LONG-ACTING INJECTABLE (LAI) SYSTEMS - CURRENT PROGRESS IN CHRONIC DISEASE THERAPY

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ABSTRACT

Long-acting injectable (LAI) systems are considered one of the greatest improvement in the mechanism of chronic disease treatment as this type of drug delivery system ensures controlled achievement of drug release with only one injection. They are mainly useful in the treatment of chronic illnesses like schizophrenia, HIV and cardiovascular disorders because the formulations clearly assist in increasing patient compliance, decrease in dosing frequency, and steady plasma drug levels. LAI systems employ a wide variety of formulation strategies to deliver both small molecules and biologics, such as polymeric microspheres, in situ forming depots, nanosuspensions and implants. The key component of these designs is biodegradable polymer that allow us to tune the release profile depending on physicochemical properties. Nevertheless, in the formulation stability, manufacturing, and regulatory challenges, which are still present, especially where peptide-based drugs and protein-based drugs are concerned. Nevertheless, future innovations and an increasing number of approved LAI therapies confirm their role in overcoming adherence gaps and introducing efficiencies into chronic diseases management.

Keywords: Chronic disease; Long-acting injectables; Polymeric microspheres; In situ forming depots; Nanosuspensions.

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1. INTRODUCTION

Long-acting injectable (LAI) systems are a new form of transformative pharmaceutical technology permitting extended and regulated release of medicines through a single injection [1]. These formulations have attracted more attention due to the fact that they help in enhancing patient compliance, varying dosing frequencies, and sustaining plasma drug levels, and this is especially important in the treatment of chronic disease conditions like schizophrenia, HIV and heart conditions [2]. As both therapeutic agents and formulation strategies, the vast range of LAIs includes polymeric microspheres, in situ forming depots, nanosuspensions, and implants, and has targeted the delivery of small molecules, peptides, and proteins of varied physicochemical traits [3].

The increasing disease burden related to chronic illnesses around the world creates the need to develop therapeutic approaches that maximize patient response and minimize issues related to daily dosing of medications [4]. As a case in point, antipsychotics LAI has transformed treatment outcomes in schizophrenia management in psychiatric term, improving clinical outcomes and quality of life by increasing medication compliance and reducing relapse [5]. At-inferior-command Similarly in infectious diseases, especially HIV, LAI antiretrovirals, specifically cabotegravir, are a promising alternative to daily small-molecule oral medicine, prolonging antiretroviral exposure to weeks to months by using their long half-lives and biocompatible nanosuspension-swelling technology [6]. Besides, recent studies support the formulation of LAI using popular medicines, including statins, to overcome adherence barriers in managing cardiovascular diseases and enhance pharmacokinetic profiles [7.] Polymer science and formulation technology is highly integrated into the design and development of LAI systems. Biodegradable polymers and in particular poly(lactic-co-glycolic acid) (PLGA) and polylactic acid (PLA) also are key materials in the construction of microsphere-based depots with either molecular weight, copolymer ratio, or end-

group chemistry having critical roles in drug release kinetics, stability, and encapsulation efficiency [8]. At the same time, in situ forming depots are an emerging type of LAIs with easy manufacturing procedures and delivery and avoiding reconstitution issues and producing customized release patterns by stimuli-responsive gelation during injection [9]. Furthermore, the injectability, biocompatibility and overall therapeutic performance of the formulation largely depend on the physicochemical character of the active ingredient in the pharmaceutical product, as well as the choice of the carrier [10].

Nevertheless, issues still remain in the production of robustness, sterilization methods, in vitro-in vivo correlation, and congruent clinical competent efficacy mainly in protein and peptide therapeutics, which are readily degraded throughout formulation operations [11]. The development pipeline is further complicated by regulatory and quality concerns which require advanced analytical techniques and an in-depth knowledge of the effects of polymers on drugs. However, the current size and growing number of products used clinically with LAI combined with continuous innovation highlights the need and importance of this technology in managing therapeutic gaps in chronic conditions [12].

2. OVERVIEW OF LAI SYSTEMS

2.1. Definition and classification of LAIs

Long-acting injectables (LAIs) are drug products that deliver the active drug substance over a prolonged period of time with only a single dosing event, hence increasing patient compliance with dose regimens and decreasing dosing frequency. They are extensively used in many fields of therapy, such as in the treatment of antipsychotics, HIV, and hormone therapies. LAIs are often divided according to their formulation technology, and their physicochemical character into aqueous or oily suspensions, emulsions, in-situ forming gels, and implants, each of which has unique properties and purposes [13].

2.2. Types of LAIs

2.2.1. Aqueous / Oily Suspensions

This is a widely used formulation in which the drug is suspended in an aqueous or oily vehicle which breaks up slowly after administering the injection. As an example, aqueous suspension-based LAIs could be discussed to treat HIV with nanosuspensions of cabotegravir [14].

2.2.2. Emulsions

These are two immiscible liquids in which one liquid has the dispersed drug in them. Emulsions allow controlled release of drugs through controlled drug diffusion and absorption of the drug vehicle [15].

2.2.3. In Situ Gels

These are injectable formulations whose phase transition is enabled after administration, e.g. a sol-gel transition caused by a change in temperature or media, and they form a depot that regulates drug release. Second-generation ISFDs using technologies such as BEPO (c) and FluidCrystal (c) are renowned as being simple to use and relatively easy to produce [16].

2.2.4. Implants

Solid or semisolid devices containing the drug are placed surgically or minimally invasively beneath the skin or into the muscle to deliver long-term drug release in weeks to months [17].

3. Key components of LAI formulations

3.1. Drug

A drug to be used in LAIs typically needs certain physicochemical characteristics (low aqueous solubility, in vivo and formulation stability, and compatibility with polymers and vehicles that maintain release) as the active pharmaceutical ingredient (API) [12].

3.2. Polymer

Biocompatible and biodegradable polymers including poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA) are widely utilized in LAIs particularly microsphere-based ones. These polymers affect important product properties such as release kinetics, encapsulation efficiency and biocompatibility. To produce customized release profiles, the properties associated with the build of the polymer, such as molecular weight, ending groups, and ratio between lactide and glycolide are crucial [18].

3.3. Vehicle

The matrix of formulation or vehicle can be aqueous system, oily vehicle, or a polymer solution which regulates drug outflow, stability, and injectability, and also patient acceptability. The presence of vehicles influences the physicochemical environment of the drug, its distribution and therefore pharmacokinetic behaviour following administration[1]. Collectively, the interaction between drug properties, polymer characteristics, and vehicle choice determine the performance of LAI systems, and optimal formulation should be developed through rigorous optimization to produce desired therapeutical results [19-20].

4. MECHANISM OF ACTION AND DESIGN CONSIDERATIONS OF LONG-ACTING INJECTABLE (LAI) SYSTEMS

The ultimate goal of the long-acting injectable (LAI) systems is to prolong the local effect by regulating the delivery of drugs in a depot created in the location of the injection. Depending on the formulation design, the various drug release processes actively involved are mostly diffusion, polymer degradation, osmotic pressure-driven release, or a combination of both [21]. Figure 1 shows the primary mechanisms of sustained drug release employed in long-acting injectable formulations.

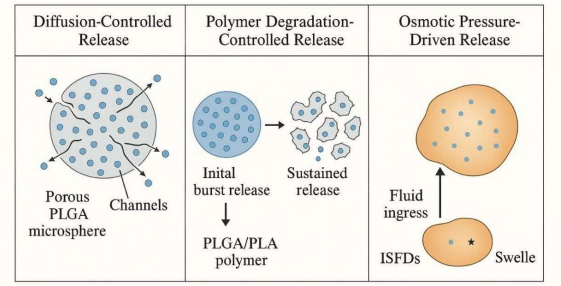

Figure 1. Mechanisms of Drug Release from long acting Injectable Drug Delivery Systems

4.1. Drug Release Mechanisms

4.1.1. Diffusion-Controlled Release

In drugs in suspension or polymer matrices that cannot degrade, the release of the drug is generally controlled more by diffusion of the drug molecules out of the depot into the surrounding tissue. This mechanism is greatly affected by porosity and particle size. As an example, porous poly(lactic-co-glycolic acid) (PLGA) microspheres show preferred and enhanced release kinetics without lag time, relative to nonporous counterparts; this results largely due to increased channel length when using a sponge-like 3D architecture of the polymeric material network [22].

4.1.2. Polymer Degradation-Controlled Release

Biodegradable polymers encompassing PLGA and polylactic acid (PLA) are the most common in LAIs as microsphere-based. These polymers are then degraded hydrolytically in a biological manner, and eventually wear down to get some enclosed drugs released. The degradation rate and associated release kinetics is directly predetermined by the molecular weight of the polymer, the ratio of the copolymer (lactide:glycolide), and the chemistry of the ends of the polymers [23]. Release profile of drugs contained within PLGA-based systems is subject to an initial drug burst as a result of surface-mediated drug diffusion, however sustained drug release can then be obtained as the polymer degrades and further drug is released in a Continuous manner [24].

4.1.3. Osmotic Pressure-Driven Release

Certain implantable LAIs function via osmotic mechanisms, where ingress of bodily fluids causes swelling or solvent exchange, thereby exerting pressure that drives drug release. In situ forming depots (ISFDs), such as BEPO® and FluidCrystal®, utilize this concept with polymer solutions that solidify upon injection due to solvent diffusion, forming a gel depot that releases drug as the polymer matrix solidifies and later degrades [25].

5. FACTORS AFFECTING PHARMACOKINETICS

The pharmacokinetic profile of LAIs is influenced by several design and biological variables:

5.1. Site of Injection

Intramuscular (IM) and subcutaneous (SC) routes are preferred for LAIs, but the degree of vascularization, tissue composition, and enzyme activity at the injection site impact drug absorption and depot erosion. For example, long-acting cabotegravir administered IM shows prolonged elimination half-life (~40 days) with predictable plasma levels suited for monthly to bimonthly dosing [26].

5.2. Depot Design

Particle size, porosity, polymer type, and drug loading modulate drug release kinetics. Porous PLGA microspheres provide enhanced encapsulation efficiency and faster onset of release compared to nonporous microspheres [1]. Depot morphology and density influence the surface area exposed to biological fluids, providing additional control over release rates [27].

5.3. Drug Properties

The physicochemical nature of the active drug (hydrophobicity, solubility, molecular weight) interacts with polymer and vehicle components to affect release. Hydrophobic drugs encapsulated in PLGA often benefit from sustained release, while hydrophilic peptides require tailored polymer

characteristics to preserve stability and control release [28].

5.4. In Vivo Environment

Local pH, enzyme presence, and immune responses can accelerate or retard polymer degradation and drug liberation, thereby altering pharmacokinetics [29].

6. BIOCOMPATIBILITY AND STABILITY

Ensuring biocompatibility and chemical/physical stability of LAI formulations during manufacturing and in vivo use is critical. Biodegradable polymers like PLGA are extensively studied and considered biocompatible due to their hydrolysis into lactic and glycolic acid, which enter natural metabolic pathways [30]. Nevertheless, encapsulated bioactive molecules, especially peptides and proteins, are susceptible to degradation caused by processing stresses (organic solvents, shear forces, temperature fluctuations) and long-term exposure within depots, potentially affecting bioactivity and immunogenicity [31]. Advances in gentle fabrication techniques and polymer chemistry aim to mitigate these stability challenges.

Injection site reactions are common considerations; while many LAIs exhibit minimal injection discomfort, the formation of localized depots may cause inflammation or irritation impacting patient compliance [32]. The chemical stability of drugs within polymer depots also depends on the microenvironment generated by polymer erosion, which may result in acidic conditions accelerating degradation. Thus, balancing polymer composition and drug formulation is essential to optimize both release characteristics and biocompatibility [33].

7. APPLICATIONS IN CHRONIC DISEASE MANAGEMENT

The applications and technologies of Long-Acting Injectable (LAI) systems in healthcare are shown in Figure 2. It highlights their role in managing schizophrenia, HIV, and chronic diseases through delivery platforms such as polymeric microspheres, nanosuspensions, and implants. The benefits of LAI systems include enhanced patient compliance, reduced dosing frequency, and sustained plasma drug levels.

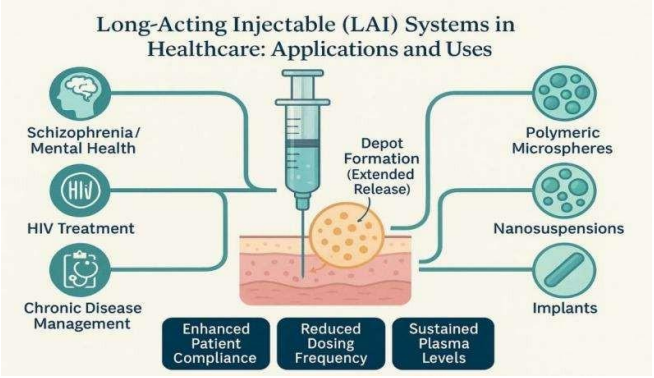

Figure 2. Long-Acting Injectable (LAI) Drug Delivery Systems: Technologies, Applications, and Benefits

7.1. Psychiatric Disorders

Long-acting injectable (LAI) formulations are widely used in the management of psychiatric disorders, particularly schizophrenia and schizoaffective disorder, where medication adherence is a major clinical challenge. LAIs improve adherence by reducing dosing frequency and maintaining stable plasma drug concentrations, which helps prevent relapse and rehospitalization [34]. Specifically, LAI second-generation antipsychotics demonstrate effectiveness in reducing psychotic symptoms and are increasingly accepted among early-phase schizophrenia patients when adequate education and support are provided. However, some clinical trials show mixed outcomes comparing LAIs to oral second-generation antipsychotics regarding relapse prevention. Overall, LAIs remain a critical tool in psychiatric care for improving symptom control and patient compliance [35].

7.2. Diabetes

While explicit examples of LAI drug delivery systems for diabetes from the referenced articles are limited, the development of long-acting injectables for chronic conditions like diabetes is an active area of research aimed at improving patient adherence and glycemic control. By extending the dosing intervals of insulin and other peptide-based therapeutics through polymeric or in situ depot formulations, LAI systems have the potential to address the challenges of daily injections, though clinical translation and commercial products are still evolving [36].

7.3. HIV/AIDS

LAI formulations have significantly advanced the treatment and prevention of HIV/AIDS by offering alternatives to daily oral antiretroviral therapy. The long-acting injectable

nanosuspension of cabotegravir, a potent integrase strand transfer inhibitor, enables monthly or bi-monthly intramuscular dosing, facilitating sustained plasma drug concentrations suitable for both maintenance therapy and pre-exposure prophylaxis [37]. Complementary agents such as rilpivirine, formulated similarly as nanosuspensions, are combined with cabotegravir to form two-drug regimens with improved adherence and reduced side effects. Clinical studies demonstrate these LAI regimens are noninferior to daily oral therapy and may reduce HIV stigma and treatment fatigue. Challenges include injection site reactions, management of residual drug exposure after discontinuation, and ensuring broad patient access [38].

7.4. Tuberculosis

Although the referenced articles do not focus specifically on LAI applications for tuberculosis, the principles of sustained-release injectable depot systems developed for other chronic diseases hold promise for tuberculosis therapy, where long treatment durations and adherence issues pose significant barriers [39]. PLGA-based microspheres and in situ forming depots could be adapted to achieve prolonged antimicrobial exposure, reducing dosing frequency and improving therapeutic outcomes [40].

7.5. Oncology, Pain, Hormonal Disorders

LAI technologies are increasingly utilized in oncology for sustained delivery of chemotherapeutics and hormonal agents to improve efficacy and reduce systemic toxicity. Similarly, long-acting formulations are developed for pain management to provide continuous analgesia, enhancing patient comfort and compliance. Depot formulations are also appropriate in hormonal disorders, eg, ELIGARD(r) for prostate cancer [41]. The invention of polymer science, specifically to biocompatible and biodegradable polymers such as PLGA, and in situ forming depot technology, such as that represented by BEPO and FluidCrystal, has enabled these LAI formulation advances, by supplying controlled release and patient convenience [42].

8. CURRENT FDA-APPROVED LAI PRODUCTS [43-48]

Table 1. List of recently FDA approved LAI products

Drug	Indication	Polymer/Vehicle & Formulation	Duration	Company / Sponsor	Year Approved
Risperdal Consta	Schizophrenia, Bipolar I Disorder	PLGA microspheres	Every 2 weeks	Janssen	2003
Invega Sustenna	Schizophrenia, Schizoaffective disorder	Aqueous suspension of paliperidone palmitate	Monthly	Janssen	2009
Invega Trinza	Schizophrenia	Paliperidone palmitate depot injection	Every 3 months	Janssen	2015
Invega Hafyera	Schizophrenia (maintenance therapy)	Paliperidone palmitate (extended dosing formulation)	Every 6 months	Janssen	2021
Abilify Maintena	Schizophrenia, Bipolar I Disorder	Aqueous suspension of aripiprazole monohydrate	Monthly	Otsuka Pharmaceutical / Lundbeck	2013
Aristada	Schizophrenia	Lipid-based prodrug (aripiprazole lauroxil) suspensions	4 to 8 weeks	Alkermes	2015
Vivitrol	Opioid and Alcohol Dependence	PLGA microspheres (naltrexone)	Monthly	Alkermes	2006
Bydureon	Type 2 Diabetes Mellitus	PLGA microspheres (exenatide extended-release)	Weekly	AstraZeneca (originally Amylin/BMS)	2012

		release suspension)			
Lupron Depot	Prostate Cancer, Endometriosis, Precocious Puberty	PLGA microspheres (leuprolide acetate)	1 to 6 months	AbbVie	Since 1989
Zoladex	Prostate & Breast Cancer, Endometriosis	Biodegradable implant (goserelin acetate implant)	1 or 3 months	AstraZeneca	1989
Sublocade	Opioid Use Disorder	ATRIGEL delivery system (polymer-based depot of buprenorphine)	Monthly	Indivior	2017
Perseris	Schizophrenia	ATRIGEL delivery system (risperidone)	Monthly	Indivior	2018
Cabenuva (Cabotegravir + Rilpivirine)	HIV-1 Treatment	Crystalline nanoparticle suspension	Monthly or every 2 months	ViiV Healthcare (GSK)	2021
Cabotegravir Long-Acting (CAB-LA)	HIV-1 Pre-exposure Prophylaxis (PrEP)	Long-acting nanoparticle injectable suspension	Monthly or bimonthly	ViiV Healthcare	2021

9. ADVANCES IN FORMULATION TECHNOLOGIES

The development of advanced formulation technologies has significantly expanded the range and performance of long-acting injectable (LAI) systems, allowing better patient compliance, dose release kinetics, and dose scheduling of chronic conditions. Important developments have been made in the following areas:

9.1. Microspheres and Nanospheres (e.g. PLGA-Based Systems)

Poly (lactic-co-glycolic acid) (PLGA) microspheres and nanospheres form one of the underlying technologies in LAI formulations, because they are biodegradable and biocompatible, and they can encapsulate a broad variety of therapeutic agents, such as small molecules, peptides, and proteins. Microsphere production methods, including the new and improved double emulsions, coacervation, and spray drying and highly developed microfluidics, permit optimal control of particle size distribution, drug incorporation and release characteristics, reduce the time of burst release, but permit a period of weeks or months of sustained release deliver [49]. A more recent advance has been the use of soybean lecithin in entrapment and controlled release of hydrophilic proteins into hydrophobic PLGA matrices, with a huge increase in payload and retention of bioactivity of protein therapeutics [50]. Moreover, the historical challenges of protein denaturation under PLGA systems have been addressed by stabilization approaches, including complexation with zinc and microenvironmental buffering of pH in the presence of antacid excipients that have expanded the practicality of biologics in injectable depots [51]. The regulatory implications and quality-by-design (QbD) strategies have also optimized the properties of the PLGA formulations in terms of associating the polymer molecular weight, lactide-to-glycolide ratios, end group chemistries with in vivo pharmacokinetics and bioequivalence, lending potent product development [52].

9.2. In Situ forming Gels and Implants

In situ forming injectable injectable gels and implants are made of biodegradable polymers or polymer solutions, which are introduced into the body in a liquid form, flowing to achieve a semi-solid or solid depot when injected. This change can usually be activated by a temperature, pH, or a solvent change, allowing minimally invasive administration followed by prolonged release. Examples of this technology include systems such as the ATRIGEL platform which is an in situ depot formed by a polymer matrix that has the drug encapsulated within, such as formulations, Sublocade (buprenorphine) and Perseris (risperidone) [53]. Recent developments in hydrophobic injectable polymers, such as aliphatic polyesters and polyanhydrides, have achieved solvent-free pasty or liquid biomaterials that predictably degrade without incurring any toxic

side effects (they also enable the localized drug or tissue regeneration) [54]. These systems allow less volume of injection, less surgical implant and better control of the drug release kinetics by changing composition and formulation of polymers.

9.3. Long-Acting Injectables based on Lipids

LI-based LAI formulations and, more specifically, antiretroviral therapy have opened several new treatment paradigms, taking advantage of the distinctive physicochemical characteristics of drugs like rilpivirine and cabotegravir. The drugs establish crystalline nanoparticle suspension with high drug loading and aqueous stability making injection volumes relatively low and monthly or bimonthly dosage intervals possible [55]. Lipid prodrug approaches, such as the aripiprazole lauroxil suspension (Aristada), leverage enzymatic hydrolysis of lipid-conjugated prodrugs to achieve sustained release that extends dosing intervals from weeks up to two months [56]. The formulation of such lipid-based nanoparticles entails optimization of particle size, crystallinity, and stabilization to maximize depot residence time and bioavailability while reducing local adverse reactions. Additionally, lipid excipients contribute to improved drug solubility and bio-distribution, enhancing pharmacokinetic profiles critical for chronic infectious diseases and psychiatric conditions [57].

9.4. 3D Printing and Injectable Devices

Emerging additive manufacturing technologies, particularly 3D printing, are being explored to fabricate customized, complex LAI depot geometries and injectable devices tailored to individual patient needs and novel drug delivery kinetics. Although still in early translational stages, 3D printing enables precise control over implant shape, porosity, and multilayer construction, which can modulate drug release profiles and mechanical properties suited for sustained local or systemic delivery [58]. Combined with injectable microsphere or hydrogel formulations, 3D-printed devices promise to integrate structural support with controlled drug release, offering versatility beyond conventional spherical depot injections. Innovations in this area dovetail with the development of smart injectable devices that incorporate sensors or responsive elements to adaptively control dosing or provide real-time monitoring, broadening the therapeutic impact of LAI modalities [59].

10. CHALLENGES AND LIMITATIONS

10.1. Challenges and Limitations of Long-Acting Injectable (LAI) Systems

Long-acting injectable systems have revolutionized the management of chronic diseases by enhancing levels of compliance and treatment outcomes. Nevertheless, in spite of these benefits, there are still several challenges and limitations in their development, production, and clinical application that influence the overall implementation [60].

10.2. Injection Site Reactions

Among the most reported side effects related to the use of LAI, injection site reactions (ISRs) are also considered as a barrier to patient acceptance and maintenance. Such responses can take the form of pain, edema, erythema, and/or nodules or induration at the injection site and are principally a local inflammatory reaction to the injected depot or the excipients. As an illustration, when using long-acting antiretroviral formulations, including rilpivirine nanosuspensions, there is evidence of satisfactory systemic tolerability yet elicit injection site discomfort issues, which can be a barrier to patient adherence to HIV prevention and treatment [61]. On the same note, localized injection site pain and swelling have been seen in antipsychotic LAIs, as well; involving risperidone and aripiprazole formulations; however, these are mostly mild to moderate [62]. Minimizing ISRs involves optimizing formulation viscosity, particle size, injection volume, and administration technique, yet interindividual variability and local immune responses remain challenging to predict and fully control.

10.3. Dose Dumping

Dose dumping, defined as the rapid, unintended release of the drug from the depot, posing risks of toxicity or treatment failure, is a critical safety concern in LAI systems. Controlled and predictable release is mandatory for sustained therapeutic plasma levels without peaks that cause adverse events 63. However, the physicochemical instability of some drugs in polymeric matrices, incomplete encapsulation, or manufacturing inconsistencies may lead to an initial burst release or loss of controlled kinetics. PLGA-based microsphere systems are particularly susceptible to burst release phenomena if polymer degradation rates or matrix porosity are not finely tuned [64]. Several formulation strategies, such as complexing proteins with stabilizing agents, coating microspheres, or employing hybrid polymers, have been employed to mitigate this risk [65]. Nevertheless, failure to address dose dumping can compromise drug safety, limiting regulatory approval and clinical acceptance.

10.4. Manufacturing Scale-Up

Scaling up from laboratory or pilot scale to commercial manufacturing of LAI products represents a multifaceted challenge that encompasses reproducibility, quality control, and process robustness. The manufacturing route for PLGA microspheres or nanosuspensions involves sensitive steps such as emulsification, solvent removal, lyophilization, and sterilization, all of which significantly influence particle size distribution, drug loading, and release profiles [66]. Variations in polymer molecular weight, lactide-to-glycolide ratios, and subtle processing parameter shifts can cause batch-to-batch variability, impacting clinical efficacy and safety. Moreover, handling of organic solvents and maintaining aseptic conditions increase complexity and cost. The highlighted difficulty in protein and peptide encapsulation, wherein biomolecule conformational integrity must be preserved during manufacturing, further complicates scale-up [67]. Regulatory agencies require thorough characterization, validated in vitro release testing, and demonstration of bioequivalence for scale-up batches, often demanding extensive resources and iterative optimization [68].

10.5. Regulatory Hurdles

Regulatory approval of LAI products is challenged by the complexity of their formulation and the need for rigorous demonstration of safety, efficacy, and quality. Regulatory authorities such as the FDA mandate a comprehensive understanding of the release mechanisms, polymer biodegradation, pharmacokinetics, and potential immunogenicity [69]. The complex interplay of drug-polymer interactions and their in vivo performance often requires application of Quality by Design (QbD) principles and extensive in vitro-in vivo correlation studies. Additionally, generic development of PLGA-based LAIs is particularly difficult due to proprietary polymer characteristics and manufacturing processes, necessitating advanced analytical techniques and formulation consistency documentation [70]. Proteins and peptide-based LAIs face even greater hurdles due to their inherent instability and sensitivity to processing, requiring innovative approaches in formulation and non-traditional sterilization methods, which are still under active development and regulatory scrutiny [71]. Post-market pharmacovigilance is also critical, especially regarding injection site reactions and rare adverse events that may arise with long-term depot presence.

11. REGULATORY & MARKET LANDSCAPE

11.1. EMA & FDA Perspectives on LAIs

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) appreciate the dramatic clinical benefits associated with long-acting injectable systems, especially in chronic illnesses like schizophrenia, HIV, and endocrine diseases. The regulation in LAI formulations has allowed innovation with the FDA historically granting several approvals since the inception of LAI-based products twenty years ago. The FDA has authorized at least 13 long-acting injectable antipsychotics to treat schizophrenia in just the last seven years (2008-2024), and there is a profound commitment to broadening therapeutic opportunities with better adherence and patient outcomes [72]. Regulatory requirements of the FDA prioritize the characterization of the polymer/drug interactions, bioequivalence testing, and in vitro/in vivo correlation studies of most common LAI-related polymer systems including PLGA to ensure product quality and predictable pharmacokinetics. The FDA has also put funding into research programs to generate new tools and methodology designed to accommodate the complex physicochemical and biological dynamics of LAI, with the goal of simplifying generic development and lifecycle of such products [73].

In the same way, the EMA will promote a quality-by-design (QbD) process of LAI development, fostering good scientific knowledge of release mechanism and polymer biodegradation kinetics. Such a regulatory approach guarantees that LAIs can show uniform efficacy and safety, especially due to the risk of dose dumping or immunogenicity during prolonged exposures to the polymers. EMA also embraces intensive directions to new LAI molecular products and combination drug products with long-acting antiretroviral agents, with precarious consideration of benefit-significance bravura in the plant of illness, with acute profusion. Both agencies will want strong clinical trial data with evidence of sustained efficacy, injection site reactions that can be managed, and unconfused safety profiles in order to be approved [74].

11.2. Market Trends and Demand

International LAI medicine market has continued to grow significantly, as evident in the increasing prevalence of chronic diseases characterized by low adherence to medication and in which achieving steady plasma levels of the drug implies improved clinical response. A significant proportion is in psychiatric LAIs particularly those of schizophrenia and bipolar disorder: the number of these is increasing since newer formulations can permit more convenient dosing frequency, biweekly up to each six months At the same time, in the field of infectious diseases, there have been breakthroughs, including long-acting injectable

antiretroviral therapy (ART) to treat HIV and to prevent HIV (pre-exposure prophylaxis; PrEP), including with cabotegravir and rilpivirine nanosuspensions, which allow monthly or every two months to dosing and improve adherence and decrease risk of resistance associated with inadequate oral combinations [75].

Further still, endocrines (e.g. leuprolide, goserelin) have long-established markets complemented by continuous innovations, in peptide, protein based LAIs in diabetes, and osteoporosis with PLGA-based depots being very beneficial to patient compliance. The improvement in technology with nanoparticle suspensions, lipid-based prodrugs, and in situ forming depots have increased the number of products offered which has also increased market coverage under LAI. On a demographic level, the growing populations of the aged and the rising burden of chronic diseases drive the demand in a globalized world, which makes LAIs economically feasible as it causes a reduction of hospital visits and enhances therapeutic compliance [76]. Another trend is more interest in personal medicine using 3D printing and injection-aided device, which will suitably cope with patient variations in reaction and dosing.

11.3. Patent Landscape

Patent coverage of LAIs can be very nuanced and sometimes includes multiple layers related to the active pharmaceutical ingredient (API), delivery vehicle (e.g., using polymers such as PLGA), method of manufacturing, structure of formulations. Some core patents covering PLGA polymers, coating technologies, and microencapsulation technologies expired or will in the near future, meaning that generic entrants are possible but also that there is concern over bioequivalence since product performance can be highly solution dependent on minor manufacturing changes [12]. Innovative patents now focus on novel polymer blends, prodrug conjugates, nanoparticle suspensions, and advanced delivery technologies such as ATRIGEL in situ forming depots [13].

In the area of antipsychotics, companies have extended exclusivity by patenting specific extended-release formulations, prodrug versions, or dosing regimens that improve adherence and reduce injection frequency, as seen with paliperidone palmitate (Invega Trinza and Hafyera) and aripiprazole lauroxil (Aristada). Similarly, in HIV treatment, patent portfolios cover crystalline nanoparticle suspensions of cabotegravir and rilpivirine, along with their co-formulation and dosing schedules, contributing to sustained market exclusivity despite generic pressure [77]. Patent strategies increasingly incorporate process patents and device-related intellectual property, such as injection delivery systems and reconstitution technologies, providing additional competitive barriers and opportunities for innovation.

12. FUTURE DIRECTIONS

12.1. Future Directions in Long-Acting Injectable (LAI) Systems

The future of LAI systems is poised to incorporate advanced technologies and personalized approaches to overcome current therapeutic limitations and better address patient-specific needs in chronic disease management.

12.2. Personalized Long-Acting Injectables

Personalized LAIs are expected to revolutionize chronic disease therapy by tailoring release profiles, dosage, and formulation to individual patient characteristics such as metabolism, disease severity, and comorbidities. Integration of advanced pharmacogenomics and biomarker data can inform the design of LAIs that optimize therapeutic index while minimizing side effects. For example, in psychiatry, personalized dosing intervals and polymer matrix compositions may improve adherence and clinical response in treatment-resistant schizophrenia, as suggested by the evolution of diverse antipsychotic LAIs approved recently [78]. Such patient-centric design will likely be supported by machine learning algorithms predicting drug release kinetics and patient outcomes.

12.3. Smart Injectables with Stimuli-Responsive Release

Injectable depots responsive to specific stimuli represent a highly promising direction for controlled and on-demand drug release. Stimuli-responsive hydrogels and polymeric systems that alter their physical or chemical properties in reaction to temperature, pH, redox environments, enzymatic activity, or external triggers such as light or magnetic fields enable spatiotemporal control of drug delivery. Current developments in stimuli-responsive injectable hydrogels offer platforms whose sol-to-gel transitions can enable targeted and time-specific release of payloads in vivo to boost therapeutic effects and limit systemic exposure [79]. The systems are promising to deal with disease progression or physiological alterations by dynamically responding to adjust drug release.

12.4. Implantable and Biodegradable Systems

Polymers like PLGA and PLA still form the base of any implant and biodegrade based

implants are still trying to improve with advancements in polymer chemistry, microstructure and fabrication techniques enhancing predictability of release and biocompatibility to serve the purpose of LAI better. The possibilities going forward are implants or multifunction implants, with features that include drug depots and sensor/feedback systems that can monitor therapeutic response in real-time. These combined implantable systems would have the ability to adjust the medication delivery in real-time based on biomarker values or remote control, improving personalized medicine. In addition, second-generation in situ forming depots that are simpler to administer and less invasive in procedure but based on technologies such as ATRIGEL and BEPO are likely to increase clinical use [58].

12.5. Combination Therapies and Dual Depot Systems

Combination LAI systems that provide two or more therapeutic agents sequentially or together are gaining growing interest. This model is pertinent particularly in multi-mode diseases that necessitate multi-modal interventions like HIV, where long-acting antiretroviral implementation combines integrase inhibitors with non-nucleoside reverse transcriptase inhibitors to initiate synergistic versatile suppression [80]. Dual depot systems offer the possibility of controlling the release rates and dosing frequencies of individual agents independently of each other, improving efficacy, decreasing the frequency of injection and systemic toxicity. Also, combinations can consist of small molecules to biologics or a drug to immunomodulators, opening the door to novel treatment paradigms. Recent innovations in co-formulation of nanoparticles and depot architecture layering promote rational development of such combination LAIs [81].

13. CONCLUSION

Long-acting injectable (LAI) systems have become part of a transformation in the treatment of chronic diseases, providing substantial deliverables on patient compliance rates, efficacy and outcomes in quality of life. The major conclusions and findings of the reviewed literature report consistent growth and range of FDA approved LAI products in the fields of psychiatry, infectious diseases, endocrinology, and addiction medicine. Specifically, the introduction of 13 different long-acting injectable antipsychotics with schizophrenia between 2008 and 2024 represents a landmark step in customizing long-acting and effective remedies that enhance the ability to prevent relapses and favorable clinical measure successes. Moreover, the development of biodegradable polymer microspheres, particularly those made of PLGA/PLA, has enabled the delivery of both small molecules and sensitive biologics (peptides and proteins) in a controlled way, notwithstanding the inherent difficulties of production and stability.

Innovative formulation platforms, including in situ forming gels, lipid-based nanosuspensions and stimuli-responsive hydrogel, are actively being developed and further expand on the promise of LAIs through the potential of dose sparing, less invasive administration and on-demand spatiotemporal control of drug release. Within the field of infectious diseases, the introduction of long-acting HIV-medication prevention and treatment such as cabotegravir and rilpivirine nanosuspension, is an interpretation of how LAIs overcome the most significant obstacles to medication adherence, lowering the risks of viral transmission and the development of resistance. Trends in the market are associated with increased demands due to demographic changes and high chronic illness burden, whereas regulatory bodies like FDA and EMA focus more on strict quality controls, bio-equivalence, and innovative product characterization to guarantee steady performance in a clinical setting.

The need for LAIs is explained by the fact that they reduce the overall problem of nonadherence to medications pervasive across conditions that cause chronic conditions that are the main determiners of poor health outcomes. LAIs decrease relapse rates and clicks to the hospital and treatment failures due to continuous exposure to therapeutic levels with less frequent dosing. Moreover, such systems enable the implementation of the patient-centric care model, by avoiding daily pills load and providing discreet, controlled drug administration.

In the future, clinical integration and research should place more emphasis on optimizing LAI drug delivery by personalizing therapies by incorporating the concept of pharmacogenomics and predictive drug release models to maximize individualized dosing frequencies. Biocompatible, injectable, actuatable, and stimuli-responsive smart polymers, which have the potential to selectively control drug release in a physiological environment, are also being developed in an attempt to further bridge therapeutic windows, and reduce side effects. In addition, development of real-time monitoring and adaptive dosing opportunities through biodegradable implantable devices interfaced with sensor technologies can contribute mightily to the management of chronic diseases. Lastly, combination treatments with two or more-drug depots have the potential to be an efficient solution to complex disease mechanisms using ease of administration as a relief to resource-constrained settings.

In summary, although significant obstacles remain to be surmounted, such as difficulties in formulation and tolerability at injection sites, as well as scale-up and regulatory issues the current interdisciplinary advances discussed in this paper are encouraging the increased use of LAIs in the therapy of chronic diseases. The evolution of these systems, in the fashion consistent with the principles of precision medicine and patient-centered design, will become the key to optimizing their therapeutic value and their availability.

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