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Review Article

Long-Acting Injectable Drug Systems (LAI) – New Generation Therapies

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ABSTRACT

Long-acting injectable (LAI) drug delivery systems represent a considerable advance in controlled and sustained release therapy to address the limitations of traditional oral drug administration as well as short-acting parenteral drug delivery. Global therapeutic challenges, especially chronic diseases that require treatment for a lifetime, underscores the importance of better clinical adherence, improved pharmacokinetic properties, and reduced dosing frequency, all key advantages of LAI depot formulations. LAI depot formulations can effectively maintain sustained plasma concentrations for weeks to months based on controlled release of the drug, which occurs through mechanisms such as polymer degradation, drug diffusion, osmosis or dissolution of nano-carriers. Innovation in this drug delivery paradigm includes several biodegradable polymers including poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL) and polylactic acid (PLA), lipid nano-carrier delivery systems, drug nanocrystals or nano-suspensions, long-acting prodrugs, and in situ forming depots. Improved injectable nanosuspension formulations like Cabotegravir LA and Rilpivirine LA can extend dosing intervals for HIV prevention and treatment, as well as controlled release systems like Risperidone and Lupron Depot microsphere systems based on polymer erosion release. Newer smart depots developed responsive to pH, temperature, and enzymatic triggers, 3D printed scaffolds, and LAI platforms for mRNA vaccines point to important advances towards the goal of precision medicine. Modern LAIs are often modelled with mathematical release models including zero-order, Higuchi, and Korsmeyer-Peppas kinetics to predict drug diffusion and polymer erosion release behavior. Long-acting injectables (LAIs) are now entering areas apart from those associated with infectious diseases, neuro-psychiatric disorders, oncology, contraception, and opioid dependence. Regulatory emphasis has shifted to include

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requirements for sterile manufacturing conditions, injectability, quality assessment, in vitro-in vivo correlation (IVIVC) and bioequivalence for complex generics. Future developments will likely focus on medication that has ultra-long-acting dosing (>6 months) values, IV formulations driven by artificial intelligence, and the methodology to support depot-based delivery for biologics, vaccines and cell therapy.

INTRODUCTION

The implications of chronic and refractory diseases like HIV/AIDS, schizophrenia, diabetes, hormone-dependent cancers, and opioid dependency present major unmet needs regarding sustained pharmacotherapy and long-term medication adherence. Inadequate adherence to daily treatment is generally linked to therapy failure, drug-resistant crises, hospitalization events, and cost burdens. Conventional oral and short-acting injectable (injections with short half-lives) dosage forms are often subject to variability of plasma concentration, frequent dosing, patient burden, and reliance on their gastrointestinal or liver metabolism. The necessity to overcome these drawbacks has led to the development of long-acting injectable (LAI) systems as precision drug delivery devices to provide therapeutic levels over long periods ranging from weeks to months. The application of LAIs in precision medicine is based on the principles of PK optimization and controlled PD response to minimize peak–trough variability, decrease monitoring, have better adherence, and provide patient convenience. LAIs produce depot through novel controlling release technologies including diffusion-modulated polymeric carriers, enzyme-triggered prodrugs, nano-suspension dissolution, and in situ-formed phase change systems. Moreover, investigation of LAIs across IM, SC, IV and specialized intravitreal consolidates targeted anatomical distribution and improve clinical use. The past, present and future development trajectory of injectable depots began in the 1950s with the emergence of early oil-based suspensions and hormone depots, followed by polymer-based microsphere technologies in the 1980s that led to early products with depot formulations such as leuprolide and risperidone microspheres. The field has now moved into engineering nano-formulations, biodegradable polymer chemistry, lipidic carrier systems, and injections of solid drug nanoparticle suspensions as the background for modern LAI therapeutics. The current generation of products now includes stimuli-responsive hydrogels, ultra-long-acting depot scaffolds, and depot-based platforms for mRNA and gene therapies. The pharmaceutical market for LAI systems will continue to grow, and be validated with greater clinical use, the evolution of regulatory pathways, and industry investment. The market for LAI formulations has been influenced by the demand for decreased dosing frequency, adherence in the "real-world" execution of treatment paradigms, and now long-acting biologics in the personalized treatment space. LAI systems are quickly becoming a fundamental aspect of the future of pharmacotherapy and drug delivery systems with precision dosing paradigms. [1-2]

1. SCIENTIFIC AND TECHNOLOGICAL BASIS OF LONG-ACTING INJECTABLE SYSTEMS:

Having the variable sub types are as included below in it which follows as under given.

1.1 Pharmacokinetic & Pharmacodynamic Principles:

Long-acting injectable (LAI) depot systems are purposefully designed to achieve controlled and sustained exposure of therapeutic molecules through modulation of release kinetics at the administration site and systemic absorption pathways. LAI pharmacokinetics (PK) are

primarily determined by their mechanism of depot formation, the physicochemical properties of the drug, and the anatomical features of the injection route. The principal mechanistic pathways affecting depot release include:

Diffusion-Controlled Release:

Drug molecules are released from a polymeric matrix or lipid depot via diffusion, which generally occurs along concentration gradients. This mechanism is more commonly observed in microspheres, hydrogels, and liposomal depots wherein matrix porosity, tortuosity, and water uptake all affect the rate of diffusion.[3]

Degradation-Controlled Release:

Biodegradable polymers (e.g., PLA and PCL) will undergo hydrolytic or enzymatic erosion forming hydrolysis and cleavage of the polymer chain, which limits exposure of the encapsulated drug. This mechanism is often used in microsphere formulations (e.g., risperidone, leuprolide depots).

Swelling-Controlled Release:

Hydrophilic networks swell when hydrated, thereby affecting the route of diffusion, while also promoting drug motility. Thermo-sensitive gels and stimuli-responsive hydrogels often utilize this behaviour.

Release Dependencies on Osmotic Pump Mechanisms of Delivery:

Release is from osmotic pressure gradients in the implant or nanosuspension, which promote drug release through controlled orifices or porous matrices.[4]

Administrative Route Effect on Bioavailability: The rate at which a depot absorbs will vary by the anatomical environment:

• **Intramuscular (IM)-** rich vascularity allows consistent absorption of the drug systemically and allows for larger volumes to be injected.

• **Subcutaneous (SC)-** slower uptake because of less perfusion, but better patient acceptability.

• **Intravenous (IV) -** depot suspensions rely on the particle dissolution rate which will be controlled if nanoparticles are used.

• **Intravitreal -** generally for retinal therapies relies on diffusion through the vitreous gel and clearance routes.

Mathematical Models for Passive and Active Release Kinetics:

The quantitatively predict pharmacokinetic (PK) release from the depot through established kinetic models:

• **Zero-order model** assumes a constant rate, consistent with the goal of constant plasma concentration

• **Higuchi Model** drug release proportional to the square root of time and is related to diffusion-controlled depots.

• **Korsmeyer-Peppas Model** descriptive characterizes anomalous (combined diffusion + erosion).

These mathematical models allow for the integration of PK-PD to improve a physician's optimization of dose interval, depot size, particle characteristics, and predictability in clinical response of LAIs to affect a patient's quality of life with less contrast than oral delivery. Modelling provides critical information that informs in vitro in vivo at the time of regulatory approval and/or provides the FDA with for success in examining equivalence in generic LAIs. [5-6]

1.2 Drug Properties Governing LAI Suitability:

The process of selecting a drug candidate for long-acting injectable (LAI) formulation involves significant assessment of physicochemical characteristics, as well molecular stability, as well as biopharmaceutical characteristics which determine depot duration and sustained systemic availability. Important drug characteristics affecting suitability for LAI development are:

Physicochemical Properties

• **Solubility:** The preference will always gravitate towards drugs with low aqueous solubility. The reason for this is that they provide slow dissolution-controlled release and minimal burst, if any, due to the limited rate of dissolution. Easily soluble compounds may require conversion into salts, formation of complex, or change into a prodrug to prolong the dissolution phase.

• **Lipophilicity (log):** Moderately to highly lipophilic drug candidates are desirable for depot retention and prolonged dilution through tissue membranes.

• **pKa:** Ionization affects solubility, crystallinity, partitioning, and depot medium interactions.

• **Particle Size and Morphology:** The use of engineered nanoparticles, microparticles, or crystalline suspensions offer control over surface area-dependent dissolution kinetics and depot duration.

• **Chemical and Physical Stability:** Stability against hydrolysis, oxidation, polymorphic transitions, and agglomeration is key to ensuring release is predictable.

Formulation Dependent Modifications to Release

Drug release from depot system may be modified by the following,

• Polymer choice (PLGA, PCL, PLA composition, and molecular weight modifying rate of degradation).

• Surface modification and use of stabilizers to prevent agglomeration.

• Solvent systems that permit in-situ solidification.

• Lipid carrier that may affect diffusion and membrane interactions.

• Additives that control viscosity and depot structure. [7-8]

Interrelationships Regarding the Conversion Rate of Prodrugs

Prodrug approaches become viable only when native molecules are incapable of providing inherently long-acting properties. Drug delivery via esterification or a link to lipids can provide the benefit of depot formation through lower solubility, and predictable conversion of prodrug to active drug with an enzymatic release profile over time. The success of the long-acting injectable formulation of cabotegravir esters is an example of this rationale, as it effectively leads to sustained drug release through gradual cleavage of the cabotegravir esters by tissue esterases eventually yields active cabotegravir. Likewise, as with the characterized conversions of prodrugs, optimization of both the physicochemical and formulation properties will allow for stability in PK properties, lower the potential for an initial burst, minimize the risk of dose dumping, and longer dosing intervals aligned with pharmacotherapeutic objectives.[9]

2. ADVANCED TYPES AND STRATEGIES IN LAI FORMULATION:

Having the variable sub types are as included below in it which follows as under given.

3.1 Biodegradable Polymer-Based Systems:

Biodegradable polymer-based long-acting injectable formulations are among the most characterized and clinically established options to provide sustained release of drug delivery. These systems utilize polymers that exhibit predictable hydrolytic or enzymatic degradation and allow for controlled release of encapsulated drug payloads over months.

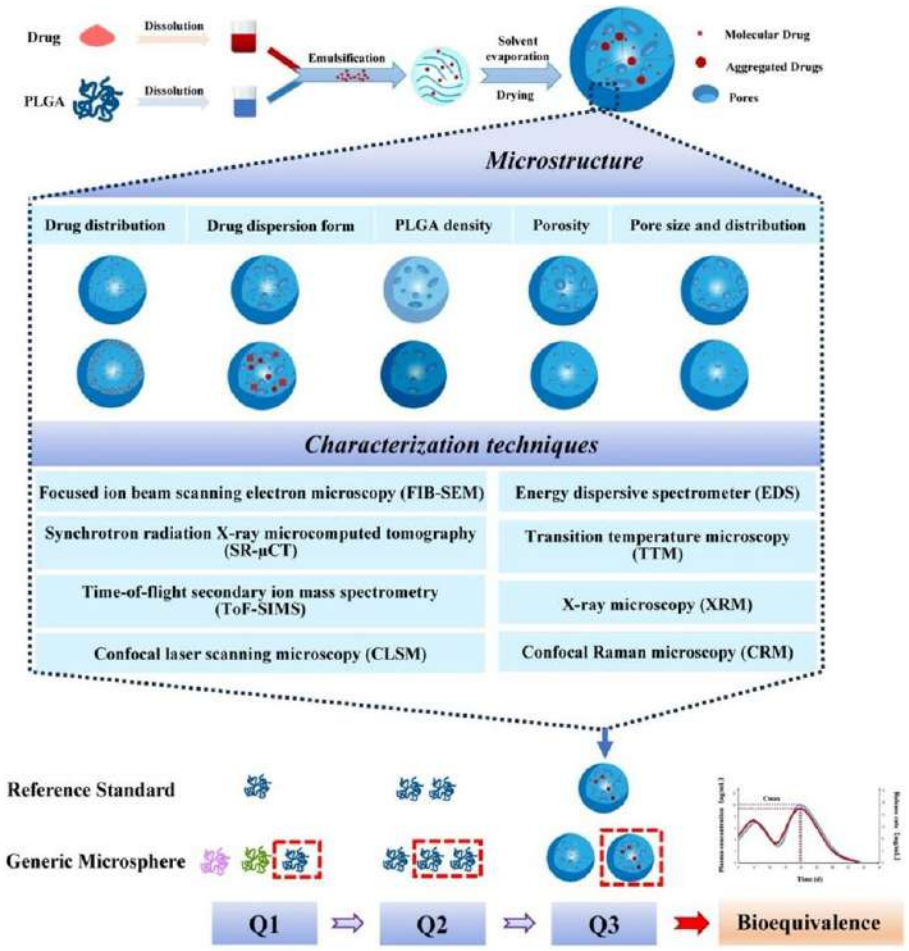

Fig 1: Biodegradable Polymer-Based

The primary biodegradable polymers that are of most frequent use include poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and polylactic acid (PLA), and are selected based on degradation time, mechanical strength, or biocompatibility based on the desired time of target release.[10] Polymeric micro- and nanoparticles can be fabricated to encapsulate therapeutic molecules using solvent evaporation, spray drying, or microfluidic approaches to create a polymeric matrix that dissolves into biocompatible monomeric acids (lactic and glycolic acid) and metabolized through normal metabolic pathways thereafter. Drug release generally depends on the ratio of copolymer composition (example PLGA 50:50 vs 75:25), molecular weight of the polymers, end-group chemistry, and particle size. Micro- and nanoparticles allow for tuning of drug release behaviour from weeks to months and less fluctuation from peak–trough while decreasing the need for dosing. Clinically proven examples are:

• **Risperidone microspheres (Risperdal Consta):** PLGA microspheres via intramuscular injection for schizophrenia and bipolar disorder, where hydration leads to a series of events: pore formation, diffusive release, and erosion of the polymer.

• **Lupron Depot (Leuprolide acetate):** PLGA microspheres for the treatment of prostate cancer, endometriosis, and precocious puberty. Provides a solution for month-to year dosing using controlled degradation.

Benefits from these products include the advantage of biodegradability so no removal is necessary, less systemic side effects because of area depot retention, the compatibility using small molecules, peptides, and in some cases proteins, and more intuitively broad regulatory acceptance among safety due to usage experience. Research and development are directed towards surface-modified polymeric particles to better injectability in vivo, decreased inflammatory effects, and programmable release profiles. Additionally, there is engineering of microfluidic particles and/or uniform monodisperse microsphere systems to improve reproducibility and lessen from batch-to-batch variability.[11]

3.2 Long-Acting Injectable Nano-Suspensions:

Long-term injectable formulations such as nano-suspensions are a significant technological advancement in sustained delivery of poorly water-soluble drugs. Nano-suspensions are formulations that contain solid crystalline drug nanoparticles in the aqueous medium, stabilized with excipients to inhibit aggregation. The duration of action of these formulations is determined primarily by the slow dissolution of drug crystals at the depot site, followed by slow absorption into the systemic circulation. The use of nano-suspension technology is particularly beneficial for highly lipophilic compounds where polymer encapsulation or use of implants presents considerable challenges.

Nano-suspensions are fabricated using methods such as wet media milling, high-pressure homogenization, or precipitation. These approaches are capable of generating a nano-sized product with a large surface area while maintaining the crystalline structure of the drug substance. The duration of release can be modified by controlling the particle size, the surface energy of the drug crystals, and the type of stabilizers used (such as surfactants or polymers). In general, nanocrystal formulations can demonstrate sustained exposure without the need for use of biodegradable carriers and avoiding the inflammatory response associated with polymeric materials.[12]

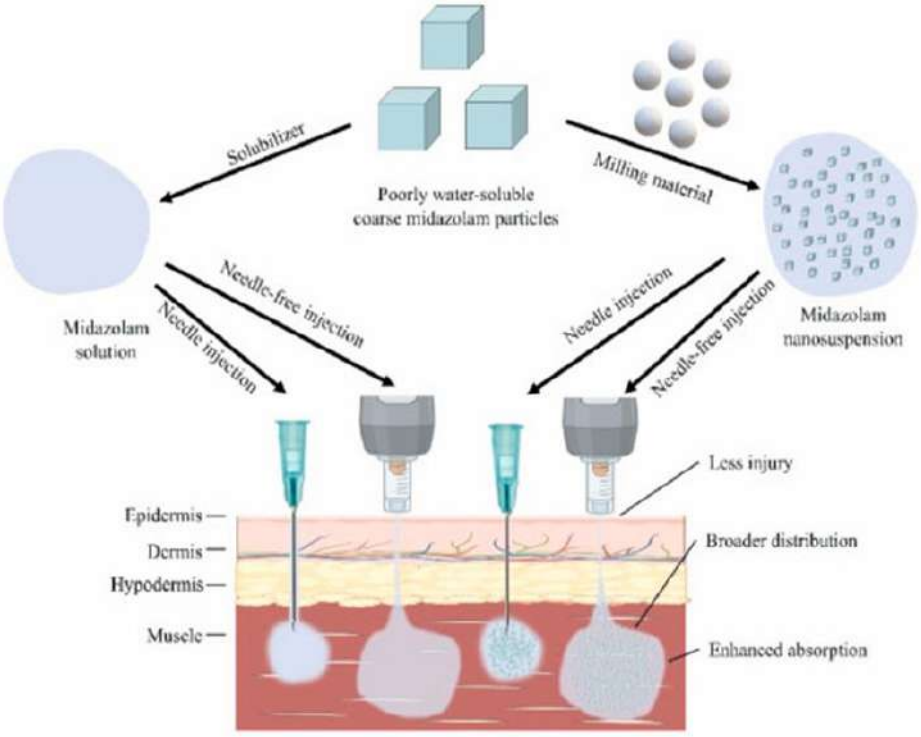

Fig 2: LAI Nano-suspensions

Prominent clinical examples include:

• **Cabotegravir Long-Acting (Cabotegravir LA):** A nanosuspension of an integrase inhibitor cabotegravir dosed for treatment and pre-exposure prophylaxis of HIV-1 via intramuscular injection. Has prolonged release based on slow dissolution and high lipophilicity allowing for once-a-day dosing.

• **Rilpivirine Long-Acting:** Nanosuspension for long-acting HIV treatment based on sustained release from muscle reservoirs.

• **Cabotegravir LA and rilpivirine LA** combination injectables have the potential as a paradigm for long-acting antiretroviral medications that could better adherence while mitigating the risk of viral resistance when doses are missed.

Advantages of nano-suspension LAIs include:

• Moderate to high drug loading in the absence of polymer mass.

• Controlled and predictable release as a function of particle dissolution.

• Excellent performance with very hydrophobic drug substances.

• Less burst release than solution, or suspension injections.

• Appropriate with IM or SC form.

Current strategies of research are focused on the modulation of crystal morphology, formula that involves hybrid lipid polymer stabilizers and profiles with an ultra-long-acting profile higher than monthly treatments.[13]

3.3 In-Situ Forming Injectable Depot Systems:

In-situ forming depots (ISFDs) are innovative LAI systems that change from a flowable liquid to a

solid or semi-solid depot after administration. This change creates a sustained-release matrix at the injection site, allowing the drug to stay localized and be released slowly without needing pre-formed microspheres or implants. Depot solidification can occur due to physiological conditions, solvent exchange, temperature changes, ionic interactions, or pH variations.

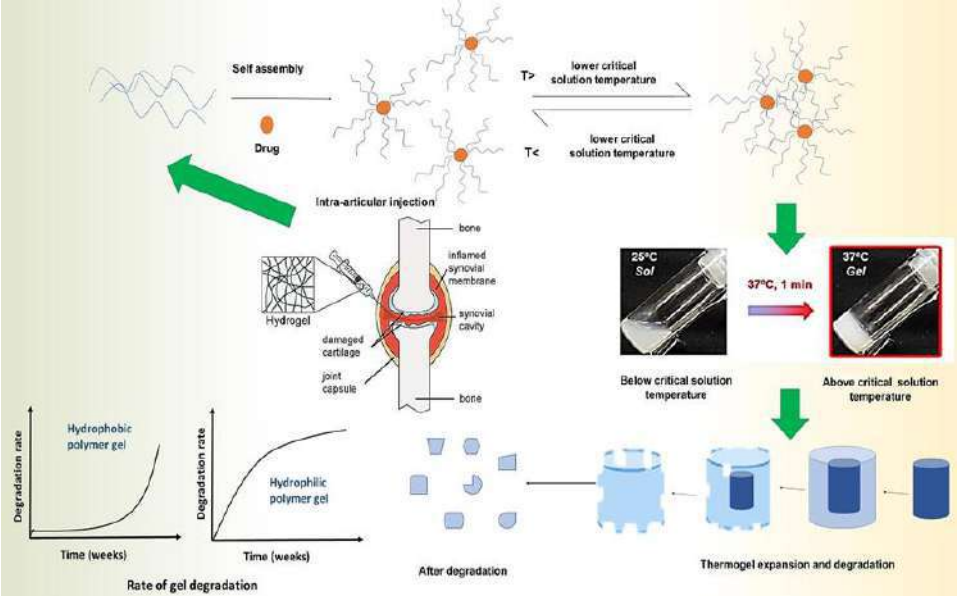

Fig 3: In-Situ Forming Injectable

Thermosensitive In-Situ Gels

Thermosensitive polymers like **poloxamers and PLGA-PEG-PLGA** triblock copolymers stay liquid at room temperature but turn into gels at body temperature. Hydration and the formation of the gel network enable controlled drug release. These systems are used for localized oncology drug delivery, ophthalmic applications, intrathecal uses, and depot analgesics.

Solvent-Exchange, Phase-Inversion Systems (e.g., Atrigel Technology)

Atrigel technology uses PLGA dissolved in a biocompatible solvent like **N-methyl-2-pyrrolidone (NMP).** When injected, water diffuses into the depot, which causes rapid solvent displacement and polymer precipitation. This process forms a solid implant-like matrix. Release is controlled through polymer erosion and diffusion. This platform is used in commercial products, including leuprolide acetate formulations.

Advantages in Targeting Difficult Anatomical Locations

• Ideal for intravitreal, periarticular, periodontal, and post-surgical delivery where traditional systems do not work well.

• Allows for minimally invasive, single-injection administration, replacing the need for surgical implantation.

• Capable of delivering peptides, proteins, small molecules, and antibodies while reducing the burst effect.

• Depot design fits the cavity space, which improves how it interacts with tissue.

System performance relies on polymer concentration, solvent polarity, injectability,

viscosity, mechanical strength after solidification, and minimizing inflammation. Current developments focus on improving biodegradation predictability, reducing initial burst, and integrating with smart stimuli-responsive chemistries for adaptive drug release.

3.4 Lipid-Based Long-Acting Injectable Systems:

Lipid-based sustained-release injectables use lipid matrices that are compatible with the body to trap drug molecules. This setup allows for controlled and prolonged release. These systems rely on biodegradable and biocompatible lipid elements like phospholipids, triglycerides, cholesterol, and lipid surfactants to create structured carriers. [14-15] Compared to polymer systems, lipid-based depots generally provide better tolerability, less inflammation, and are more suitable for hydrophobic compounds and biological treatments.

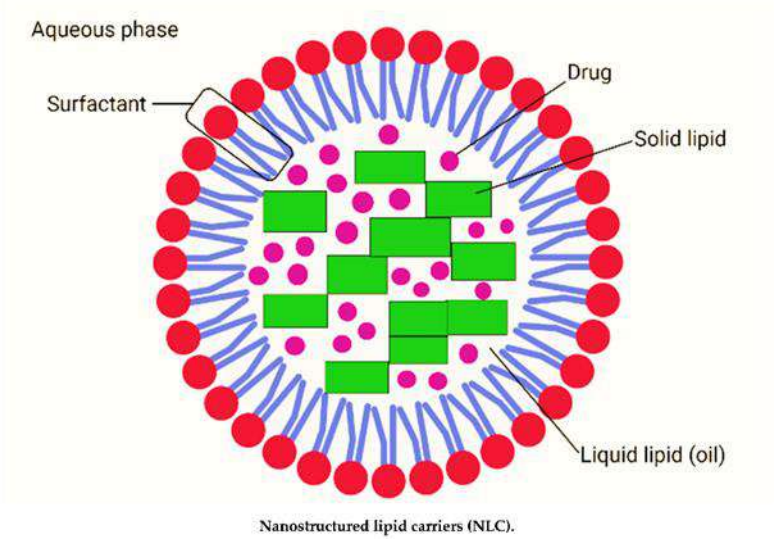

Fig 4: Lipid based LAI

Liposomes:

Liposomes are phospholipid bilayer vesicles that can hold both water-soluble and fat-soluble agents. Drug release happens through the bilayer's diffusion or erosion. Liposomal depot injectables allow for longer-lasting presence in the body, lower toxicity, and targeted uptake by tissues. Important design factors include vesicle size, number of layers, surface charge, and PEGylation to prolong circulation. Liposome depots are increasingly used in cancer treatment, pain relief, and vaccine retention strategies.

Solid Lipid Nanoparticles (SLNs):

SLNs consist of solid lipids suspended in water, creating a strong crystalline matrix that traps drug molecules. The sustained release is controlled by slow lipid recrystallization and diffusion through the solid centre. SLNs show high stability, controlled burst release, and are suitable for temperature-sensitive drugs.

Nanostructured Lipid Carriers (NLCs):

NLCs blend solid and liquid lipids to form an imperfect crystalline structure, allowing for higher drug loading and less loss during storage. Their release can be adjusted by changing the lipid mix, type of surfactant, and internal structure. NLC injectables are being tested for long-lasting pain

relief, antipsychotic treatments, and peptide delivery.

Advantages of Lipid-Based LAIs

• High compatibility with the body and less irritation at injection sites.

• Ability to deliver both small drugs and biologics.

• Longer circulation through lymphatic absorption and cellular uptake.

• Improved stability for sensitive compounds that do not work well with polymers.

Current research is focused on modifying surfaces for targeting specific cells, strategies for co-delivery, and long-lasting depot systems for immunotherapies and gene delivery.[16]

3.5 Long-Acting Prodrug Technologies:

Long-acting prodrug strategies are becoming an effective way to extend the pharmacokinetic profile of therapeutic agents that do not have the right properties for depot formation or sustained release. Prodrug design alters the parent drug by linking it to hydrophobic parts, lipids, or chemical groups that significantly lower its solubility in water and improve retention at the injection site. After administration, enzymes gradually break down the prodrug, releasing the active drug and allowing controlled exposure over weeks to months. Release duration can be finely tuned by optimizing the chemical structure, linker length, steric substituents, enzyme affinity, and tissue microenvironment. This method avoids issues related to variability in polymer degradation and enables high drug loading without using other ingredients.

Enzyme-Mediated Release Mechanism

• Prodrugs stay stable and only minimally dissolve within the tissue depot.

• Esterases and other local enzymes gradually break down the prodrug.

• The parent drug is released into systemic circulation at a steady rate.

• The pharmacokinetic curve shows extended maintenance levels with low fluctuations between peak and trough.

Example – Cabotegravir Ester-Based LAI Formulation

Cabotegravir LA uses a long-chain fatty acid ester modification to improve lipophilicity and depot retention. This change allows prolonged dissolution and enzymatic conversion to active cabotegravir.

Advantages of Prodrug-Based LAIs

• Extended duration without polymeric carriers or implants.

• Minimal local inflammation since there are no degradation by-products.

• High-dose delivery capability for potent small molecules.

• Applicable to oncology, antivirals, pain management, and hormonal treatments.

• Potential for synergy with nanosuspension and lipid-based systems.

Current development focuses on customizing enzyme-responsive linkers, dual-active prodrug hybrids, and prodrug-nanoparticle conjugates to achieve precise release kinetics.[17]

3.6 Implantable Injectable Systems:

Implantable injectable systems are solid or semi-solid depot implants that are introduced using minimally invasive injection methods instead of surgical placement. These systems can be biodegradable or non-biodegradable, allowing precise control of the release duration from weeks to several months or even years. Implantable long-acting injectables (LAIs) are especially useful for conditions that need long-term treatment, where sticking to the regimen, stability, and predictable drug behaviour are crucial.

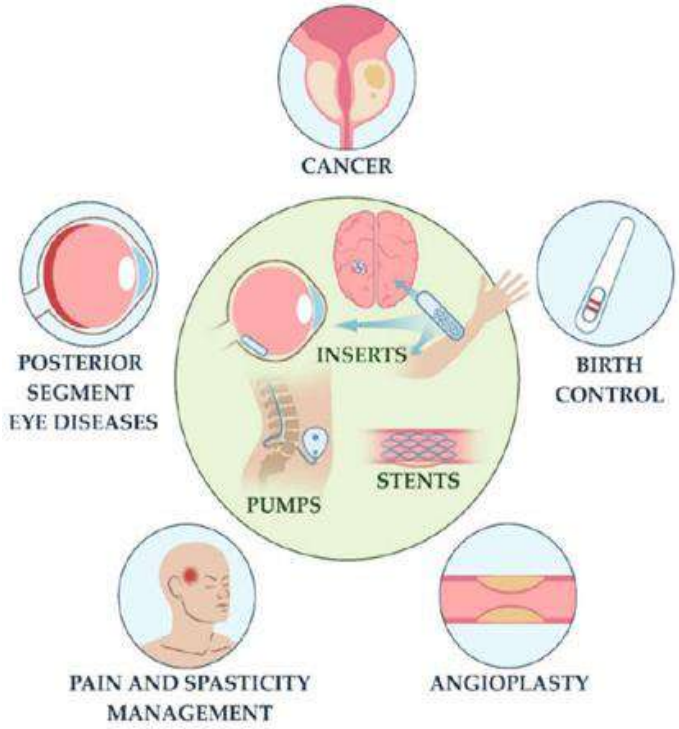

Fig 5: Implantable Injectable Systems

Table 1: Biodegradable Injectable Implants vs Non-Biodegradable Injectable Implants

Parameter	Biodegradable Injectable Implants	Non-Biodegradable Injectable Implants
Material Composition	PLGA, PLA, PCL, poly (ortho esters)	Silicone elastomer, EVA (ethylene-vinyl acetate), metal/titanium devices
Degradation Behaviour	Gradually degrade into non-toxic metabolites eliminated naturally	Do not degrade; remain structurally intact
Need Surgical Removal	**Not required** (eliminates removal procedure)	**Required** once drug reservoir is exhausted
Release Mechanism	Polymer erosion + diffusion	Diffusion-controlled or osmotic release through device matrix
Duration of Action	Weeks to several months (tunable by polymer chemistry)	Months to years depending on system design
Drug Loading Capacity	Moderate to high, depending on compatibility	Very high payload capacity
Suitable Drug Types	Small molecules, peptides, some proteins	Small molecules, peptides, drugs requiring ultra-stable release
Injection Placement	Minimally invasive injectable implant	Often requires specialized applicator or minor surgical procedure

Parameter	Biodegradable Injectable Implants	Non-Biodegradable Injectable Implants
Advantages	Avoids surgical removal, good biocompatibility, degradable, flexible formulation control	Extremely stable long-term dosing, precise release rate control, suitable for narrow therapeutic index drugs
Limitations	Potential inflammatory response from polymer degradation products; difficult control of tail phase	Risk of migration or breakage, requires removal surgery, not suitable if long-term reversibility is needed
Examples / Applications	Hormone therapy, cancer therapy, ophthalmic depot systems, analgesics	Contraceptive implants, long-term neuro-therapeutics
Engineering Focus	Controlled polymer degradation kinetics, reduced burst release, reduced inflammatory response	Device design precision, long-term structural integrity, retrieval strategies

3.7 Emerging Technologies in Long-Acting Injectable (LAI) Systems:

Emerging depot technologies are moving beyond traditional polymer and nanosuspension methods. They offer precision-controlled, responsive, and customizable release behaviours. These systems use innovative biomaterials, smart polymers, engineered scaffolds, and genetic delivery methods for next-generation therapeutics like biologics, vaccines, and cell-based therapies.

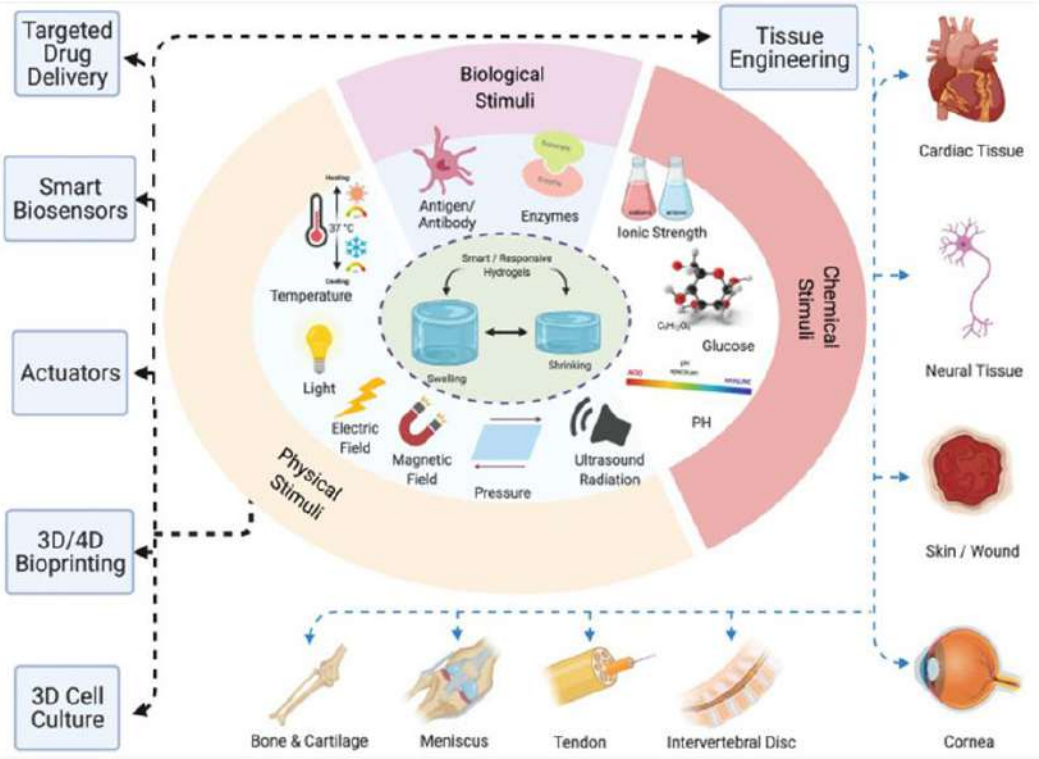

Fig 6: Emerging Technologies in Long-Acting Injectable

Smart Stimuli-Responsive Depot Systems:

Stimuli-responsive or "intelligent" depots change release behaviour based on physiological or external triggers. These triggers include pH, temperature, enzyme levels, redox potential, magnetic fields, light, or ultrasound.[18]

• Hydrogels designed for on-demand release.

• Depot activation based on disease markers allows site-specific treatment adjustment.

These platforms are useful for conditions needing flexible dose changes, such as cancer treatment and inflammation disorders.

Bio-Responsive Hydrogels:

Bio-responsive hydrogels consist of cross-linked polymer networks that can change structure in response to biological signals. Drug release occurs due to swelling, degradation, or affinity-based separation. Uses include ophthalmology, diabetes treatment, and injectable regenerative therapies.

3D-Printed Depot Scaffolds:

3D printing creates personalized depot structures for customized release and placement. Materials used are biodegradable polymers, bio-inks, and composite hybrid structures. This technology allows for precise control over internal porosity to set release rates and supports loading multiple drugs. 3D-printed depots show promise in oncology, orthopaedics, and tissue engineering.

LAI mRNA Vaccine Depot Concepts (Investigational Stage):

Current research looks into depot formulations that help stabilize mRNA and control antigen expression over longer periods. Goals of these depots include:

• Reducing the need for multiple booster shots.

• Improving immune responses through sustained antigen exposure.

• Streamlining distribution and access for large-scale vaccination.

Investigational efforts involve lipid-polymer hybrid matrices and hydrogel-based storage.

Future research will focus on hybrid multi-functional depots, AI-driven formulation models, extending intervals beyond six months, combination therapy depots, and merging with cellular immunotherapy platforms.[19]

3. CRITICAL DESIGN CONSIDERATIONS FOR LONG-ACTING INJECTABLE (LAI) SYSTEMS:

Development of long-acting injectable depot formulations requires a complete evaluation of materials, processes, pharmacokinetics, and clinical use. To ensure consistent, predictable, and safe drug release over time, we need to optimize various related design parameters.

Particle Engineering and Depot Formation Characteristics:

Controlling particle shape, size, surface charge, and crystallinity is crucial for regulating the dissolution rate, injectability, and stability of the depot. Uniform particle engineering helps reduce variability in absorption and limits dose dumping. The physical properties of the depot, like porosity, mechanical strength, and hydration behaviour, affect local diffusion patterns and how the polymer breaks down.

Sterility, Syringe ability, Injectability, and Viscosity:

Long-acting injectables (LAIs) are often thick suspensions or polymer systems. Therefore, how well the device works and how easy it is to inject play a big role in clinical acceptance. The rheology of the formulation must strike a balance between depot stability and the forces needed for injection with standard gauge needles. Aseptic processing and terminal sterilization should maintain physical

stability, crystallinity, and particle distribution without causing aggregation or chemical breakdown.

In-Vitro / In-Vivo Correlation (IVIVC): Creating strong IVIVC models is important to predict how the drug will behave in the clinic based on in-vitro tests. For complex LAIs like microspheres, nanosuspensions, and hydrogels, traditional dissolution equipment often does not suffice. Customized release systems that mimic physiological conditions are necessary. IVIVC aids in optimizing the dosage form, navigating regulatory approval processes, and assessing bioequivalence for generic versions.

Mathematical Modelling and Release Kinetics:

Using kinetic modelling such as zero-order, Higuchi, Korsmeyer-Peppas, and Weibull helps forecast sustained release behaviour and establish specifications for quality assessment. Modelling influences decisions regarding depot design, polymer ratios, particle engineering, and dosing schedules.

Scale-Up and Aseptic Manufacturing Challenges:

Manufacturing LAI formulations becomes more complex due to requirements for sterility, precise particle size control, and sensitivity to processing conditions. Techniques like microfluidics, controlled crystallization, and continuous manufacturing are being used to lessen batch variability and enhance reproducibility. Process analytical technology (PAT) tools enable real-time monitoring and consistency in performance.

Key Stability Factors

Long-term stability must take into account:

• Physical stability (aggregation, sedimentation, viscosity changes, crystallization)

• Chemical stability (hydrolysis, oxidation, pH-related degradation)

• Sterilization compatibility (heat, gamma irradiation, filtration suitability)

Optimizing these critical factors leads to reliable performance, patient acceptance, and meeting regulatory standards.[20]

4. CLINICAL LANDSCAPE AND THERAPEUTIC APPLICATIONS:

Long-acting injectable therapies have shown their value in various medical fields. These therapies help keep a steady level of medication in the body, which is important for managing diseases, sticking to treatment plans, and preventing relapses. Extended-release profiles lower fluctuations between high and low drug levels, reduce how often patients need to take doses, and lessen the risks that come with not following treatment, especially in chronic and lifelong conditions. Long-acting injectables (LAIs) play an important role in the clinical management of neuro-psychiatric disorders for patients with schizophrenia, bipolar disorder, and schizoaffective disorders, where continued non-adherence to daily oral medication often leads to repeated relapse, emergency room admissions, and further functional decline.

Long-acting injectable formulations of antipsychotics such as risperidone, paliperidone, and aripiprazole offer sustained control and management of symptoms, minimize burdens placed on caregivers, and promote structured follow-up of mental health clinical care. In the oncological framework, and other disorders where growth is regulated by hormonal factors in

prolonged therapeutic place, depot formulations of GnRH analogue hormones such as leuprolide and goserelin facilitate long-term endocrine suppression and control of advanced hormone-regulated malignancies (e.g., prostate cancer, breast cancer and endometriosis) while increasing the survivability of patients with advanced-stage cancers. Long acting injectables also play an important role in the recovery and management of opioid dependence with opioid agonist or antagonists of long-acting injectable formulations that allow for extended controlled relief in the therapeutic place that also promote reduction in the symptoms of withdrawal and abuse, with notable improvement in similar recovering, chronic pain medication management with opioid maintenance and recovery.

The increasingly relevant clinical context demonstrates that LAI systems are not only alternatives to dosage forms, but therapeutic interventions aimed at overcoming fundamental deficiencies related to adherence to treatment, instability of pharmacokinetic action, and overall convenience for the patient.

Infectious Diseases (HIV Treatment and Pre-Exposure Prophylaxis, PrEP): Long-acting antiretroviral injections help people stick to their treatment when taking daily pills is difficult. These depot formulations provide stable levels of the drug in the blood necessary for keeping the virus under control and preventing new infections.

The combinations of Cabotegravir and Rilpivirine are used for treating and preventing HIV, allowing for monthly or even less frequent dosing schedules. LAI PrEP options tackle issues like sticking to the treatment, developing resistance, and the stigma tied to daily oral regimens.

Neuro-Psychiatric Disorders: LAI antipsychotics help control illness by lowering the chances of relapse and the need for emergency hospitalization. Depot formulations are well established for conditions like schizophrenia, bipolar disorder, and severe depression. Examples of these therapies include risperidone, paliperidone, and aripiprazole extended-release systems. Benefits include steady symptom control, reduced strain on caregivers, and reliable drug levels in the body.

Oncology and Hormone-Regulated Cancers: For hormone-dependent cancers such as prostate and breast cancer, depot LHRH analogues and therapies that suppress hormones are given at longer intervals. LA formulations of leuprolide and goserelin are used for lowering testosterone levels and stopping menstrual cycles. New depot chemotherapy carriers are being developed for targeted tumour treatment with better patient comfort.

Opioid Dependence Therapy: Extended-release depot systems provide ongoing blocking of opioid receptors or controlled delivery of agonists. LAIs encourage adherence and lower the risk of misuse in people with substance use disorders. These formulations keep stable drug levels and reduce the chances of misuse.

Contraception and Fertility Regulation: Depot contraceptive injections allow for longer periods of pregnancy prevention and better access to birth control. LA formulations lessen the need for daily doses and assist family planning efforts. Research is ongoing to extend the duration of effectiveness beyond current limits.

Vaccines and Gene-Based Therapeutics (Emerging Applications): Depot-based vaccine systems aim to prolong antigen presentation, which strengthens the immune response and reduces the need for multiple booster doses. Early studies are looking into depot platforms to enhance

immune memory duration. Interest is growing in mRNA depot stabilization and the delivery of gene-based therapies designed for personalized treatment. [21-22]

5. CURRENT FDA/EMA APPROVED LONG-ACTING INJECTABLE (LAI) PRODUCTS:

Approved LAI products show proven clinical usefulness and regulatory acceptance of depot-based treatment strategies. These products include polymer-based microspheres, nanosuspensions, in-situ forming depots, and implantable formulations.

Table 2: Product summaries with mechanism of depot formation

Product / Drug	Technology / Depot Mechanism	Indication & Route of Administration	Key Clinical Characteristics / Dosing Interval	Regulatory Notes
Risperidone (Risperdal Consta)	PLGA microspheres	Schizophrenia, bipolar disorder; IM	Sustained release via polymer degradation; biweekly dosing	FDA approved; established generic development
Paliperidone palmitate	Long-acting ester prodrug	Schizophrenia; IM	Extended release through enzymatic conversion; monthly–3-monthly interval	Complex generic pathway due to prodrug/PK profile
Cabotegravir LA (HIV)	Nanosuspension crystalline depot	HIV therapy/prevention; IM	Extended exposure via slow dissolution; monthly or extended	FDA & EMA approved
Rilpivirine LA	Nanosuspension depot	HIV therapy; IM	Slow dissolution from depot site; monthly administration when co-administered	Combined LA regimen approved
Leuprolide acetate (Lupron Depot)	PLGA microspheres	Prostate cancer, endometriosis, precocious puberty; IM	Controlled polymer erosion; dosing every 1–6 months	Approved multiple strengths/durations
Goserelin implant	Biodegradable implant depot	Hormone-driven cancers; SC implantation	Slow polymer erosion; multi-month action	Approved implant with resorbable polymer matrix
Buprenorphine LA	Extended-release injectable depot	Opioid dependence therapy; SC	Stable long-term release supporting addiction treatment	Safety oversight due to dependence profile
LAI contraceptive injectables	Hormonal depot suspensions	Long-term birth control; IM/SC	Extended fertility suppression; multi-month duration	Widely approved globally

Safety and Injection Site Considerations:

- Depot formations can cause localized inflammation, pain, or nodules based on the composition of the depot and the method of injection.
- Injection site reactions can differ among microspheres, nanosuspensions, and implants.

• Safety evaluation focuses on systemic toxicity, limits for residual solvents, particle movement, and immunogenicity.[23]

Regulatory Review Pathways:

FDA pathways used historically include:

• **505(b)(2)** for modified-release formulations that reference existing safety and effectiveness data**.**

• **ANDA** for generic long-acting injections that require specialized pharmacokinetic comparisons and in-vitro release equivalence.

• Complex Generic Guidance because long-acting injections are seen as complex parenteral dosage forms.

EMA review mechanisms include:

• Scientific advice and support for innovation.

• Evaluation of quality, manufacturing process, in-vitro-in-vivo correlation data, and stability.

6. CHALLENGES AND LIMITATIONS:

Although LAIs have significant clinical potential, they come with unique scientific, clinical, regulatory, and economic challenges. These challenges must be managed carefully during development and throughout their lifecycle. While Long-Acting Injectable (LAI) systems offer a revolutionary way to tackle the problems of medication non-adherence and unstable drug release, their development and use in clinics face many technical, biological, and regulatory challenges. These issues require ongoing innovation seen in what we call "New Generation" therapies.

Technical and Formulation Challenges

The main technical problem is creating a delivery system that provides a steady, months-long release from a small injection. Early LAI systems, and many modern ones, struggle to achieve true zero-order release. This often results in an initial burst, where a large amount of the drug is released too quickly after injection. Such rapid release can cause temporary toxicity or side effects, putting patient safety and comfort at risk. After this burst, many polymer-based depots enter a lag phase, where drug release slows down. This situation can drop plasma concentration below the minimum effective level, leading to a temporary loss of effectiveness.

Additionally, the effectiveness of LAI technology is limited by the properties of the drug being used. Traditional LAI systems work best for highly potent, small, lipophilic molecules. Formulating hydrophilic drugs, peptides, and large protein biologics is much harder. These molecules often aggregate, denature, or leak from the delivery system. Moreover, drugs that require high doses usually need larger injection volumes (often over 2 mL), which can cause significant pain and inflammation at the injection site. This discomfort can push patients away from sticking to the LAI regimen. Lastly, the stability of advanced formulations like nanosuspensions and microparticles is a constant worry. These systems can change physically, affecting their release rates.

Pharmacokinetic and Clinical Risks

The depot nature of LAIs brings a unique set of safety risks. The biggest concern is that once a patient starts treatment, it cannot be reversed. If a patient has a severe adverse drug reaction (ADR) or needs to stop the medication suddenly, the drug will continue to be released for weeks to months. Handling such serious ADRs with LAIs requires careful clinical judgment.

Patient acceptance largely depends on how well they tolerate the drug at the injection site. Injection Site Reactions (ISRs), such as pain, swelling, and redness, are commonly reported, especially with concentrated formulations, and they can hinder continued use of LAIs. Also, LAIs often have delayed effectiveness; therapeutic levels aren't reached immediately, leading some to require an oral lead-in period or a high starting dose. Moreover, achieving consistent drug release across different patients is tough because of significant variability in absorption. Factors like the injection site, differences in body tissue (such as fat and muscle), and a patient's activity level can all affect how quickly the drug clears from the depot.

Manufacturing and Regulatory Complexities

Creating and getting LAI systems approved takes much more time and resources compared to standard oral drugs. From a manufacturing view, the complex polymer and particle systems are sensitive to tiny changes, requiring strict Quality by Design (QbD) approaches and thorough analytical checks to ensure consistent quality. Also, many therapeutic agents in these formulations cannot undergo terminal sterilization (like autoclaving), which leads to the need for costly and complex aseptic manufacturing.

The regulatory path for LAIs is also difficult. A major hurdle is proving bioequivalence (BE) for generic versions, as standard BE studies are not practical due to the long half-life and action duration. Both regulators and the industry face challenge in developing predictive In Vitro Release (IVR) tests that can reliably predict in vivo performance. Without strong IVIVC models, maintaining product quality, releasing batches, and approving generics are significant hurdles. Lastly, many LAIs need special delivery devices, such as auto-injectors or advanced pre-filled syringes, which classify them as combination products. This adds to the regulatory demands and testing requirements.[24]

7. REGULATORY PERSPECTIVES & QUALITY ASSESSMENT OF LONG-ACTING INJECTABLE (LAI) DRUG PRODUCTS:

Long-acting injectables (LAIs) are new drug delivery systems designed to tackle important issues in managing chronic diseases. These include patient non-compliance, unstable drug plasma levels, and frequent dosing. By offering sustained drug delivery over weeks to months, LAIs help patients stick to their treatment, keep steady therapeutic levels, and reduce the risk of relapses and resistance in conditions like cancer, mental health disorders, and infectious diseases. LAIs are now commonly used to treat various chronic conditions, including mental illnesses, diabetes, cancers, and HIV/AIDS, as well as serving as contraceptives.

Developing and approving LAIs involves complex regulatory and quality assessment processes from agencies like the USFDA, EMA, and ICH. Regulatory bodies require thorough safety, efficacy, and stability data for new LAIs. Generic LAIs must show Q1, Q2, and Q3 sameness, which means they need to match the reference product in terms of quality, quantity, and physical-chemical properties. The complex nature of LAIs, including their controlled release systems and formulation challenges, makes regulatory approval harder compared to standard oral or immediate-release injectable products. Proving sameness can be particularly tough for complicated depot formulas influenced by factors like manufacturing variations and release patterns.

Quality assessment for LAIs demands detailed physical and chemical analysis, such as checking

particle size, drug encapsulation efficiency, and release profiles. In vitro-in vivo correlation (IVIVC) is significant but hard to achieve with these products. Consequently, regulatory agencies promote the development of predictive models and advanced analytical tools for both new and generic LAI formulations. All LAIs must meet current Good Manufacturing Practices (GMP), with a special focus on sterility, process controls, and lifecycle management according to ICH Q7 to Q14 guidelines. Stability studies under ICH Q1 conditions ensure that drug release and product integrity remain consistent over time.

8. CURRENT RESEARCH TRENDS & FUTURE PROSPECTS IN LONG-ACTING INJECTABLE (LAI) DRUG DELIVERY:

- Personalized Long-Acting Injectable (LAI) Therapy
- Ultra-Long-Acting Injectables (>6–12 Months Duration)
- AI/ML-Based Formulation Modelling and PK Prediction
- Depot Delivery Platforms for CAR-T, Biologics, and Immunotherapies
- LAI mRNA Depot Platforms for Vaccines and Oncology
- Hybrid and Multifunctional Depot Systems [25]

CONCLUSION:

Long-acting injectable (LAI) drug delivery systems play an important role in modern medicine. They change how we think about long-term drug use and treatment adherence. By combining new material science, changes in how drugs are released in the body, and precise delivery systems, LAIs overcome the limits of traditional oral and short-acting injectable drugs. They provide longer-lasting, predictable, and stable release of medication. The use of biodegradable polymer blends, nano-suspension platforms, prodrug technologies, in-situ forming depots, lipid carriers, and implantable reservoirs has resulted in various delivery methods. These methods can effectively deliver both small-molecule drugs and complex biologics. These innovations have greatly improved the treatment of challenging health issues such as HIV prevention, mental health disorders, hormone-related cancers, opioid addiction, reproductive health, and new vaccine and gene therapies. Even with their significant potential, LAIs face serious scientific, regulatory, and practical challenges. Key issues include how reversible the depot is, tolerance at the injection site, prevention of dose dumping, strict standards for quality and stability, and the need for in vitro-in vivo correlation (IVIVC) and proving bioequivalence in complex generics. Addressing these challenges will require teamwork across various fields, including drug materials science, computer modelling, AI design, immuno-engineering, and regulatory science. In the future, LAI therapies are likely to progress toward ultra-long-acting systems that provide doses every six to twelve months. We may see personalized depot designs based on genetic insights and smart, responsive systems for on-demand drug release. As these technologies develop, they are expected to significantly impact precision medicine, improve healthcare access worldwide, and make long-acting injectables central to next-generation drug delivery. The merging of biomaterials, nanotechnology, and molecular engineering has led to the creation of various LAI platforms. These include biodegradable polymer microspheres, crystallized nano-suspensions, prodrug-based depots, lipid carriers, and minimally invasive implant systems. These technologies have

widened treatment options in important clinical areas, especially for chronic infectious diseases, neuropsychiatric disorders, cancer, hormone treatment, addiction medicine, and new vaccine delivery methods. Despite their potential, LAIs encounter serious technical and practical issues. These include limitations on depot reversibility, the risk of unintentional dose dumping, injection-site tolerance, complicated manufacturing and stability issues, and strict regulatory processes that require a solid understanding of release rates and strong in vitro-in vivo correlation. Ongoing advancements in analytical technologies, AI-based predictive modelling, adjustable depots, and long-lasting formulations will be crucial to tackle these complex challenges.

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