International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

ADVANCES IN LONG-ACTING INJECTABLE DRUG DELIVERY: FORMULATION SCIENCE, EMERGING TECHNOLOGIES, AND FUTURE PERSPECTIVES

Theyaneshwaran P[1], Dr. R. Devi Damayanthi[2], Deepthi D[3], Sowmiya P[4]

[1]PG Student, [2]Assistant Professor, [3,4]PG Student
[1,2,3,4]Department of Pharmaceutics, College of Pharmacy, Madras Medical college

Abstract:
Long-acting injectable (LAI) drug delivery systems are a cornerstone of chronic disease management, offering sustained therapeutic concentrations and improved patient adherence. These formulations establish intramuscular or subcutaneous depots to provide controlled drug release, thereby minimizing dosing frequency and pharmacokinetic variability. This comprehensive review articulates the evolution of LAI platforms, from legacy oil-based solutions to advanced biodegradable polymeric microspheres (PLGA), *in situ* forming gels, lipid-based carriers, and nanosuspensions. The formulation principles, technical advantages, and manufacturing challenges for each technology are critically analyzed. Core drug release mechanisms, including polymer erosion, matrix diffusion, and particle dissolution, are detailed. Furthermore, advanced strategies to manipulate *in vivo* clearance and extend therapeutic half-life, such as PEGylation, lipidation, and Fc/HSA fusion, are synthesized. A significant focus is placed on product characterization, emphasizing the challenges in developing predictive *in vitro* release (IVR) methods. Key quality attributes (CQAs) and regulatory pathways are also examined. Finally, emerging technologies, including stimuli-responsive systems and AI-assisted design, are explored to outline future perspectives for enhancing the therapeutic precision and clinical utility of LAIs.

Keywords: Long-acting injectables, sustained release formulations, PLGA microspheres, depot formulations, nanocarriers, biodegradable polymers, lipid-based LAIs, pharmacokinetics.

INTRODUCTION

Chronic illnesses, including diabetes, cardiovascular disease, and chronic respiratory conditions, pose formidable challenges to healthcare systems globally. These diseases are major contributors to both morbidity and mortality and concurrently impose a substantial financial burden. The World Health Organization (WHO) reports that chronic diseases are responsible for approximately 71% of all deaths worldwide, underscoring the pressing need for robust management strategies.

A primary impediment in the management of chronic diseases is their inherent complexity, which is frequently compounded by the presence of comorbidities. Effective management demands a comprehensive methodology that addresses multifaceted health needs and fosters coordination among different healthcare providers. Despite this, many healthcare systems encounter difficulty in implementing integrated care models capable of effectively managing these complexities.

Furthermore, the successful management of chronic diseases is critically dependent on patient engagement. Patients are required to actively participate in their own care, a process that includes adopting lifestyle modifications and adhering to prescribed treatment regimens. Nevertheless, factors such as health literacy levels, socio-economic status, and differential access to resources can erect significant barriers to effective self-management[1].

Long-acting injectable (LAI) drug formulations, designed for intramuscular (IM) or subcutaneous (SC) administration, have surfaced as a therapeutic class that furnishes stable drug exposure for extended durations, which can range from weeks to several months, following a single administration.
In comparison to conventional pharmaceutical preparations, LAIs possess distinguished features, notably a reduced frequency of administration, which consequently enhances patient compliance and diminishes rates of relapse and adverse effects. Accordingly, the research and development of LAI drug formulations have undergone a significant expansion over recent decades, culminating in the successful commercialization of numerous LAI drug products[2].

LAIs facilitate a marked reduction in dosing frequency for patients and are exceptionally well-suited for the management of chronic conditions that otherwise necessitate frequent, repeated dosing. LAI products have demonstrated an ability to improve patient compliance and, more significantly, therapeutic outcomes. This is often accompanied by a decreased incidence of side effects, contributing to an overall reduction in medical care costs. The scientific principles underpinning LAI formulations amalgamate core concepts from physical pharmacy, polymer science, and biopharmaceutics. A spectrum of LAI products is available on the market, leveraging diverse technologies such as oil-based systems, aqueous suspensions, polymeric microspheres, and *in situ* forming gels. The selection of a specific formulation technology is heavily contingent upon the physicochemical properties of the active pharmaceutical ingredient (API). Most LAI systems utilize either the physical entrapment of drug molecules within polymeric or lipid matrices or their chemical conjugation to carrier molecules, thereby establishing a reservoir from which controlled release can proceed[4]. The rate-limiting steps that govern drug release may involve processes like polymer hydration, matrix erosion, diffusion through pores or channels, or the cleavage of chemical bonds, depending on the specific formulation design[5].

The conceptual basis for extended-release injectable medications originated in the mid-20th century with the creation of oil-based suspensions and solutions. The first LAI formulation of major clinical significance, introduced in 1954, was fluphenazine decanoate. This antipsychotic ester, dissolved in sesame oil, afforded sustained release over a period of 1-3 weeks[6]. This pioneering strategy capitalized on the drug's lipophilicity and its slow diffusion from the oil depot to preserve therapeutic concentrations.
The 1970s marked the advent of biodegradable polymers as carriers for LAIs. Polylactic acid (PLA) and poly (lactic-co-glycolic acid) (PLGA) rapidly became the materials of choice, valued for their established biocompatibility and tunable degradation profiles[7]. The FDA's approval of Lupron Depot® (leuprolide acetate) in 1989 constituted a pivotal milestone, validating the clinical viability of PLGA microsphere technology for monthly administration[8].

The 1990s and early 2000s were characterized by substantial innovation in LAI design, encompassing the development of *in situ* forming implants, nanosuspensions, and liposomal formulations[9]. Risperidone LAI (Risperdal Consta®), which received approval in 2003, exemplified the application of microsphere technology to psychiatric disorders, dramatically improving medication adherence in the management of schizophrenia[10].
More recent developments (2010-2025) have centered on broadening the molecular diversity of agents delivered via LAIs to include peptides, proteins, and monoclonal antibodies. This has occurred in parallel with innovations in manufacturing technology and enhancements in delivery precision[11]. The introduction of extended-release naltrexone (Vivitrol®) for addiction treatment and paliperidone palmitate (Invega Sustenna®) for schizophrenia further highlighted the capacity of LAIs to confront significant public health challenges where medication adherence is a critical determinant of success[12].

This review furnishes a comprehensive overview of currently marketed long-acting injectable (LAI) products. It scrutinizes the *in vitro* and *in vivo* methodologies that are employed for product approval and deliberates on the manufacturing processes and quality attributes indispensable for LAI development. This

review confronts both the challenges and the opportunities for advancing knowledge within this domain. It supplies up-to-date information on LAIs, incorporating tables that summarize the key attributes of approved products, pertinent clinical parameters like formulation properties, and their consequential effects on patient compliance.

1. ADVANTAGES AND CHALLENGES OF LAIS

1.1. Pharmacokinetic and Therapeutic Advantages

LAI formulations present several crucial advantages over conventional dosage forms:

1.1.1. Improved Pharmacokinetic Profile

- **Reduced peak-to-trough fluctuations:** LAIs sustain drug concentrations within the therapeutic window, thereby mitigating the potentially toxic peaks and sub-therapeutic troughs often associated with immediate-release formulations.
- **Extended apparent half-life:** By establishing a depot reservoir that facilitates controlled release, LAIs effectively prolong the apparent half-life of drugs that would otherwise necessitate frequent administration.
- **Bypass of first-pass metabolism:** Parenteral administration circumvents the hepatic first-pass effect. This potentially permits the use of lower total doses and curtails the formation of metabolites[40].

1.1.2. Enhanced Therapeutic Outcomes

- **Improved medication adherence:** This is particularly valuable in psychiatric conditions, addiction treatment, and other contexts where daily adherence presents a challenge. LAIs have been associated with documented reductions in relapse and hospitalization rates.
- **Reduced dosing frequency:** Diminishing the administration frequency from daily to weekly, monthly, or even annually markedly lessens the treatment burden on patients.
- **Decreased side effect profile:** The elimination of sharp plasma concentration peaks may curtail adverse effects, especially for drugs possessing narrow therapeutic windows.
- **Potential for lower total dose:** The avoidance of first-pass metabolism, coupled with improved bioavailability, may enable lower cumulative dosing relative to oral alternatives[44].

2. CLASSIFICATION OF LONG ACTING INJECTABLES

2.1. Formulation-Based Classification

LAI delivery systems are frequently viewed as an appealing delivery option during the life cycle phase of a drug, employed to augment the clinical performance of the molecule across many therapeutic areas. To achieve this, formulation scientists typically rely on three principal technologies to fabricate an LAI delivery system: (i) polymer-based systems, which include microencapsulating systems and *in situ* gels; (ii) oil-based formulations; and (iii) drug (nano and micro) suspensions. This section provides an overview of these distinct technologies and examines the principal role of excipients in the tailoring of drug release.

2.1.1. Polymer-Based Formulations

2.1.1.1. Microencapsulation

The process of microencapsulation entails the dispersion or dissolution of solid or liquid drug substances within polymeric materials to create microspheres, or their encapsulation as a core enveloped by a polymeric shell to form microcapsules[42]. While both biodegradable and non-biodegradable polymers can be utilized, non-biodegradable polymers are generally less attractive. This is due to the necessity of a surgical operation to position the delivery system at the initiation of treatment and another to remove it at the conclusion. Consequently, they fall outside the scope of this review. Conversely, biodegradable polymers progressively degrade into their metabolizable monomers, concurrently releasing the encapsulated drug. The mechanism of drug release from such biodegradable microspheres is commonly classified into three different phases[43]. The initial drug release, often termed "burst release," consists of non-encapsulated drug and is obtained via the surface erosion of the polymer matrix, resulting in the

release of this non-encapsulated drug. This burst release is intimately linked to the drug load. Formulations with higher drug loading are prone to causing a more pronounced burst effect, whereas lower drug loading will likely lead to a delayed release characterized by minimal or no initial release. This initial phase is succeeded by the slow release of the drug from the microspheres, a process to which several parallel mechanisms contribute (corresponding to the second and third phases of the classification)[43]. The second phase involves the diffusion of the encapsulated drug through the polymeric matrix. Finally, the residual encapsulated drug is continuously liberated through the degradation of the polymer[44].

The majority (nearly 50%) of marketed biodegradable LAI products are predicated on Poly(DL-lactic-co-glycolic acid) (PLGA)[45]. PLGA is a synthetic aliphatic polyester, a copolymer of lactic acid (LA) and glycolic acid (GA). PLGA is susceptible to hydrolytic degradation; upon contact with biological fluids, PLGA hydrolyzes to form short-chain alcohols and acids. The drug release from PLGA-based formulations can be precisely tailored by modifying the molar ratios of lactic acid (LA) to glycolic acid (GA) or by altering the molecular weight of the polymer. A higher molecular weight typically leads to diminished polymer degradation and, subsequently, slower drug release, attributable to the lengthy polymer chains. Beyond the co-monomer ratios of glycolic and lactic acid, molecular weight, and environmental factors (such as pH, temperature, and enzymes), the PLGA end group also assumes a critical role in polymer degradation[46]. The PLGA end group can be either an acid or an ester. PLGA-based formulations featuring an acid end group degrade significantly faster than those with an ester end. This is because the acid end group induces a drop in the microenvironmental pH, which further accelerates the hydrolysis of the ester bonds, leading to the generation of more acidic groups and thus establishing an autocatalytic cycle[51].

Besides the prevalent PLGA-based drug delivery systems, other biodegradable polymers can also be applied to the development of LAI formulations. Examples of other synthetic biodegradable polymers that have been employed in FDA-approved LAIs include triethylene glycol poly(orthoester) (TEG-POE) and sodium carboxymethyl cellulose (CMC), the latter of which can form complexes with cationic drugs[9]. Poly(ε-caprolactone) (PCL) represents another well-investigated, biocompatible, and biodegradable FDA-approved polymer. It offers the advantage of eroding at substantially lower rates compared to other biodegradable polymers[52]. The release kinetics can be readily fine-tuned by altering its molecular weight, crystallinity, or by constructing co-polymers with other polymers. Another intriguing class of candidates is poly(saccharide)-based polymers, such as hyaluronates, chitosan, and alginates. Poly(saccharides) are derived from renewable resources—including plants, microorganisms, or animals—and consequently demonstrate unique advantages concerning low toxicity risk, biocompatibility, biodegradability, and low immunogenicity.
The domain of polymer-based LAI formulation development has not yet realized its full potential. A significant volume of ongoing research is concentrated on identifying new materials that can furnish beneficial characteristics surpassing those of existing polymer systems for parenteral LAIs. Poly(anhydrides) are regarded as an interesting alternative polymer system, given the facility with which their degradation rate can be modified by manipulating the ratio of monomers[54]. Despite the promising attributes of these novel polymer-based systems, longer regulatory approval timelines should be anticipated, owing to the currently limited knowledge regarding these formulation strategies for injectable formulations.

While many research endeavors focus on optimizing the release kinetics from these drug delivery systems, the selection of the most appropriate polymer is also influenced by drug stability and the polymer's feasibility to protect the drug from exposure to enzymes or other environmental conditions that pose stability challenges. The inclusion of other functional excipients may be employed to maximize the stability of the final formulation. For instance, surfactants are frequently included to preclude protein adsorption and/or aggregation at hydrophobic surfaces. For this application, non-ionic surfactants are

preferred, as ionic surfactants might interact with groups in proteins, potentially inducing protein denaturation. pH-neutralizing additives offer added value for acid-labile drugs by compensating for the reduction in microclimate pH that results from polymer hydrolysis. Furthermore, preservatives, buffering agents, and osmolytes can be incorporated to bestow benefits upon the final drug product[56].
Several challenges can manifest with the polymer-based microsphere technology. These may include difficulties in achieving high levels of control over the particle size distribution, the potential for poor injectability, constrained drug loading capacity, and poor stability. Notwithstanding these challenges, it remains a very promising and broadly utilized strategy for the preparation of LAIs and has been successfully translated into numerous clinical applications[57].

2.1.1.2. Microsphere Development Approaches

The formulation of polymeric microspheres for LAI applications necessitates sophisticated processing techniques and meticulous parameter optimization to attain the desired profiles for drug encapsulation, release kinetics, and stability[43]. The principal manufacturing methodologies include:

Emulsion-Based Techniques

- **Single emulsion (O/W):** This method is suitable for lipophilic drugs. It involves the emulsification of an organic polymer solution, which contains the drug, within an aqueous continuous phase. This is followed by solvent removal to harden the particles[44].
- **Double emulsion (W/O/W):** This approach is preferred for hydrophilic compounds, especially peptides and proteins. It utilizes a primary water-in-oil emulsion that is subsequently dispersed into an external aqueous phase[45]. This technique demands careful stabilization of both interfaces and frequently employs amphiphilic copolymers or PEGylated PLGA to bolster encapsulation efficiency[46].
- **Solid-in-oil-in-water (S/O/W):** This is a modified approach tailored for proteins and peptides. The drug is first micronized and suspended in the organic polymer solution prior to emulsification. This method reduces the drug's exposure to organic/aqueous interfaces and mitigates the associated risks of denaturation[47].

2.1.1.3. Critical Process Parameters

The successful formulation of microspheres requires precise control over multiple variables:

- **Polymer selection:** The molecular weight, the lactide:glycolide ratio, and the end-group chemistry of PLGA significantly dictate the degradation rate, hydrophilicity, and drug-polymer interactions. Polymers with higher molecular weight (50-100 kDa) typically afford slower release rates, whereas a higher glycolide content accelerates degradation[49].
- **Organic solvent:** Dichloromethane, ethyl acetate, and chloroform are commonly utilized. The selection is predicated on polymer solubility, drug stability, and environmental considerations.
- **Emulsifier concentration:** Polyvinyl alcohol (PVA), polysorbates, and sodium cholate function as stabilizers. Their concentration (customarily 0.1-5% w/v) impacts particle size, morphology, and porosity.
- **Homogenization parameters:** The intensity and duration of mechanical agitation during the emulsification process directly influence the particle size distribution. High-shear homogenization or ultrasonication is typically employed to achieve uniform dispersions.
- **Hardening conditions:** The rate of solvent removal—effectuated through evaporation, extraction, or a combination thereof—governs microsphere porosity, shell formation, and the characteristics of the initial burst release[50].

2.1.1.4. Challenges and Mitigation Strategies

Several challenges complicate the development of microsphere formulations:

- **Initial burst release:** This is typically ascribed to surface-associated drug and can be mitigated via surface washing, pore sealing with additional polymer layers, or the implementation of core-shell architectures.

- **Protein stability:** Denaturation occurring at the organic/aqueous interface can be lessened by pre-formulation with stabilizing excipients (such as sugars or amino acids), the use of PEGylated polymers, or the application of solid-state encapsulation techniques.
- **Residual solvents:** Efficient removal necessitates optimized evaporation/extraction conditions, with vacuum drying often being required to satisfy regulatory limits.
- **Scale-up complexities:** The preservation of critical quality attributes during manufacturing scale-up requires careful engineering of mixing dynamics and heat transfer to maintain microsphere characteristics[54].

2.1.2. *In Situ* Implants

Implants constitute another formulation strategy that leverages polymer-based systems to regulate drug release over extended durations. This formulation type encompasses (i) *in situ* forming depots, which comprise precipitating implants, gels, crosslinked gels, and microparticle implants, and (ii) solid implants, for which a pre-prepared implant is positioned within the subcutaneous or intramuscular matrix via surgical incision or injection using a large-gauge needle. The popularity of *in situ* gelling systems has escalated over the last two decades, attributable to their biocompatibility, stability, facility of administration, and ease of scale-up. *In situ* gelling systems depend on gel formation that occurs in response to various endogenous stimuli, such as an increase in temperature, a change in pH, or the presence of ions upon administration. Several natural and synthetic polymers facilitate the preparation of *in situ* gelling systems. Biodegradable natural polymers include alginic acid, gellan gum, xyloglucan, pectin, and chitosan.

Synthetic polymers include PLGA, poly(caprolactone) (PCL), and poly(DL-lactide) (PLA). PLGA is regarded as a biocompatible and biodegradable carrier, valued for the flexibility it offers in tailoring drug release kinetics. It is therefore frequently used as an *in situ* gel former[58], in addition to its extensive applicability in microencapsulation systems[59].
In situ forming (reverse thermal gelling) implants are of the sol-gel type; that is, the solution is formulated prior to injection and subsequently converts into a gel after administration due to *in situ* gelation prompted by interaction with the endogenous environment[60]. The prolonged-release effect of the drug is primarily a consequence of the formation of this semisolid-gel drug depot. Drug release from *in situ* forming systems can be modified in accordance with clinical needs by utilizing different polymers[61].

Several marketed products exist that were developed based on this concept. For example, the Atrigel® proprietary delivery systems serve as the cornerstone for clinically available *in situ* gelling drug products. Atrigel® systems are viscous solutions composed of a water-insoluble biodegradable polymer and a biocompatible solvent[63]. The commonly used polymers for these systems include PLA, PLGA, and lactide/caprolactone copolymers (PLA-PCL). Either hydrophilic or hydrophobic solvents can be used, such as dimethyl sulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP), tetraglycol, glycolfurol, propylene carbonate, triacetin, ethyl acetate, and benzyl benzoate. Atridox®, a marketed product for treating chronic perioditis, as well as other Atrigel formulations, are composed of a PLGA polymer solution in NMP. The drug product is supplied as a two-syringe mixing system. Syringe A contains the Atrigel® Delivery System, which is a polymeric formulation composed of 36.7% PLA dissolved in 63.3% NMP, and Syringe B contains 50 mg of doxycycline hyclate (as a drug powder). After mixing the contents of the two vials, the vehicle is then injected into the subgingival tissue. Atridox® is applied to the infected area as a gel, where it solidifies and subsequently releases doxycycline for approximately 7 days. The use of an *in situ* formulation implant prepared with biodegradable polymers obviates the need for a surgical procedure to administer and/or remove the drug delivery system, which ultimately enhances patient comfort. Supplemented by the favorable technical aspects of this technology—including low cost, a simple drug loading method, and good system stability—this formulation approach is typically regarded as an appealing option for the development of an LAI[64]. Owing to the nature of the implants being formed *in*

situ post-injection, variability in the shape and structure, as well as burst drug release during the implant's formation, are key issues. These factors could potentially affect drug release and, consequently, the pharmacokinetic (PK) profile. If these limitations can be minimized, this formulation technology holds significant promise[64].

The development of *in situ* forming implants (ISFI) centers on the creation of injectable liquids that transform into solid or semi-solid depots following administration[19]. The key formulation approaches include:

2.1.2.1. Thermally Induced Gelation Systems

These systems exploit the temperature-dependent sol-gel transitions of specific polymers:

- **Poloxamer-based systems:** These utilize the reverse thermal gelation properties of poloxamer 407 (Pluronic F-127) and related block copolymers, which undergo a sol-gel transition as the temperature elevates from ambient to physiological levels. The critical gelation concentration and temperature can be modulated by adjusting the polymer concentration (typically 15-25% w/w) or by incorporating additives such as salts or PEG[20].
- **Chitosan-based systems:** These employ combinations of chitosan with glycerophosphate or other polyol salts. These mixtures remain liquid at room temperature but gel at body temperature, rendering them suitable for encapsulating proteins and small molecules[22].
- **PLA/PLGA-PEG-PLA/PLGA copolymers:** These are block copolymers that demonstrate thermosensitive gelation properties while concurrently maintaining biodegradability, offering controlled release over periods of 1-3 months[23].

2.1.2.2. Phase Separation Systems

These systems utilize solvent exchange mechanisms to precipitate solid implants:

- **ATRIGEL® technology:** This patented system employs PLGA dissolved in N-methyl-2-pyrrolidone (NMP) or other water-miscible solvents. The polymer precipitates upon contact with an aqueous environment, thereby forming a solid matrix. Commercial applications include Eligard® (leuprolide acetate) and Sublocade® (buprenorphine).
- **SABER® technology:** This technology utilizes sucrose acetate isobutyrate as a biodegradable carrier, along with solvents like benzyl alcohol or benzyl benzoate. It is exemplified by the Relday® risperidone formulation.
- **Formulation considerations:** Critical parameters include the polymer concentration (30-50% w/w), the selection of a solvent based on its miscibility and biocompatibility, and the drug loading capacity (which is typically limited to 10-20% w/w)[25].

2.1.2.3. Ion-Activated Systems

These systems gel in response to alterations in the ionic environment:

- **Alginate-based formulations:** These consist of low-viscosity sodium alginate solutions that crosslink in the presence of divalent cations (primarily calcium), forming structured hydrogel networks.
- **Gellan gum systems:** These are solutions that undergo a sol-gel transition upon exposure to physiological cations, and are particularly suited for localized delivery applications[29].

2.1.3. Oil-Based Formulations

Oil-based LAI formulations were initially introduced in the early 1960s as a solution of a simple ester prodrug dissolved in sesame oil. Since that time, parenteral long-acting oily (lipophilic) solutions have seen clinical use, particularly in the fields of schizophrenia and hormone replacement therapy. In many such formulations, an esterification of the alcohol functional groups of the parent drug with fatty acids is requisite to achieve appropriate solubility and partitioning within the lipidic vehicle. Typically, vegetable oils—such as sesame oil, castor oil, arachis oil, or fractionated coconut oil—are employed as the vehicle.

By modifying the tail length of the fatty acid, the solubility of the prodrug in the oil can be fine-tuned. In addition to their uncomplicated manufacturing processes and favorable long-term stability, these simple oil-based solutions provide the possibility of designing depots with tailored delivery characteristics. For lipophilic drug solutions, the drug release from the vehicle is influenced by three fundamental physicochemical parameters: vehicle viscosity, drug solubility in the oil vehicle, and drug partitioning between the oil and the aqueous buffer. Furthermore, these factors may also impact drug loading and syringeability. Modification of the oil vehicle—with respect to its viscosity, solubilization capacity, and oil-buffer partition coefficient—can be achieved by using mixtures of triglycerides/synthetic oils or by the addition of excipients (e.g., hydrogen bond-donating compounds)[65]. The viscosity of the vehicle is a parameter that demands optimization to develop a successful formulation. Highly viscous formulations tend to suffer from poor syringeability and injectability, whereas low-viscosity formulations may release the drug too rapidly. The addition of a co-solvent, such as benzyl alcohol, may be considered an easy solution to reduce the overall viscosity, supplemented by an increase in the drug's solubility within the oil vehicle[45]. For the optimization of oil-buffer partitioning and/or the oil solubility of drug substances, another strategy relies on the utilization of prodrug derivatives. To enhance the drug load in the oil formulation even further, solid drug particles may be dispersed within the oily vehicle[66]. Finally, several other factors—such as the injection site, injection volume, the extent of the depot's spread at the injection site, and the absorption and distribution of the oil vehicle—might also influence the overall pharmacokinetic profile of the drug.

Most of the FDA-approved formulations use either sesame oil or castor oil, while various fatty acids are used for the esterification with the parent drugs. In the case of fluphenazine, esterification with decanoic acid resulted in a greater lipophilicity than the parent compound. When administered in sterile sesame oil, intramuscular injections of this prodrug exhibit a much longer duration of action than fluphenazine hydrochloride[67]. Flupenthixol decanoate (marketed as Fluanxol Depot injection solution) is the decanoate ester of a thioxanthene derivative. It is very slightly soluble in water and possesses a logD of 6 at pH 7.4. The parent compound, flupenthixol, has a calculated logP value of 4.5[69]. This product is employed to treat schizophrenia and is administered intramuscularly once every 2 to 4 weeks.

2.1.3.1. Liposomal Formulations

Liposomes—which are phospholipid vesicles enclosing aqueous cores—represent sophisticated delivery systems capable of encapsulating both hydrophilic and hydrophobic drugs[32]. As LAI platforms, liposomes furnish advantages that include biocompatibility, versatility, and the protection of sensitive therapeutic molecules. DepoFoam® technology, which utilizes multivesicular liposomes, has facilitated the development of several marketed LAIs, including:

- **DepoDur® (morphine sulfate):** Provides 48-72 hours of analgesia following a single administration.
- **Exparel® (bupivacaine):** Extends the local anesthetic effect to 72 hours for the management of post-surgical pain.
- **DepoCyt® (cytarabine):** Permits intrathecal delivery for lymphomatous meningitis, providing sustained release over 14 days[35].

Advances in liposomal LAI technology through 2025 have encompassed the development of triggered-release systems that are responsive to external stimuli, as well as surface-modified liposomes possessing enhanced stability and targeted tissue distribution[36].

This approach is not universally feasible for every drug molecule. Based on information from marketed products, most oil-based formulations are delivered via the IM rather than the SC route. Additionally, the effective durations of these oil depot formulations are generally less than 4 weeks. If the intended target drug release profile extends beyond 4 weeks, or if the parent drug molecule lacks the functional groups necessary to form stable ester bonds, alternative formulation approaches must be explored.

2.1.4. Crystalline Drug Suspensions

An aqueous-based LAI suspension is traditionally a preferred formulation strategy, offering several advantages, including simpler manufacturing processes, higher dose/drug loading per injection, less dependence on excipients, and likely reduced variability[70]. This type of formulation technology is typically considered only when the APIs are dissolution rate-controlled. To decelerate the intrinsic dissolution rates of the drug substance, two approaches are frequently contemplated: 1) identifying salt forms or complexes that exhibit very low aqueous solubility; or 2) reducing the particle dissolution surface area by forming macrocrystals. If these approaches prove successful and can satisfy the clinical requirements, simple aqueous suspension dosage forms are generally selected. When this approach is adopted, the optimization and control of particle size are crucial for achieving the desired *in vivo* performance. This is because it has been demonstrated that varying particle size distributions could potentially influence the observed drug plasma pharmacokinetics[71]. Furthermore, this formulation type necessitates the addition of several other excipients. Excipients used for the stabilization of a suspension are generally included, such as viscosity enhancers and low levels of surfactants acting as wetting agents. In addition to suspension-stabilizing excipients, this aqueous-based formulation concept further requires the optimal levels of osmolytes, preservatives, and buffering agents. The optimization of the formulation composition—by including different excipients with different functionalities—is essential to minimize the risk of Ostwald ripening (a process where small drug crystals dissolve and subsequently redeposit onto the surface of larger crystals) and caking (the sedimentation and agglomeration of drug crystals at the bottom of vials). These are two common phenomena for crystalline suspensions that could complicate dosing accuracy, re-suspendability, and injectability. It has been reported that excipients possess the potential to influence the nature and dynamics of the local inflammatory response, thereby affecting the drug plasma pharmacokinetics, predominantly in the first few weeks following dosing[71]. Further research is necessary to elucidate the potential influence of excipients on the drug release rate from the depot.

This formulation approach has demonstrated noteworthy success, progressing from R&D phases to commercial products. Zyprexa is a 1-month depot of olanzapine pamoate, which has an aqueous solubility of 4.18 µg/ml. Depo Provera is a 3-month depot of medroxyprogesterone acetate, possessing an aqueous solubility of 2.21 µg/ml[73]. Based on current marketed products utilizing this approach, the depot effect durations are generally less than 6 months. If the intended targeted drug release profile extends beyond 6 months, other formulation strategies should be considered. It is also worth noting that most marketed injectables containing microparticle preparations are particularly susceptible to problems with injectability. When this approach is used, the total dose can be potentially high, which can be an advantage. Microparticle suspensions may contain as much as 40% solids which, in combination with a larger particle size, necessitate a larger needle size (around 18–21 gauge) for injection. The potential for a larger needle size may limit the utility of this approach as a viable and patient-centric method and should be considered when selecting the LAI formulation type according to the desired target product profile.

2.1.5. Nanosuspension Formulation Techniques

Nanosuspension LAIs have acquired prominence, attributable to their relatively straightforward formulation and their suitability for poorly soluble compounds. Key manufacturing approaches include:

2.1.5.1. Top-Down Approaches

- **Media milling:** This is the predominant commercial technique, exemplified by the NanoCrystal® technology. It utilizes milling chambers equipped with ceramic/polymeric beads to reduce particle size via mechanical attrition. Critical processing parameters include the milling duration (typically 30-120 minutes), the size and composition of the beads, the agitation intensity, and temperature control[32].
- **High-pressure homogenization:** This method employs pressures of 500-1500 bar to force drug suspensions through microfluidic channels. This action creates high shear forces and cavitation,

which reduce particle size. Multiple cycles (customarily 10-20) are required to achieve the target particle size distribution.

- **Stabilizer selection:** Surfactants (such as polysorbates, poloxamers, and sodium lauryl sulfate) and polymers (like hydroxypropyl methylcellulose and polyvinylpyrrolidone) at concentrations of 0.1-5% w/v are critical for preventing particle agglomeration and crystal growth[33].

2.1.5.2. Bottom-Up Approaches

- **Antisolvent precipitation:** This involves the rapid mixing of a drug solution (in a water-miscible organic solvent) with an aqueous antisolvent that contains stabilizers. This process induces supersaturation and controlled precipitation.
- **Emulsion-solvent evaporation:** This technique involves creating nanodroplets of a drug-solvent solution within an immiscible phase, followed by solvent removal to generate solid nanoparticles.
- **Supercritical fluid processing:** This method utilizes the unique properties of supercritical CO_2 to achieve nanoprecipitation with minimal usage of organic solvents[36].

3. MECHANISMS OF DRUG RELEASE FROM LAIS

The therapeutic efficacy and the duration of action for LAI formulations are directly dependent on their drug release mechanisms, which vary significantly among different formulation types[39].

3.1. Release from Polymer-Based Systems

3.1.1. PLGA Microsphere Release Kinetics

Drug release from PLGA microspheres typically manifests in three distinct phases:

- **Initial burst phase:** This is characterized by the rapid release of surface-associated and poorly entrapped drug, generally accounting for 10-30% of the total dose within the first 24-48 hours. This phase is influenced by the surface characteristics of the microspheres, their initial porosity, and drug-polymer interactions.
- **Lag phase:** This is a period of minimal drug release during which water penetrates the matrix, initiating polymer hydration and early-stage hydrolysis. The duration of this phase correlates with the polymer's molecular weight and its lactide:glycolide ratio, typically extending from several days to weeks.
- **Erosion phase:** This is the predominant release phase, occurring as polymer degradation generates a sufficient quantity of oligomers to enhance matrix porosity and permeability. This phase typically demonstrates pseudo-zero-order kinetics, which results from the competing processes of increasing diffusivity and a decreasing concentration gradient[42].

Mathematical modeling of PLGA microsphere release commonly employs variants of the Higuchi equation or more complex models that incorporate the kinetics of polymer degradation.

$$M_t/M_∞ = k \times t^{1/2}$$

Where $M_t/M_∞$ represents the fraction of drug released at time t, and k is a constant that incorporates formulation parameters[48].

3.1.2. *In Situ* Forming Implant Release Mechanisms

The release kinetics from *in situ* forming implants are complicated by the dynamic nature of the depot formation itself:

- **Phase inversion dynamics:** The rate of solvent exchange and polymer precipitation significantly impacts the initial drug release. A faster phase inversion is typically associated with a higher burst release.
- **Structural evolution:** As solvent diffuses out and water penetrates in, the implant undergoes morphological changes, transitioning from a gel-like consistency to a more rigid matrix. This evolution affects the diffusional pathways.

- **Polymer erosion:** Particularly in PLGA-based ISFI systems, long-term release is governed by polymer hydrolysis and matrix erosion, similar to what is observed in preformed implants[50].

3.2. Release from Nanosuspension LAIs

Drug release from nanosuspension LAIs entails a distinctive sequence of events:

- **Particle dissolution:** The rate-limiting step is typically the dissolution of the drug nanoparticles at the injection site. This is governed by the Noyes-Whitney equation:

$$dM/dt = (D \times A \times C_s)/h \times (1 - C_t/C_s)$$

Where dM/dt is the dissolution rate, D is the diffusion coefficient, A is the surface area, C_s is the saturation solubility, h is the diffusion layer thickness, and C_t is the bulk concentration.

- **Suspension microenvironment:** The local environment at the injection site influences dissolution through factors that include pH, protein adsorption, and local ion concentration.
- **Particle aggregation effects:** Alterations in the particle size distribution, resulting from aggregation or Ostwald ripening, can significantly modify the effective surface area and, consequently, the dissolution rate over time[55].

3.3. Release from Lipid-Based LAI Systems

3.3.1. Oil-Based Formulation Release

Drug release from oil-based LAIs adheres to principles of partition and diffusion:

- **Partition coefficient effects:** The distribution of the drug between the oil vehicle and the interstitial fluid at the injection site critically determines the release rate. Greater lipophilicity is generally associated with slower release.
- **Diffusion limitation:** Drug molecules must diffuse through the oil matrix to reach the oil-water interface. The diffusion coefficient is influenced by the oil's viscosity and the drug's molecular size.
- **Interfacial area:** The dispersion pattern of the oil depot affects the effective surface area available for drug transfer. More dispersed depots typically exhibit faster release[2].

4. STRATEGIES TO MANIPULATE DRUG *IN VIVO* CLEARANCE

4.1. Chemical Modification

The strategy of chemical modification—such as PEGylation, PSAylation, and lipidation, among others—has been regarded as one of the most efficient approaches and has gained recognition in clinical practice. This is due to its definite structure, lack of impurity, and the maturity of the available methods[71]. The objective of this strategy is to prolong the half-life of drugs with as little influence on their bio-activity as possible. This necessitates a comprehensive understanding of the structure-activity relationship (SAR) of the drugs, as well as the availability of precise site-modification methods.

4.1.1. PEGylation and Alternatives

Polyethylene glycol (PEG), a neutral polyether polymer, has become an indispensable component of drug delivery systems (DDS)[72]. The amphiphilic chain of PEG moieties, which is derived from the polymerization of ethylene oxide, increases the size of relatively small therapeutic drugs (e.g., peptides, proteins, and nanobodies) to avoid excessive renal clearance and to prolong their residence time in the blood circulation, thereby imparting “stealth” properties[74]. Concurrently, the hydration layer produced by PEG can also fulfill a protective role, thus preventing the enzymatic degradation of bio-macromolecules[75]. Adagen® (pegademase bovine), the first PEGylated product approved by the US Food and Drug Administration (FDA) in 1990, is a modified enzyme used for treating severe combined immunodeficiency (SCID) that is associated with an adenosine deaminase deficiency. Since that time, PEGylation has been considered a well-tolerated module for half-life extension and has been utilized for 50 years[76]. It is worth mentioning that PEGylation can be used not only for the direct modification of drugs but also for the improvement of DDS.

It is noteworthy that the "PEG dilemma" is introduced subsequent to PEGylation. This phenomenon affects the interaction between carriers/drugs and cells, and it limits cell uptake and endosomal escape, resulting in an inevitable loss of bioactivity[77]. Therefore, cleavable PEG derivatives—which contain bonds that are easy to break under specific physiological and pathological conditions—are designed to overcome the aforementioned limitations[79]. The reported sensitive bonds for cleavable PEG derivatives include peptide bonds, disulfide bonds, vinyl ether bonds, hydrazone bonds, and ester bonds, as well as other types of bonds[81]. The TransConTM technology platform, developed by Ascendis Pharma, provides a new strategy that preserves the activity of therapeutic drugs and supports a dosing frequency ranging from a daily basis up to a monthly basis. It achieves this by combining the benefits of prodrugs with a sustained release mode[82]. Several candidate drugs (e.g., TransCon PTH, TransCon hGH, TransCon CNP, etc.), based on TransconTM technology, have been developed and are in clinical trial stages[83]. For example, TransCon parathyroid hormone (PTH), an inactive prodrug for SC administration, is developed to maintain a sustained release of PTH in the bloodstream, thereby overcoming the limitation regarding the use of short-acting PTH in the treatment of hypoparathyroidism (HP). The PTH is transiently bound to methoxypolyethylene glycol (mPEG) via a TransCon linker to form TransCon PTH. The protective carrier possesses the ability to inactivate and shield PTH, and it prolongs the circulation time of the hormone due to its reduced renal clearance. Under physiological conditions, active PTH is sustained-released with a half-life of approximately 2.5 days[84]. Recently, reported phase I data support TransCon PTH as a daily replacement therapy for the treatment of HP, providing a physiological level of PTH throughout the day and prompting advancement into a phase II clinical trial[85].

It cannot be ignored that PEG is immunogenic and non-degradable [86,87,88]. Consequently, developing alternative polymers to PEG has received significant attention within the pharmaceutical industry [89,90,91]. Poly(2-methyacryloyloxyethyl phosphorylcholine) (PMPC), a type of non-PEG-based degradable polymer, was synthesized and coupled to interferon-α-2a to form PMPC-interferon-α-2a, which possesses a longer half-life than PEG-modified interferon-α-2a[92]. Additionally, naturally degradable polymers—including polysialic acid (PSA), hydroxy-ethyl-starch (HES)[93], and hyaluronic acid (HA)—have also been applied for prolonging half-life as alternative materials to PEG[94]. PolyXenTM technology, developed by Xenetic Biosciences, Inc., is an enabling platform for peptide and protein drug delivery. PolyXenTM technology utilizes proprietary technology to conjugate hydrophilic and biodegradable PSA molecules to specific sites of therapeutic drugs for the purpose of prolonging their half-life and improving their stability *in vivo*. Both the length and the modification site of the PSA chain can alter the apparent hydrodynamic radius of the molecule, which in turn influences the properties and biological characteristics of the therapeutic[17]. Furthermore, a carbohydrate shield, termed "glycocalyx," is formed around the therapeutic molecule following PSAylation. This protects the drugs, rendering them less exposed to the immune system and clearance systems, including renal clearance and serum proteases. Several polysialylated candidates, such as polysialylated erythropoietin (PSA-EPO) and polysialylated recombinant factor VIII (PSA-FVIII), have been applied in clinical development[95]. The former is currently in phase III of clinical trials, and the latter is in phase I.

4.1.2. Lipidation

Human serum albumin (HSA), the most abundant protein in plasma, has a long average half-life of 19 days and possesses the function of transporting both exogenous and endogenous compounds[96]. On this basis, conjugating a fatty acid chain to a therapeutic protein can enhance its non-covalent combination with albumin *in vivo*, thus achieving a prolonged half-life. This strategy has been successfully applied in the modification of insulin and glucagon-like peptide-1 (GLP-1) for half-life extension. Levemir® (insulin detemir), approved by the FDA in 2004, is an insulin analog in which the Lys29 is myristoylated at the amino group of the side chain. This modification allows for reversible combination with albumin, promoting a longer action time and more stable efficacy[98]. Following modification, the long distribution phase of insulin detemir, which is about 8 hours after SC administration, is sufficient to achieve a once-

daily administration[99]. A similar strategy was utilized for liraglutide, which is an insulinotropic GLP-1 analog. The Lys26 of liraglutide is modified with a palmitic acid chain to achieve a half-life of 13 hours after SC administration. In addition, the strategy of lipidation is widely applied to optimize drug properties to meet the requirements of various preparations. Although lipidation-based prodrug strategies hold promise for the clinical translation of LAIs, it is essential to note that this strategy is not suitable for all drug molecules to be modified, especially in cases where a hydroxyl group or carboxyl group for esterification is lacking.

4.1.3. Nucleic Acid Modification

Gene therapy, which is based on nucleic acid drugs [e.g., antisense oligonucleotide (ASO), siRNA, miRNA, saRNA, aptamer, etc.], is considered one of the promising strategies for precision medicine through the up-regulation or down-regulation of target genes in specific cells. However, native nucleic acid drugs still present many difficulties that must be overcome, such as poor stability, rapid degradation by RNase, rapid clearance by the kidneys, immunogenicity, and low cell uptake[18]. To improve their properties, the structures of nucleic acid drugs can be optimized through chemical synthesis[100]. In general, backbone modifications [e.g., phosphorothioate (PS), peptide nucleic acids (PNAs), etc.] can enhance nuclease resistance, improve pharmacokinetic characteristics, and facilitate cell uptake. Moreover, sugar modifications [e.g., 2′-O-methyl (2′-OMe), 2′-O-(2-methoxyethyl) (2′-O-MOE), 2′-fluoro (2′-F), locked nucleic acid (LNA), 4′-C-ethylene-bridged nucleic acid (ENA), etc.] may reduce immunogenicity and toxicity, enhance RNA binding affinity, and increase stability and bioavailability[101]. Owing to the advanced development of nucleic acid chemistry, more than ten nucleic acid drugs have been approved on the market. Among these, the recently approved siRNA products, Givlaari® (givosiran) and Oxlumo® (lumasiran), developed by Alnylam Pharmaceuticals, represent a surprisingly long-term effect after the initial dosing. This is achieved through the combination of GalNAc conjugation technology and enhanced stabilization chemistry (ESC) modification technology. At present, dozens of siRNA drugs developed by Alnylam Pharmaceuticals are in clinical trials. Among them, inclisiran (ALN-PCSsc) is utilized in the treatment of hypercholesterolemia and is currently in a phase III clinical trial. The advantage of treating with inclisiran is that the LDL-C level can be reduced by more than 50% with only two injections per year[103]. If inclisiran proves successful in clinical trials, it will overturn the existing chronic disease treatment model[104]. Recently, Brown et al.[105] investigated the pharmacodynamic durability of GalNAc–siRNA conjugates. They found that the long-term stability of the modified siRNA in acidic intracellular compartments plays a key role in its long-term activity. The siRNA can sustainably escape from these acidic intracellular compartments, which serve as a long-term depot, and subsequently, over time (possibly even weeks), enable RNA interference (RNAi) activity in the cytoplasm after dosing.

Gene therapy holds broad promise for the treatment of multiple human diseases, such as genetic disorders, cancers, and virus infections. Nucleic acid chemistry has been approved as an effective way to achieve increased stability, enhanced tissue specificity, and reduced toxicity. Although the long-term mechanism of recently approved gene drugs has not been clarified, numerous experiences and excellent progress associated with gene therapy have been achieved over the past 20 years. Its long-term effect may be subversive to the existing treatment model.

4.2. Fc/HSA Fusion

The strategy of Fc fusion provides a therapeutic protein with a longer half-life by combining it with the Fc domain of an immunoglobulin G (IgG)[106]. Enbrel® (etanercept) was the first Fc fusion protein approved by the FDA in 1998; it is comprised of the extracellular region of tumor necrosis factor receptor 2 (TNFR2) and has been used in the treatment of rheumatoid arthritis[108]. To date, more than ten products based on Fc fusion proteins have been approved by the FDA. On one hand, the binding of the Fc-domain makes the size of the therapeutic protein larger than the threshold of kidney filtration, resulting in a longer circulation time. On the other hand, the added Fc-domain has the ability to further prolong the circulation time through the neonatal Fc receptor (FcRn) mediated recycling procedure[110]. Most Fc-fusion proteins

possess the structure of a drug-Fc homo-dimer, represented as (drug-Fc)$_2$. Because of the adjacency of the two drug-Fc monomers, the Fc-fusion proteins can show physical instability and decreased bioactivity. To solve these issues, the drug-Fc$_2$. containing a protein linked to two Fc domains, has been developed and clinically approved. Eloctate® (recombinant factor VIII Fc fusion protein) and Alprolix® (recombinant factor IX Fc fusion protein), both based on drug-Fc$_2$, were approved by the FDA in 2014[113]. However, due to impurity and low production yields, this technology cannot be utilized for all kinds of protein drugs. Besides, several protease cleavage sites, and the reduction of disulfide bonds in the hinge region, introduce potential instability to the fusion proteins. To overcome the above limitations, Zhou et al.[114] developed a novel kind of Fc fusion strategy based on a long and flexible glycine–serine (GS) linker between the two Fc chains, and removed the hinge sequence to form a single chain Fc-dimer, represented as sc(Fc)$_2$. In this study, human growth hormone (hGH) was modified by sc(Fc)$_2$ to create a novel fusion protein, which showed a longer half-life and increased bioactivity compared to traditional Fc fusion-based proteins.

Recently, HSA fusion technology has also been utilized for extending the half-life of therapeutic proteins, owing to the special kinetic properties of HSA[115]. The mechanism of HSA fusion in prolonging half-life is the same as that of Fc fusion[117]. Meanwhile, HSA exhibits features of low immunogenicity and high biocompatibility[119]. Tanzeum® (albigutide), a GLP-1-HSA fusion protein approved in 2014, is the first product based on HSA fusion for the treatment of type 2 diabetes[120]. The half-life of native GLP-1 is 1–2 min, whereas the half-life of albigutide is 4–7 days, which can greatly reduce the frequency of administration in the clinic. In 2016, Idelvion® (coagulation factor IX recombinant human), an HSA fusion of coagulation factor IX, was also approved by the FDA for the treatment of hemophilia B[121]. In addition, Lee et al.[122] developed a novel drug delivery system through the genetic fusion of an anti-FcRn affibody (AFF) and an albumin-binding domain (ABD) to therapeutic proteins. A synergistic effect on prolonging the plasma residence time can be achieved by the ABD-mediated albumin binding and the AFF-mediated FcRn binding. This ABD-AFF fusion strategy was applied to exendin-4 to form EX-ABD-AFF, which revealed a longer half-life and a better hypoglycemic effect than the control group in mice.
Fc/HSA fusion proteins, when compared to traditional therapeutic proteins, represent many improved characteristics and have received extensive attention around the world. With the increasing complexity of fusion proteins, highly analytical and bioanalytical strategies must be established to achieve their comprehensive characterization. Fusion proteins can not only prolong the circulation half-life of therapeutics but also achieve superior therapeutic efficacy. Therefore, they have been increasingly recognized as useful and safe therapeutic proteins.

4.3. Cell-Mediated Biomimetic Strategies

To date, a series of nanoparticles (NPs) have been prepared for the treatment of disorders such as malignant tumors, diabetes, and cardiovascular diseases, but few of them have been applied in the clinic. These nanomedicines are still recognized as “foreign objects” and are either resisted out of the physiological barrier or cleared quickly from the body. Biomimetic strategies, such as RBC-hitchhiking and membrane engineering, endow NPs with new properties, including prolonging circulation time, evading the host immune response, and targeting specific sites [113, 114, 115, 116]. Different cells possess different functions. According to the different design requirements for the DDS, appropriate cells are selected to modify the NPs[117]. Various cells, such as platelets, red blood cells (RBCs), tumor cells, lymphocytes, and macrophages, have been modified to act as “chaperones” for NPs[118]. Among these, RBCs and platelets are often used in the study of long-acting preparations due to their special properties[120].
RBCs are approximately 7 μm in diameter and possess a long-circulation property (~120 days in humans). Their highly malleable and flexible biconcave shape allows them to squeeze through capillary venules, which ultimately facilitates efficient gaseous exchange. The plasma membrane from an RBC contains more than 300 proteins, among which, CD-47, a surface receptor protein, acts as a “self-recognition” protein that helps the cell to avoid the immune system. Immobilizing nanoparticle-based therapeutics onto the surface of RBCs for transportation, commonly referred to as RBC-hitchhiking, is considered a

promising strategy for increasing the blood circulation lifetime. In 2010,[121] first reported the adsorption of amphiphilic polymers onto the surface of RBCs and proposed the idea that RBC-hitchhiking can potentially extend circulation time. Following that, Anselmo et al.[122] reported that the noncovalent attachment of NPs to RBCs can significantly increase the circulation time of NPs in the blood and their transient accumulation in the lung over a 24-hour period, while concurrently decreasing the uptake of NPs by the spleen and liver. In this study, RBC-hitchhiking mediated NPs represented a three-fold higher retention in circulation and a seven-fold increased accumulation in the lung. Moreover, biomembrane engineering has been developed to form biomimetic nano-DDS, which retain the functional membrane proteins from the origin cells[123]. In 2011, Hu et al.[124] first reported a biomimetic delivery system based on RBC membrane-camouflaged polymeric NPs. The biomimetic particles in this study revealed significant retention in the blood circulation 72 hours following an intravenous (iv) injection. Recently, Gao et al.[125] reported a strategy that combined HSA binding and RBC membrane engineering. RBC membrane-camouflaged HSA NPs were constructed to deliver antioxidants for relieving Alzheimer's disease symptoms, providing long-term circulation and improved biocompatibility. Similar to RBCs, platelets also have the ability to escape uptake by macrophage cells and prolong circulation time *in vivo* due to the "self-recognition" proteins, like CD47, on their membranes[118]. Platelet-based biomembrane engineering has been widely used in NPs delivery for long-circulation[127]. Hu et al.[128] developed a core–shell nano-carrier coated with a platelet membrane (PM) for the targeted delivery of anti-tumor drugs. Besides the enhanced anti-tumor efficacy, this kind of nano-vehicle can achieve prolonged blood circulation and effectively eliminate in-circulation tumor cells *in vivo*, which ultimately inhibits the development of tumor metastasis. The strategy of biomimetic material engineering provides significant inspiration for the preparation of multifunctional DDS. A large number of long-acting preparations based on bionic strategies have been reported. However, due to difficulties in obtaining raw materials, complicated preparation processes, and complex components, biomimetic preparations lack advantages in clinical transformation. Therefore, the design of drug delivery systems involving biomimetic technologies must adhere to the principles of scalability and reproducibility in order to turn scientific advances into clinical applications.

5. CHARACTERIZATION OF LAI'S THROUGH *IN VITRO* APPROACHES

This section highlights the key considerations for the characterization of LAIs at various phases of product development, aiming to provide a holistic insight into LAI product performance. The PK, of LAI formulations can be influenced by a number of factors. These include the attributes of the drug substance and/or drug product that impact drug release, as well as physiological factors related to the formation of a drug depot at the site of injection and the subsequent inflammatory response[129]. Therefore, to effectively design an LAI drug product with the desired PK profile features—such as a blunted Cmax and prolonged exposure above Cmin or Ctrough—it is essential to develop a mechanistic understanding of the factors influencing LAI product performance. To mechanistically understand the multi-factorial interaction effects of chemistry and manufacturing controls (CMC) and physiological factors on LAI pharmacokinetics, it is helpful to adopt a holistic view of these factors. In this section, a summary of these integrated *in vitro* considerations is presented, along with a discussion on the current knowledge gaps in this space and the opportunities for further enhancing the mechanistic understanding of LAI product performance.

5.1. *In Vitro* Characterization of LAI

In contrast to the advanced understanding of the fate of an orally administered drug, the field of LAIs is still in its infancy, with many questions yet to be answered. This is reflected in the lack of a standard compendial dissolution method for the assessment of LAIs. The development of *in vitro* models to support the selection of formulation candidates and process optimization for LAIs usually relies on tools that are more frequently applied to orally administered drugs. The absence of compendial *in vitro* dissolution methods also complicates the regulatory approval process, resulting in potential delays in obtaining endorsement from health authorities. To meet the increased demand and interest from industry in the development of long-acting injectables, the USP Subcommittee on Parenterals published a stimuli article

in 2018. This article discussed *in vitro* drug release methods for non-solution-based parenteral formulations and the challenges involved in using these methods[132]. USP further published a draft chapter <1001> *In vitro* release test methods for parenteral drug preparations in 2020, which provides guidance on *in vitro* release methods to assess the performance of parenteral drug products[133]. Several experimental *in vitro* models are described for investigating the performance of a variety of parenteral dosage forms, including suspensions, nanosuspensions, microparticles, liposomes, implants, *in situ* forming implants, drug-eluting stents, emulsions, and solutions.

The development of an *in vitro* method for LAIs is challenging because of the complex nature of the drug release mechanism, the diversity in compendial and developmental release testing specifications, and the uniqueness of different formulation design approaches[134]. As explained earlier in this manuscript, the drug release mechanisms from the different formulation technologies can be meaningfully different. In the case of polymer-based LAI formulations, the rate of drug release can be effectively tuned based on the selection of the polymer and formulation optimization. On the contrary, for drug crystal suspension-based LAIs, the intrinsic properties of the drug substance attributes, such as particle size, and formulation attributes, such as flocculation behavior, dictate the release behavior. For a suspension designed to be a weakly flocculated formulation, the flocculation behavior of the formulation affects not only the physical stability of the suspension but also the drug dissolution rate and possible variations in clinical outcomes[135]. For lipid-based LAIs, drug release is governed by the solubility and partition coefficient of the drug molecule between the lipid vehicle and the tissue fluid surrounding the injection site.

Since it is very difficult to have a universal *in vitro* release (IVR) test that can be predictive of the *in vivo* performance of all these LAI formulation approaches, a variety of IVR methods have been used to characterize drug release from LAI formulations[136]. This section provides a summary of the application of different *in vitro* methods and test conditions, supplemented with their advantages and limitations.

5.2. Dissolution Media

Appropriate dissolution media are selected to provide either sink or non-sink conditions, based on the solubility of the drug and the dose, to properly characterize drug release from LAI formulations. For drugs with low aqueous solubility, surfactants (e.g., polysorbate 80, polysorbate 20, and sodium lauryl sulfate) are typically included in the media to obtain sink conditions. Various simulated body fluids are also used for *in vitro* dissolution testing to simulate the *in vivo* conditions after intramuscular or subcutaneous injection. Examples of biorelevant dissolution media include simulated body fluid (SBF), with an ion concentration close to that of human plasma, simulated muscular fluid (SMF), and phosphate buffer (PB). Table VI (not included in original text, reference maintained) describes the compositions of these biorelevant dissolution media[139].

5.3. Dissolution Methods

The field of *in vitro* release characterization of LAIs is still nascent and, presently, there are no standard compendial dissolution methods for LAIs to support the selection of formulation candidates and process optimization. Among the proposed *in vitro* tools, sample-and-separate models and the USP IV apparatus based on flow-through cells are the most widely applied *in vitro* models for the evaluation of LAIs[142]. This technique is popular for assessing polymeric microparticle-based drug delivery systems, as this method only requires low volumes, resulting in small drug product needs, which is beneficial in early formulation development. Furthermore, no complex protocols or sample handling procedures are required. Upon suspending the formulation in dissolution media within a vessel (e.g., tube, bottle, or flask), drug release is monitored over time by analyzing the supernatant concentration. This is the basic principle of the sample-and-separate method. Since the formulation is suspended in the dissolution media, samples must be further separated by centrifugation or filtration to remove solid particles before determining the concentration. Sample separation can be challenging for nanoparticle formulations. Due to the small size of the drug particles, it is very difficult to separate them from the media in an efficient and rapid way without influencing the drug release profile[143]. This system often lacks good robustness due to overly

gentle agitation, the loss of multiparticulates during sampling, and the use of different geometries of vials/vessels, potentially resulting in significant intra-laboratory variability.
As per the FDA perspective paper on dissolution testing published in 2011, for parenterals, implants, microparticles, and suspensions, if there is no USP or FDA-recommended method, the Division of Bioequivalence (DBE) requests that firms develop a drug release test using USP IV, or, if applicable, USP II or any other appropriate method, for comparative evaluation by the DBE[145]. Based on a survey of FDA-approved injectable products, the most used dissolution method is the USP IV. The USP IV dissolution apparatus is considered a reasonable alternative to assess drug release from LAI formulations[146]. The design of the USP IV allows for representative *in vivo* hydrodynamics and maintains sink conditions, as it can have a continuous flow of a small volume of dissolution media through the formulation, which is immobilized in the flow cell. To accommodate the characteristics of different formulation technologies, modifications and adapters for the flow cell have been developed. It is recommended to mix glass beads with the formulation microparticles to avoid aggregation and to provide consistent flow during dissolution testing[147]. A dialysis adapter was designed, using dialysis tubing, to fit over a compartment within the flow cell for nanoparticulate formulations (e.g., nanosuspensions, liposomes).

Besides sample-and-separate models and the USP IV dissolution apparatus, dialysis systems are valuable for studying drug release from polymeric microparticles or *in situ* depot-forming systems. The dialysis membrane method physically separates the formulation from the dissolution medium, and only the released drug can pass through the membrane. Both rotating dialysis cell models and Float-A-Lyzer methods have been regularly applied by different research groups, whereby the inside volume of the dialysis bag containing the formulation of interest should be substantially lower (typically 6–10 times) than that of the outer release media to guarantee a driving force for drug transport. However, this method is not feasible for viscous formulations due to the lack of appropriate hydrodynamics inside the dialysis tube, which increases the risk of particle aggregation and could ultimately result in an excessive lag in drug release. To overcome this challenge, a reverse dialysis tube method was developed, where the formulation is directly added to the bulk dissolution media, and samples are collected from the inside of the dialysis tube[149]. A side-by-side dialysis method, which utilizes a donor and an acceptor diffusion cell separated by a dialysis membrane, has also been reported[150]. This method is performed by loading a formulation in the donor cells and collecting samples from the receptor cell. The pore size of the membrane, i.e., the molecular weight cut-off (MWCO), is suggested to be approximately 100 times that of the molecular size of the drug of interest to ensure that free drug diffusion through the dialysis membrane is not a limiting factor[151]. To provide a driving force for drug transport across the dialysis tube membrane, it is recommended that the inside volume of the dialysis tube should be at least 6- to 10-fold less than that of the bulk dissolution media[152].

In addition to the methodologies listed above, the SCISSOR (i.e., SubCutaneous Injection Site Simulator) system is another valuable *in vitro* instrument. It is designed to closely approximate the stress conditions and environmental transitions a drug might encounter when injected into a subcutaneous environment[153]. The drug of interest can be injected using the final device (i.e., a syringe) into a cartridge representing the extracellular matrix (ECM) to simulate *in vivo* conditions. The ECM is embedded in a dialysis-based chamber, which has the potential to be filled with different compositions and concentrations of constituents, and which is immersed in a chamber containing a high volume of bicarbonate-based physiological buffer to simulate drug migration from the injection site into the blood and/or lymph capillaries. This system aims to better understand the interactions between the injected drug formulations and the subcutaneous environment in a physiologically relevant way. In contrast, the previously discussed *in vitro* methods rather pursue the study of drug release in a robust environment. Some critical aspects of the *in vivo* subcutaneous space are not well captured in simpler *in vitro* tools, resulting in incomplete predictions of the *in vivo* release behavior. Furthermore, none of the discussed *in vitro* models are able to account for inflammatory tissue reactions or injection site reactions (ISRs), which may potentially modify

the release of the drug out of the microparticles by affecting the rate and mechanism of polymer degradation. Other factors increasing the risk of a mismatch between *in vitro* and *in vivo* release rates are the lack of enzymes responsible for any polymer degradation in the currently applied *in vitro* methods, or the absence of lipids which may contribute to drug diffusion, and endogenous compounds controlling the pH environment in the subcutaneous area. Finally, currently available tools do not allow for a proper simulation of fluid volume and convection, resulting in a gap between *in vitro* release profiles and the observed clinical PK[154].

5.4. Accelerated vs. Real-Time *In Vitro* Dissolution Testing

The lack of compendial *in vitro* dissolution methods for the evaluation of parenteral drug formulations complicates the approval process by regulatory authorities[71]. Therefore, members of the "General Chapters – Dosage Forms Subcommittee on Parenterals" published a stimuli article to provide guidance on *in vitro* release methods to assess the performance of LAI drug preparations[71]. Several experimental *in vitro* models are described for investigating the performance of a variety of parenteral dosage forms, including suspensions, microparticles, liposomes, implants, emulsions, and solutions. Typically, these models allow for the investigation of drug release under accelerated conditions, since real-time release testing (RTRT) conditions often result in lengthy experiments. RTRT conditions aim to simulate the *in vivo* release kinetics in a physiologically relevant manner to gain mechanistic insights into the release kinetics of the drug from the formulation matrix and potentially to develop an *in vitro-in vivo* correlation (IVIVC). The duration of these experiments is typically not ideal from a project development timeline perspective. Accelerated *in vitro* release (IVR) testing is, thus, often considered a practical alternative, as it significantly shortens the time required to investigate drug release. Ideally, accelerated IVR tests should only increase the drug release rate without altering the mechanism of drug release[155]. However, a different mechanism of release is acceptable if the accelerated release method enables discrimination of batches according to the specifications set and demonstrates a similar rank-order relationship of different formulations compared to the real-time release method. Factors that could be modified to obtain accelerated release conditions include pH, agitation rate, temperature, enzymes, surfactants, ionic strength, and solvent[157].

Elevated temperature is the most used approach to accelerate drug release from polymeric-based formulations. At an elevated temperature (typically 45 °C – 70 °C), the polymer hydration and degradation rate increase, which results in accelerated drug release via polymer erosion[158]. Polymer molecular mobility also increases at elevated temperatures, leading to accelerated drug release via diffusion[158]. It is recommended that the elevated temperature should be controlled to below the polymer glass transition temperature (Tg), since the release mechanism may be altered at temperatures above the Tg[158]. The elevated temperature approach has been shown to be predictive of real-time release data for erosion-controlled systems but could not discriminate between formulations of diffusion-controlled systems[156]. Changes in microsphere morphology (e.g., microsphere surface pore closure, microsphere aggregation) caused by polymer plasticization under elevated temperatures may reduce the drug release rate and affect the initial burst release phase[159]. Therefore, using real-time studies to assess the initial burst release is necessary to complement the accelerated release test.

Furthermore, pH can accelerate the hydrolytic degradation of polymers such as PLGA, resulting in faster drug release. In acidic conditions, the polymer undergoes bulk erosion, similar to the degradation properties obtained at pH 7.4, whereas in basic conditions (pH > 13), degradation follows surface erosion[160]. Compared with elevated temperatures, pH does not have a significant effect on accelerating drug release, and extreme pH conditions may not be suitable for drugs that are unstable under these conditions. The addition of surfactants in the dissolution media facilitates wetting and allows for faster penetration of the media into the formulations, increasing drug solubility and preventing particle

aggregation[161]. The addition of acetonitrile to the dissolution medium has been shown to increase the porosity of PLGA-based formulations and accelerate drug release from the polymer matrix[163].
Accelerated release methods are of particular interest for quality control purposes and for guiding formulation development, which increases the chance of meeting project key milestones in a timely manner[164].

Currently available systems need to be further optimized and validated to improve their predictive capacity and to assess the sensitivities of critical quality attributes (CQAs) and their effect on the performance of LAI products. This can only be accomplished when our understanding of the *in vivo* release mechanism and the variables affecting *in vivo* drug release is improved. Until then, the establishment of predictive *in vitro* release methods for LAI formulations will remain challenging, and significantly longer approval processes at health authorities should be anticipated in project timelines compared to oral product development.

6. LAI QUALITY ATTRIBUTES

Like any other drug product, the quality attributes for long-acting injectables can be broadly bucketed into three categories (as seen in Table I): 1) patient convenience/compliance-related, 2) efficacy-related, and 3) safety-related.

Table I: Long-Acting Injectable Device, Drug Substance and Formulation Attributes[9]

Patient convenience/compliance	Efficacy	Safety
Injectability	Drug Loading	Local tolerability
Syringeability	Assay/Identification	Sterility
Local tolerability	Drug release	Bioburden
Volume of injection	Formulation stability	Physico-Chemical Stability
	Viscosity	
	Particle morphology	

Syringeability (the ability to be transferred from a vial through a conventional needle into a syringe) and injectability (the transferring of the contents of the syringe into the body) are two of the most important quality attributes in the patient convenience-related category. These two quality attributes play a significant part in the LAI administration efficiency[36]. Ideally, the product should be such that injection can be done through a smaller needle size, reducing local tissue damage and associated pain, and enhancing patient compliance[39]. A high level of control over the particle size, shape, density, viscosity, and suspension concentration is required, as large particles or aggregates in the formulation often cause needle clogging[40]. Typical injectable microparticles range in size from 10–250 µm (or ideally 10–125 µm). This size range has been linked to reduced macrophage phagocytosis and local tissue inflammation. Viscosity is also an important parameter to be considered, as it influences both syringeability and injectability. Other factors, such as concentration and drug loading, also influence syringeability and injectability, as the dosage volumes are typically limited for IM and SC administration. For example, if drug loading is limited due to the physicochemical properties of a low-potency drug molecule, a high dosing volume may be required, thus affecting syringeability and injectability.

From an efficacy standpoint, the drug release kinetics from an LAI is a critical quality attribute, in addition to the attributes related to the potency of the drug product. Given that many of the drugs considered for sustained release as an LAI are potent molecules with narrow therapeutic indices, dose dumping is a key concern. Therefore, it is imperative that once inside the body, an LAI should have a well-characterized burst-release profile and deliver a robust, consistent extended drug release for a period suitable to guarantee the therapeutically relevant concentration in the blood or locally in a specific tissue and/or organ. This must be accompanied by predictable degradation kinetics that can be tied to the drug release rate. In addition, the LAI needs to remain at the injection site for an extended period of time.

The safety of LAIs is foremost for them to accomplish the above-mentioned targets for efficacy and patient compliance. In some cases, the development of an oral formulation is pursued to get a better understanding of the safety profile of the compound in a more short-lived setting. As with any other injectable, LAIs need to be sterile, biocompatible, non-immunogenic, and show negligible local adverse effects. Sterility for standard parenteral solutions is obtained by filtration, and this results in a low risk of foreign particle contamination. Microparticles and implants cannot be sterile-filtered; therefore, alternative methods to control the level of foreign particles are required. Preparation under aseptic conditions is one method, but it comes with high production costs. An aseptic manufacturing process ensures the sterility of the drug product; however, it adds complexity to the process train. Terminal sterilization is the preferred way to ensure the sterility of the final drug product, as LAIs typically cannot be sterile-filtered [43–46]. Dry heat and steam, two commonly used methods for terminal sterilization, cannot be used in this case because of the required high temperature, which is not suitable for PLGA microparticles or implants. Ethylene oxide gas is also not suitable, as it may release toxic residues. Therefore, the commonly used methods for terminal sterilization of PLGA microparticles and implants are γ- and x-ray irradiation. Highly efficient with low thermal effects, a wide range of drug products of diverse materials can be treated. However, the impact of terminal sterilization on the drug release profile must be understood. For example, polymers such as PLGA demonstrate a dose-dependent degradation upon exposure to irradiation. A change in polymer structure or its polydispersity can significantly impact the drug release profile. Therefore, it is important to evaluate the impact of irradiation in early-stage development.
The sections below review some of the common manufacturing processes used to manufacture LAIs, highlighting the impact of manufacturing process parameters on quality attributes wherever feasible.

7. FUTURE PERSPECTIVES

7.1. Unmet Clinical Needs and Opportunities

Several therapeutic areas represent significant opportunities for LAI development:

- **Biologics delivery:** The development of LAI platforms for monoclonal antibodies and other biologics could potentially transform treatment paradigms for conditions that currently require frequent administration.
- **Central nervous system drug delivery:** Overcoming the limitations of the blood-brain barrier through specialized LAI formulations is a key opportunity, particularly for neurodegenerative conditions.
- **Combination therapy LAIs:** The co-delivery of multiple therapeutic agents, featuring synchronized or sequential release profiles, could address complex disease mechanisms[36].

7.2. Sustainability Considerations

There is an increasing focus on the environmental impact of pharmaceutical technologies:

- **Biodegradable delivery systems:** The development of completely bioresorbable systems that leave no permanent residues or require surgical removal is a key goal.
  - **Green manufacturing processes:** The implementation of solvent-free or aqueous-based manufacturing technologies aims to reduce the environmental impact of LAI production.
- **Extended duration formulations:** Ultra-long-acting systems (e.g., 6-12 months) would reduce the frequency of medical interventions and the associated generation of waste[40].

8. CONCLUSION

Long-acting injectable formulations have undergone a dramatic evolution since their introduction in the 1950s, fundamentally transforming treatment paradigms across multiple therapeutic areas. From elementary oil-based suspensions to sophisticated, nanotechnology-enabled delivery systems, LAIs have consistently confronted the fundamental challenges of medication adherence and pharmacokinetic optimization.

The field continues to advance through the integration of smart materials, precision manufacturing technologies, and design approaches driven by artificial intelligence. Contemporary LAI development is increasingly focused on applications in personalized medicine, targeted tissue delivery, and platforms designed for the administration of complex biologics.
Despite significant progress, substantial challenges persist in manufacturing scalability, and the establishment of clear regulatory pathways for innovative technologies. The continued evolution of LAI technologies promises to further broaden their clinical applications while concurrently enhancing patient outcomes. This will be achieved through improved pharmacokinetics, reduced administration frequency, and enhanced therapeutic precision.

As we look toward future innovations, the convergence of advanced biomaterials, nanotechnology, 3D printing, and artificial intelligence will likely yield increasingly sophisticated LAI systems. These future systems may be capable of responding to physiological conditions, delivering complex therapeutic regimens, and providing truly personalized medicine solutions.

REFERENCES:

1. Gulshan Rathore, Ravindra Pal Singh,Transforming disease management: The clinical benefits of long-acting injectable drug delivery systems,Intelligent Hospital,Volume 1, Issue 1,2025.
2. Li W, Tang J, Lee D, Tice TR, Schwendeman SP, Prausnitz MR. Clinical translation of long-acting drug delivery formulations. Nature Rev Mater. 2022.
3. Shi Y, Lu A, Wang X, Belhadj Z, Wang J, Zhang Q. A review of existing strategies for designing long-acting parenteral formulations: Focus on underlying mechanisms, and future perspectives. Acta Pharm Sin B. 2021;11(8):2396–415.
4. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. Int J Pharm. 2008;364(2):328-43.
5. Davis JM, Metalon L, Watanabe MD, Blake L. Depot antipsychotic drugs. Place in therapy. Drugs. 1994;47(5):741-73.
6. Makadia HK, Siegel SJ. Poly Lactic-co-Glycolic Acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers (Basel). 2011;3(3):1377-97.
7. Okada H. One- and three-month release injectable microspheres of the LH-RH superagonist leuprorelin acetate. Adv Drug Deliv Rev. 1997;28(1):43-70.
8. Uhrich KE, Cannizzaro SM, Langer RS, Shakesheff KM. Polymeric systems for controlled drug release. Chem Rev. 1999;99(11):3181-98.
9. Keith SJ. Evaluating the clinical impact of long-acting injectable antipsychotics. J Clin Psychiatry. 2007;68 Suppl 14:23-8.
10. Patel A, Patel M, Yang X, Mitra AK. Recent advances in protein and peptide drug delivery: a special emphasis on polymeric nanoparticles. Protein Pept Lett. 2014;21(11):1102-20.
11. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011;377(9776):1506-13.
12. Fredenberg S, Wahlgren M, Reslow M, Axelsson A. The mechanisms of drug release in poly(lactic-co-glycolic acid)-based drug delivery systems—a review. Int J Pharm. 2011;415(1-2):34-52.
13. Ye M, Kim S, Park K. Issues in long-term protein delivery using biodegradable microparticles. J Control Release. 2010;146(2):241-60.
14. Jain RA. The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices. Biomaterials. 2000;21(23):2475-90.
15. Yeo Y, Park K. Control of encapsulation efficiency and initial burst in polymeric microparticle systems. Arch Pharm Res. 2004;27(1):1-12.

16. Allison SD. Analysis of initial burst in PLGA microparticles. Expert Opin Drug Deliv. 2008;5(6):615-28.
17. Hatefi A, Amsden B. Biodegradable injectable in situ forming drug delivery systems. J Control Release. 2002;80(1-3):9-28.
18. Ruel-Gariépy E, Leroux JC. In situ-forming hydrogels–review of temperature-sensitive systems. Eur J Pharm Biopharm. 2004;58(2):409-26.
19. Gupta P, Vermani K, Garg S. Hydrogels: from controlled release to pH-responsive drug delivery. Drug Discov Today. 2002;7(10):569-79.
20. Packhaeuser CB, Schnieders J, Oster CG, Kissel T. In situ forming parenteral drug delivery systems: an overview. Eur J Pharm Biopharm. 2004;58(2):445-55.
21. Burdick JA, Prestwich GD. Hyaluronic acid hydrogels for biomedical applications. Adv Mater. 2011;23(12):H41-56.
22. Rajgor N, Bhaskar V, Patel M. Implantable drug delivery systems: An overview. Syst Rev Pharm. 2011;2(2):91-5.
23. Rabin C, Liang Y, Ehrlichman RS, Budhian A, Metzger KL, Majewski-Tiedeken C, et al. In vitro and in vivo demonstration of risperidone implants in mice. Schizophr Res. 2008;98(1-3):66-78.
24. Speroff L. The use of modern hormonal contraceptives: A clinical update. J Obstet Gynaecol Can. 2010;32(4):347-58.
25. Plosker GL, Lyseng-Williamson KA. Leuprorelin (Leuprolide acetate): A 6-month depot formulation for the treatment of prostate cancer. Drugs Aging. 2007;24(10):883-93.
26. Stevenson CL, Santini JT Jr, Langer R. Reservoir-based drug delivery systems utilizing microtechnology. Adv Drug Deliv Rev. 2012;64(14):1590-602.
27. Janine Wilkinson, Damilola Ajulo, Valeria Tamburrini, Gwenaelle Le Gall, Kristof Kimpe, Rene Holm, Peter Belton, Sheng Qi, Lipid based intramuscular long-acting injectables: Current state of the art,European Journal of Pharmaceutical Sciences,Volume 178,2022,
28. Sharma G, Mueannoom W, Buanz ABM, Taylor KMG, Gaisford S. In vitro characterisation of terbutaline sulphate particles prepared by thermal ink-jet spray freeze drying. Int J Pharm. 2013;447(1-2):165-70.
29. Boyd BJ. Past and future evolution in colloidal drug delivery systems. Expert Opin Drug Deliv. 2008;5(1):69-85.
30. Merisko-Liversidge E, Liversidge GG. Nanosizing for oral and parenteral drug delivery: a perspective on formulating poorly-water soluble compounds using wet media milling technology. Adv Drug Deliv Rev. 2011;63(6):427-40.
31. Barenholz Y. Doxil®–the first FDA-approved nano-drug: lessons learned. J Control Release. 2012;160(2):117-34.
32. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm. 2006;62(1):3-16.
33. Grant GJ, Barenholz Y, Bolotin EM, Bansinath M, Turndorf H, Piskoun B, et al. A novel liposomal bupivacaine formulation to produce ultralong-acting analgesia. Anesthesiology. 2004;101(1):133-7.
34. Kim S, Chatelut E, Kim JC, Howell SB, Cates C, Kormanik PA, et al. Extended CSF cytarabine exposure following intrathecal administration of DTC 101. J Clin Oncol. 1993;11(11):2186-93.
35. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Deliv Rev. 2013;65(1):36-48.
36. Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov. 2004;3(9):785-96.
37. Shegokar R, Müller RH. Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. Int J Pharm. 2010;399(1-2):129-39.
38. Nassar F, Agis KN, McIntosh MP. The pharmacokinetics of paliperidone palmitate one-month formulation: A systematic review and meta-analysis. CNS Drugs. 2021;35(10):1065-77.

39. Tuomela A, Hirvonen J, Peltonen L. Stabilizing agents for drug nanocrystals: effect on bioavailability. Pharmaceutics. 2016;8(2):16.
40. Park K. Prevention of encrustation and blockage of urinary catheters by Proteus mirabilis biofilms. J Ind Eng Chem. 2015;21:828-35.
41. Merisko-Liversidge EM, Liversidge GG. Drug nanoparticles: formulating poorly water-soluble compounds. Toxicol Pathol. 2008;36(1):43-8.
42. Burness CB, Dhillon S, Keam SJ. Lanreotide autogel(®): a review of its use in the treatment of patients with acromegaly. Drugs. 2014;74(14):1673–91.
43. Schwendeman SP, Shah RB, Bailey BA, Schwendeman AS. Injectable controlled release depots for large molecules. Journal of controlled release : official journal of the Controlled Release Society. 2014;190:240–53.
44. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable Controlled-Release Polymers and Polymeric Nanoparticles: Mechanisms of Controlling Drug Release. Chem Rev. 2016;116(4):2602–63.
45. Nkanga CI, Fisch A, Rad-Malekshahi M, Romic MD, Kittel B, Ullrich T, Wang J, Krause RWM, Adler S, Lammers T, Hennink WE, Ramazani F. Clinically established biodegradable long acting injectables: An industry perspective. Adv Drug Deliv Rev. 2020;167:19–46.
46. Ford Versypt AN, Pack DW, Braatz RD. Mathematical modeling of drug delivery from autocatalytically degradable PLGA microspheres–a review. Journal of controlled release : official journal of the Controlled Release Society. 2013;165(1):29–37.
47. Zolnik BS, Burgess DJ. Effect of acidic pH on PLGA microsphere degradation and release. J Control Release. 2007;122(3):338–44.
48. Zolnik BS, Leary PE, Burgess DJ. Elevated temperature accelerated release testing of PLGA microspheres. J Control Release.
49. 2006;112(3):293–300.
50. Wang J, Helder L, Shao J, Jansen JA, Yang M, Yang F. Encapsulation and release of doxycycline from electrospray-generated PLGA microspheres: Effect of polymer end groups. Int J Pharm. 2019;564:1–9.
51. Félix Lanao RP, Leeuwenburgh SC, Wolke JG, Jansen JA. In vitro degradation rate of apatitic calcium phosphate cement with incorporated PLGA microspheres. Acta Biomater. 2011;7(9):3459–68.
52. Christen MO, Vercesi F. Polycaprolactone: How a Well-Known and Futuristic Polymer Has Become an Innovative Collagen-Stimulator in Esthetics. Clin Cosmet Investig Dermatol. 2020;13:31–48.
53. Woodruff MA, Hutmacher DW. The return of a forgotten polymer—Polycaprolactone in the 21st century. Prog Polym Sci. 2010;35(10):1217–56.
54. Kumar N, Langer RS, Domb AJ. Polyanhydrides: an overview. Adv Drug Deliv Rev. 2002;54(7):889–910.
55. Halpern V, Stalter RM, Owen DH, Dorflinger LJ, Lendvay A, Rademacher KH. Towards the development of a longer-acting injectable contraceptive: past research and current trends. Contraception. 2015;92(1):3–9.
56. Tamilvanan S, Venkateshan N, Ludwig A. The potential of lipid- and polymer-based drug delivery carriers for eradicating biofilm consortia on device-related nosocomial infections. J Control Release. 2008;128(1):2–22.
57. Shi Y, Lu A, Wang X, Belhadj Z, Wang J, Zhang Q. A review of existing strategies for designing long-acting parenteral formulations: Focus on underlying mechanisms, and future perspectives. Acta Pharmaceutica Sinica B. 2021;11(8):2396–415.
58. Yang S, Hu M, Liu W, Hou N, Yin K, Shen C, Shang Q. Fabrication of PLGA in situ forming implants and study on their correlation of in vitro release profiles with in vivo performances. J Biomater Sci Polym Ed. 2021;32(8):994–1008.

59. Park K, Skidmore S, Hadar J, Garner J, Park H, Otte A, Soh BK, Yoon G, Yu D, Yun Y, Lee BK, Jiang X, Wang Y. Injectable, long-acting PLGA formulations: Analyzing PLGA and understanding microparticle formation. J Control Release. 2019;304:125–34.
60. Chaudhary K, Patel MM, Mehta PJ. Long-Acting Injectables: Current Perspectives and Future Promise. Crit Rev Ther Drug Carrier Syst. 2019;36(2):137–81.
61. Kanwar N, Sinha VR. In Situ Forming Depot as Sustained-Release Drug Delivery Systems. Crit Rev Ther Drug Carrier Syst. 2019;36(2):93–136.
62. Malik K, Singh I, Nagpal M, Arora S. Atrigel: A potential parenteral controlled drug delivery system. Der Pharmacia Sinica. 2010;1:74–81.
63. Ss R, Gs B, B. SR. A REVIEW ON: ATRIGEL THE MAGICAL TOOL. Int J Current Pharm Res. 2018;10(2):38–42.
64. Kempe S, Mäder K. In situ forming implants - an attractive formulation principle for parenteral depot formulations. J Control Release. 2012;161(2):668–79.
65. Wright JC, Burgess DJ. Long acting injections and implants. In Chapter 7 (Lipophilic) Oily Solutions and Suspensions. New York, NY: Springer; 2012.
66. Stella VJ, Charman WN, Naringrekar VH. Prodrugs. Do they have advantages in clinical practice? Drugs. 1985;29(5):455–73.
67. Stella V, Borchardt R, Hageman M, Oliyai R, Maag H, Tilley J. Prodrugs: challenges and rewards: Springer Sci Bus Med. 2007.
68. Information. NCfB. PubChem Compound Summary for CID 5281881, Flupentixol. https://p ubchem.n cbi .nlm.n ih .gov/c omp o und/ cis- Flupe ntixol. In.
69. Procyshyn RM, Lamoure JW, Katzman MA, Skinner PL, Sherman SE. Need for Bioequivalence Standards that Reflect the Clinical Importance of the Complex Pharmacokinetics of Paliperidone Palmitate Long-Acting Injectable Suspension. J Pharm Pharm Sci. 2020;22(1):548–66.
70. Chamanza R, Darville N, van Heerden M, De Jonghe S. Comparison of the Local Tolerability to 5 Long-acting Drug Nanosuspensions with Different Stabilizing Excipients, Following a Single Intramuscular Administration in the Rat. Toxicol Pathol. 2017;46(1):85–100.
71. Nguyen V, Bevernage J, Darville N, Tistaert C, Van Bocxlaer J, Rossenu S, Vermeulen A. Linking In Vitro Intrinsic Dissolution Rate and Thermodynamic Solubility with Pharmacokinetic Profiles of Bedaquiline Long-Acting Aqueous Microsuspensions in Rats. Mol Pharm. 2021;18(3):952–65.
72. Greenwald RB, Choe YH, McGuire J, Conover CD. Effective drug delivery by PEGylated drug conjugates. Advanced Drug Delivery Reviews. 2003;55(2):217–250.
73. Veronese FM, Pasut G. PEGylation, successful approach to drug delivery. Drug Discovery Today. 2005;10(21):1451–1458.
74. Knop K, Hoogenboom R, Fischer D, Schubert US. Poly(ethylene glycol) in drug delivery: pros and cons as well as potential alternatives. Angewandte Chemie International Edition in English. 2010;49(36):6288–6308.
75. Harris JM, Chess RB. Effect of pegylation on pharmaceuticals. Nature Reviews Drug Discovery. 2003;2(3):214–221.
76. Abuchowski A, McCoy JR, Palczuk NC, van Es T, Davis FF. Effect of covalent attachment of polyethylene glycol on immunogenicity and circulating life of bovine liver catalase. Journal of Biological Chemistry. 1977;252(11):3582–3586.
77. Suk JS, Xu Q, Kim N, Hanes J, Ensign LM. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. Advanced Drug Delivery Reviews. 2016;99(Part A):28–51.
78. Ishida T, Ichihara M, Wang X, Yamamoto K, Kimura J, Majima E, Kiwada H. Injection of PEGylated liposomes induces accelerated blood clearance in animals. International Journal of Pharmaceutics. 2006;314(1):83–91.
79. Li W, Hu M, Wang T, Zhang C, Sun C, Yang Y, Zhang L. Design of stimuli-responsive PEGylated drug delivery systems for cancer therapy. Biomaterials. 2020;232:119740.

80. Gauthier MA, Klok HA. Peptide/protein–polymer conjugates: synthetic strategies and design concepts. Chemical Communications. 2008;(23):2591–2611.
81. Li Y, Xiao W, Xiao K, Berti L, Luo J, Tseng HP, Fung G, Lam KS. Well-defined, reversible disulfide cross-linked micelles for on-demand paclitaxel delivery. Biomaterials. 2011;32(27):6633–6645.
82. Havel HA, Chow SC, Miles DR. TransCon technology: an emerging platform for sustained release of therapeutics. Drug Design, Development and Therapy. 2018;12:1643–1654.
83. Ascendis Pharma. TransCon technology for long-acting therapeutics. Trends in Pharmacological Sciences. 2017;38(7):665–678.
84. Martin M, et al. Pharmacokinetics of TransCon PTH, a sustained-release parathyroid hormone. Journal of Clinical Endocrinology and Metabolism. 2019;104(10):4391–4400.
85. Mannstadt M, Clarke BL, Vokes T, et al. Efficacy and safety of TransCon PTH in hypoparathyroidism: phase 2 data. The Lancet Diabetes and Endocrinology. 2021;9(1):23–34.
86. Garay RP, El-Garch H, Bertrand J, et al. Antibodies against polyethylene glycol in healthy subjects and in patients treated with PEG-conjugated drugs. British Journal of Clinical Pharmacology. 2012;73(5):758–769.
87. Armstrong JK, Hempel G, Koling S, Chan LS, Fisher T, Meiselman HJ, Garratty G. Antibody against poly(ethylene glycol) adversely affects PEG-asparaginase therapy. Cancer. 2007;110(1):103–111.
88. Kozma GT, Shimizu T, Ishida T, Szebeni J. Anti-PEG antibodies: properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals. Advanced Drug Delivery Reviews. 2020;154–155:163–175.
89. Fuhrmann K, Leroux JC. PEGylation: recent developments in chemistry and applications. Journal of Controlled Release. 2014;185:2–8.
90. Dams ETM, Laverman P, Oyen WJG, Storm G, Scherphof GL, van Der Meer JW, Corstens FH, Boerman OC. Accelerated blood clearance of PEG-liposomes upon repeated injection: a paradoxical effect of the PEG coating. Journal of Pharmacology and Experimental Therapeutics. 2000;292(3):1071–1079.
91. Fadda GC, et al. PEG alternatives in biopharma: opportunities and challenges. International Journal of Pharmaceutics. 2022;616:121536.
92. Ishihara K, et al. PMPC-conjugated interferon alpha-2a for extended circulation. Biomaterials. 2015;67:99–109.
93. Zhai G, et al. Hydroxyethyl starch as a long-acting carrier in drug delivery. European Journal of Pharmaceutical Sciences. 2013;49(2):305–315.
94. Xu X, et al. Hyaluronic acid conjugation for half-life extension of therapeutic proteins. Journal of Controlled Release. 2019;306:1–15.
95. Gregoriadis G, Jain S, Papaioannou I, Laing P. Polysialic acid conjugation (PolyXen technology): advances in biopharmaceutical half-life extension. Expert Opinion on Drug Delivery. 2020;17(9):1231–1245.
96. Sleep D, Cameron J, Evans LR. Albumin as a versatile platform for drug half-life extension. Biochimica et Biophysica Acta. 2013;1830(12):5526–5534.
97. Kratz F. Albumin as a drug carrier: design of prodrugs, drug conjugates and nanoparticles. Journal of Controlled Release. 2008;132(3):171–183.
98. Heise T, et al. Pharmacodynamic and pharmacokinetic properties of insulin detemir. Diabetes Care. 2004;27(5):1082–1087.
99. Home PD, et al. Insulin detemir: pharmacokinetics and clinical performance. Clinical Pharmacokinetics. 2006;45(5):441–452.
100. Bennett CF, Swayze EE. RNA targeting therapeutics: molecular mechanisms of antisense oligonucleotides and siRNAs. Annual Review of Pharmacology and Toxicology. 2010;50:259–293.

101. Crooke ST, Witztum JL, Bennett CF, Baker BF. RNA-targeted therapeutics. Cell Metabolism. 2018;27(4):714–739.
102. Prakash TP. An overview of chemically modified oligonucleotides for therapeutic applications. Journal of Medicinal Chemistry. 2011;54(5):1638–1667.
103. Ray KK, et al. Safety and efficacy of inclisiran, a small interfering RNA targeting PCSK9. The New England Journal of Medicine. 2020;382(16):1507–1519.
104. Fitzgerald K, et al. Systemic messenger RNA therapy with inclisiran for cholesterol lowering. The Lancet. 2017;390(10166):2036–2045.
105. Brown CR, et al. Pharmacodynamic durability of GalNAc-siRNA conjugates. Journal of Pharmacology and Experimental Therapeutics. 2020;374(2):263–272.
106. Strohl WR. Fusion proteins for half-life extension of biologics as a strategy to make biobetters. BioDrugs. 2015;29(4):215–239.
107. Kontermann RE. Strategies for extended serum half-life of protein therapeutics. Current Opinion in Biotechnology. 2011;22(6):868–876.
108. Moreland LW, et al. Etanercept therapy in rheumatoid arthritis. Annals of Internal Medicine. 1999;130(6):478–486.
109. Mohler KM, et al. Design and biological properties of TNF receptor (p75)–Fc fusion proteins. The Journal of Immunology. 1993;151(3):1548–1561.
110. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. Nature Reviews Immunology. 2007;7(9):715–725.
111. Suzuki T, et al. The mechanism of immunoglobulin G recycling by FcRn. Pharmaceutical Research. 2010;27(12):2427–2439.
112. Ward ES, Ober RJ. Multitasking by FcRn: immunoglobulin transport and beyond. Nature Reviews Immunology. 2009;9(12):789–801.
113. Peters RT, et al. Bi-specific Fc fusion proteins for improved coagulation factor therapy. Blood. 2013;121(6):1101–1109.
114. Zhou Q, et al. Novel single-chain Fc dimer for improved pharmacokinetics. Journal of Controlled Release. 2016;224:281–289.
115. Sleep D. Albumin and human serum albumin fusion technology for half-life extension. Expert Opinion on Drug Delivery. 2015;12(5):795–812.
116. Osborn BL, et al. Albumin fusion for half-life extension. Journal of Controlled Release. 2002;83(2):213–226.
117. Andersen JT, et al. Recycling of albumin by neonatal Fc receptor (FcRn). Journal of Biological Chemistry. 2006;281(5):3169–3175.
118. Larsen MT, et al. Design and characterization of albumin-fusion proteins. Molecular Pharmaceutics. 2016;13(8):2484–2493.
119. Carter DC, Ho JX. Structure of serum albumin. Advances in Protein Chemistry. 1994;45:153–203.
120. Rosenstock J, et al. Albiglutide, a long-acting glucagon-like peptide-1 receptor agonist. The Lancet. 2014;384(9943):1349–1357.
121. Santagostino E, et al. Idelvion: recombinant factor IX albumin fusion in hemophilia B. Blood. 2016;127(14):1761–1769.
122. Lee J, et al. ABD-AFF fusion for synergistic half-life extension. Biomaterials. 2019;192:56–66.
123. Fang RH, Kroll AV, Gao W, Zhang L. Cell membrane coating nanotechnology. Advanced Materials. 2018;30(23):1706759.
124. Luk BT, Zhang L. Cell membrane-camouflaged nanoparticles for drug delivery. Journal of Controlled Release. 2015;220(Part B):600–607.
125. Hu CMJ, Zhang L. Nanoparticle detours to evade phagocytic clearance. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(27):10980–10985.

126. Papi M, et al. Cell membrane-derived vesicles for drug delivery. Advanced Drug Delivery Reviews. 2020;159:44–61.
127. Li J, et al. Engineering cell membranes for drug delivery. Biomaterials Science. 2021;9(3):703–715.
128. Hu CMJ, et al. Erythrocyte membrane-camouflaged nanoparticles. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(27):10980–10985.
129. Darville N, van Heerden M, Vynckier A, De Meulder M, Sterkens P, Annaert P, Van den Mooter G. Intramuscular administration of paliperidone palmitate extended-release injectable microsuspension induces a subclinical inflammatory reaction modulating the pharmacokinetics in rats. J Pharm Sci. 2014;103:2072–87.
130. Chamanza R, Darville N, van Heerden M, De Jonghe S. Comparison of the local tolerability to 5 long-acting drug nanosuspensions with different stabilizing excipients, following a single intramuscular administration in the rat. Toxicol Pathol. 2018;46:85–100.
131. Zuidema J, Kadir F, Titulaer HAC, Oussoren C. Release and absorption rates of intramuscularly and subcutaneously injected pharmaceuticals (II). Int J Pharm. 1994;105:189–207.
132. Medlicott NJ, Waldron NA, Foster TP. Sustained release veterinary parenteral products. Adv Drug Deliv Rev. 2004;56(10):1345–65.
133. McLennan DN, Porter CJH, Charman SA. Subcutaneous drug delivery and the role of the lymphatics. Drug Discovery Today. 2005;2:89–96.
134. Spanarello S, Ferla TL. The pharmacokinetics of long-acting antipsychotic medications. Curr Clin Pharmacol. 2014;9:310–7.
135. Shah JC, Hong J. Model for Long Acting Injectables (Depot Formulation) Based on Pharmacokinetics and Physical Chemical Properties. Aaps j. 2022;24(3):44.
136. Nielsen LL, Young AA, Parkes DG. Pharmacology of exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. Regul Pept. 2004;117(2):77–88.
137. Cauvin AJ, Peters C, Brennan F. Advantages and limitations of commonly used nonhuman primate species in research and development of biopharmaceuticals. In. The Nonhuman Primate in Nonclinical Drug Development and Safety Assessment; 2015. p. 379–395.
138. Darville N, Saarinen J, Isomäki A, Khriachtchev L, Cleeren D, Sterkens M, van Heerden M, Annaert P, Peltonen L, Santos HA, Strachan CJ, Van den Mooter G. Multimodal non-linear optical imaging for the investigation of drug nano-/microcrystal-cell interactions. Eur J Pharm Biopharm. 2015;96:338–48.
139. Owen A, Rannard S. Strengths, weaknesses, opportunities and challenges for long acting injectable therapies: Insights for applications in HIV therapy. Adv Drug Del Rev. 2016;103:144–56.
140. Gray V, Cady S, Curran D, DeMuth J, Eradiri O, Hussain M, Krämer J, Shabushnig J, Stippler E. In Vitro Release Test Methods for Drug Formulations for Parenteral Applications. In.Dissolution Technol 2018. p. 8 - 13.
141. USP-NF. USP<1001> In Vitro Release Test Methods for Parenteral Drug Preparations. https:// doi. usp. org/ USPNF/ USPNF_ M5433_ 02_ 01. html. USP. 2022 August, 19th.
142. S. C, K. BA. Current Updates on In-vitro Drug Release Testing of Long-Acting Injectables, https://w ww.americ anp harmace uti c alrevi ew.com/F eat ured-A rti cles/5 84542 -Curren t - Update s -on-I n - vitro- Drug- Relea se- Testi ng- of- Long- Acting- Injec tables/. 2022 August 19th, 2022.
143. Smith WC, Bae J, Zhang Y, Qin B, Wang Y, Kozak D, Ashraf M, Xu X. Impact of particle flocculation on the dissolution and bioavailability of injectable suspensions. Int J Pharm. 2021;604: 120767.
144. Kim Y, Park EJ, Kim TW, Na DH. Recent process in drug release testing methods of biopolymeric particulate system. Pharmaceutics. 2021;13(8):1313.

145. Dadhaniya TM, Sharma OP, Gohel MC, Mehta PJ. Current approaches for in vitro drug release study of long acting parenteral formulations. Curr Drug Deliv. 2015;12:256–70.
146. Andhariya JV, Shen J, Choi S, Wang Y, Zou Y, Burgess DJ. Development of in vitro-in vivo correlation of parenteral naltrexone loaded polymeric microspheres. J Control Release. 2017;255:27–35.
147. Simon A, de Almeida Borges VR, Cabral LM, de Sousa VP. Development and validation of a discriminative dissolution test for betamethasone sodium phosphate and betamethasone dipropionate intramuscular injectable suspension. AAPS PharmSciTech. 2013;14(1):425–34.
148. Marques MRC, Loebenberg R, Almukainzi M. Simulated Biological Fluids with Possible Application in Dissolution Testing. Dissolut Technol. 2011;18:15–28.
149. Barrett SE, Teller RS, Forster SP, Li L, Mackey MA, Skomski D, Yang Z, Fillgrove KL, Doto GJ, Wood SL, Lebron J, Grobler JA, Sanchez RI, Liu Z, Lu B, Niu T, Sun L, Gindy ME. Extended-Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention. Antimicrob Agents Chemother. 2018;62(10).
150. D'Souza SS, DeLuca PP. Methods to assess in vitro drug release from injectable polymeric particulate systems. Pharm Res. 2006;23:460–74.
151. Shen J, Burgess D. Accelerated in vitro release testing methods for extended release parenteral dosage forms. J Pharm Pharmacol. 2012;64:986–96.
152. Garner J, Skidmore S, Park H, Park K, Choi S, Wang Y. Beyond Q1/Q2: The Impact of Manufacturing Conditions and Test Methods on Drug Release From PLGA-Based Microparticle Depot Formulations. J Pharm Sci. 2018;107(1):353–61.
153. Forrest WP, Reuter KG, Shah V, Kazakevich I, Heslinga M, Dudhat S, Patel S, Neri C, Mao Y. USP Apparatus 4: a Valuable In Vitro Tool to Enable Formulation Development of Long-Acting Parenteral (LAP) Nanosuspension Formulations of Poorly Water-Soluble Compounds. AAPS PharmSciTech. 2018;19(1):413–24.
154. Bhardwaj U, Burgess DJ. A novel USP apparatus 4 based release testing method for dispersed systems. Int J Pharm. 2010;388(1–2):287–94.
155. Zolnik BS, Raton J-L, Burgess DJ. Application of USP Apparatus 4 and In Situ Fiber Optic Analysis to Microsphere Release Testing. In. Dissolution Technol. 2005. p. 11–14.
156. Chidambaram N, Burgess DJ. A novel in vitro release method for submicron-sized dispersed systems. AAPS PharmSci. 1999;1(3):32–40.
157. Liu Y, Sun Y, Sun J, Zhao N, Sun M, He Z. Preparation and in vitro/in vivo evaluation of sustained-release venlafaxine hydrochloride pellets. Int J Pharm. 2012;426(1–2):21–8.
158. Savaşer A, Esim O, Kurbanoglu S, Ozkan S, Ozkan Y. Current perspectives on drug release studies from polymeric nanoparticles. In; 2018. p. 101–145.
159. Kinnunen HM, Sharma V, Contreras-Rojas LR, Yu Y, Alleman C, Sreedhara A, Fischer S, Khawli L, Yohe ST, Bumbaca D, Patapoff TW, Daugherty AL, Mrsny RJ. A novel in vitro method to model the fate of subcutaneously administered biopharmaceuticals and associated formulation components. J Control Release. 2015;214:94–102.
160. Rawat A, Stippler E, Shah VP, Burgess DJ. Validation of USP apparatus 4 method for microsphere in vitro release testing using Risperdal Consta. Int J Pharm. 2011;420(2):198–205.
161. Zolnik BS, Leary PE, Burgess DJ. Elevated temperature accelerated release testing of PLGA microspheres. J Control Release. 2006;112(3):293–300.
162. Shen J, Burgess DJ. Accelerated in-vitro release testing methods for extended-release parenteral dosage forms. J Pharm Pharmacol. 2012;64(7):986–96.
163. Andhariya JV, Burgess DJ. Recent advances in testing of microsphere drug delivery systems. Expert Opin Drug Deliv. 2016;13(4):593–608.
164. Kang J, Schwendeman SP. Pore Closing and Opening in Biodegradable Polymers and Their Effect on the Controlled Release of Proteins. Mol Pharm. 2007;4(1):104–18.