patients with schizophrenia remain on oral antipsychotic regimens, reflecting both prescriber hesitancy and patient preference barriers that extend beyond the pharmacological.

The application of LAI technology to mood disorders, including major depressive disorder and bipolar disorder, represents a comparatively early-stage but growing area of investigation. Aripiprazole monohydrate LAI has received FDA approval for maintenance treatment of bipolar I disorder, providing evidence that the platform is not restricted to schizophrenia [30]. Emerging LAI candidates for treatment-resistant depression, including ketamine prodrug formulations designed for monthly intramuscular administration, are at various stages of clinical investigation, though the psychoactive properties of ketamine impose specific pharmacokinetic exposure constraints that complicate depot formulation design.

Infectious Disease

HIV prevention and treatment represent perhaps the most rapidly evolving frontier in LAI small-molecule applications. Cabotegravir, an integrase strand transfer inhibitor, was approved as a monthly and then bimonthly intramuscular nanosuspension (Cabenuva, in combination with rilpivirine) for HIV treatment, representing the first complete LAI antiretroviral regimen [12]. The formulation achievement underpinning this approval – stable cabotegravir nanosuspensions with predictable monthly release and acceptable injection site tolerability – required extensive characterization of particle surface properties and in vivo dissolution kinetics. For pre-exposure prophylaxis, the prospect of quarterly injectable cabotegravir could fundamentally alter the prevention landscape in populations where daily oral PrEP adherence is problematic.

Beyond HIV, the application of LAI technology to tuberculosis chemotherapy is attracting considerable attention given the catastrophic global burden of TB and the known adherence challenges associated with the standard six-month oral regimen. Rifampicin, isoniazid, and bedaquiline are among the anti-TB compounds being evaluated in LAI formulations at the preclinical stage, though the large doses required for TB therapy (often hundreds of milligrams per day) impose formulation and injection volume constraints not encountered in HIV antiviral dosing [31].

Oncology and Hormonal Therapies

Luteinizing hormone-releasing hormone (LHRH) agonist and antagonist LAI products – including leuprolide acetate PLGA microspheres (Lupron Depot) and histrelin hydrogel implants (Supprelin) – exemplify the application of sustained-release depot technology to endocrine oncology, where suppression of gonadotropin secretion must be maintained with precision over months to years [18]. These products also illustrate the regulatory and clinical implications of complex depot pharmacokinetics: the initial agonist surge associated with LHRH agonist depots can transiently worsen

hormone-sensitive prostate cancer, necessitating co-administration of anti-androgens – a clinical nuance that emerges directly from the pharmacokinetic characteristics of the depot system.

REGULATORY CONSIDERATIONS AND IVIVC DEVELOPMENT

The regulatory pathway for LAI small-molecule formulations is considerably more complex than that for oral solid dosage forms, reflecting both the specialized clinical risks associated with injectable products and the inherent difficulties in establishing bioequivalence for depot systems. The U.S. Food and Drug Administration's draft guidance on modified release injectable drug products identifies specific requirements for pharmacokinetic studies, in vitro release testing, and IVIVC development that go substantially beyond the requirements for oral extended-release products [24].

Establishing a Level A IVIVC – the most predictive correlation between in vitro drug release and in vivo pharmacokinetic performance – is analytically challenging for depot injectables because the in vitro dissolution conditions that approximate the depot microenvironment (low volume, limited agitation, physiologically relevant pH and protein content) are difficult to standardize and validate. The USP 4 flow-through cell apparatus and membrane diffusion-based release testing methods have been explored as alternatives to paddle and basket apparatuses for nanosuspension and microsphere LAI products, but no universally adopted standard methodology exists, hampering cross-laboratory comparability of in vitro release data [25].

The characterization of immunogenicity and local tissue tolerability following repeated depot injections presents additional regulatory complexity. Subcutaneous and intramuscular formulations of PLGA and other biodegradable polymers can elicit a foreign body response characterized by macrophage infiltration, fibrous encapsulation, and – in some cases – granuloma formation that alters depot geometry and drug release kinetics over time.8 Understanding whether these tissue responses affect pharmacokinetic reproducibility across injection cycles is an emerging regulatory expectation that requires integration of preclinical histopathology with clinical pharmacokinetic data.

EMERGING STRATEGIES AND FUTURE PERSPECTIVES

Several formulation technologies currently at the preclinical or early clinical stage hold particular promise for expanding the accessible design space for LAI small molecules. Supercritical fluid processing techniques – including supercritical antisolvent precipitation and particles from gas-saturated solutions – enable precise control of drug crystal size, morphology, and polymorphic form under solvent-free conditions, potentially yielding nanosuspension precursors with superior physical stability relative to milled particles [10]. The ability to engineer crystal habit through supercritical processing may also influence in vivo dissolution kinetics at the depot site in ways not achievable through aqueous milling alone.

Three-dimensional printing technologies, particularly selective laser sintering and inkjet printing of biodegradable polymer matrices, offer unprecedented spatial control over drug distribution within a depot implant, enabling gradient drug loading profiles designed to linearize release kinetics or provide sequential multi-drug delivery from a single implantable device [23]. While regulatory acceptance of additively manufactured implants remains nascent, the accelerating clinical experience with 3D-printed oral solid dosage forms provides a translational precedent. The application of microfluidic fabrication to LAI microsphere manufacture – enabling tighter particle size distributions and more complex core-shell architectures than conventional emulsion-solvent evaporation methods – is similarly advancing from research tools toward scalable manufacturing platforms.

Theranostic LAI formulations – systems designed to simultaneously deliver therapeutic drug and diagnostic imaging agent from the same depot – represent a conceptually attractive convergence of precision medicine and sustained-release technology. By incorporating FDA-approved imaging agents, such as iron oxide nanoparticles or iodinated contrast media into LAI depots, in vivo depot visualization by MRI or CT could provide non-invasive, patient-specific confirmation of depot formation and

potentially correlate with pharmacokinetic exposure in individual patients.16 Such capabilities would be particularly valuable during dose individualization in heterogeneous patient populations where pharmacokinetic variability currently necessitates therapeutic drug monitoring.

Machine learning and artificial intelligence approaches are beginning to influence LAI formulation development, primarily in the domains of physicochemical property prediction, excipient compatibility screening, and process optimization. Quantitative structure–property relationship models trained on existing nanosuspension stability datasets may accelerate stabilizer selection by predicting adsorption affinity and desorption kinetics for new drug candidates [20]. Similarly, Bayesian optimization frameworks applied to high-throughput formulation screening can efficiently identify regions of the excipient design space associated with desired quality attributes, reducing the experimental burden relative to traditional design of experiments approaches while handling the non-linear, multi-parameter interactions characteristic of LAI formulation systems.

CONCLUSION

Long-acting injectable formulations for small molecules occupy a uniquely challenging position at the intersection of physical pharmacy, materials science, clinical pharmacology, and regulatory science. The diversity of physicochemical properties among small-molecule drug candidates precludes any single formulation platform from serving as a universal solution; instead, rational platform selection must be guided by a systematic evaluation of drug-specific parameters – solubility, permeability, dose, polymorphic behavior – against the backdrop of target clinical application, injection route, desired duration, and manufacturing feasibility.

The nanosuspension platform, supported by the most extensive clinical validation record among contemporary LAI technologies, will likely remain a cornerstone of new LAI development. However, its applicability is bounded by the requirement for sufficiently low aqueous solubility, and by the particle engineering complexity that limits its use for drugs below approximately 200 mg/mL intrinsic solubility. In situ forming systems, lipid nanocarriers, and polymer microspheres each address different segments of the physicochemical and dose design space, and hybrid systems that combine elements of multiple platforms represent an increasingly important frontier for drugs that resist conventional categorization.

The translation of promising LAI platforms to approved products continues to be constrained by deficiencies in our mechanistic understanding of depot-tissue interactions, the lack of standardized in vitro release methodology, and the pharmacokinetic complexity introduced by long dosing intervals and heterogeneous patient populations. Addressing these gaps through interdisciplinary collaboration – integrating computational biophysics, advanced materials characterization, and population-level clinical pharmacokinetics – will be essential to realizing the full therapeutic potential of LAI technology for the growing portfolio of small-molecule drug candidates in chronic disease management.

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