The Future of Long-Acting Medicines: From Antiretroviral Therapy to Diabetes Management

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Abstract

The future of long-acting (LA) therapeutics is transitioning toward ultra-long-acting (ULA) platforms, which aim to extend delivery windows to six or twelve months. In HIV care, next-generation innovations, including subdermal implants, self-administered microneedle array patches (MAPs), and LASER ART nanocrystals, are targeting annual dosing frequencies to revolutionize the standard of care.

Concurrently, diabetes management is moving toward a "set-and-forget" approach. This evolution includes once-weekly biochemical agents like Insulin Icodec and implantable microchips capable of providing automated, multi-month dosing. Future platforms are expected to merge digital health sensors with responsive delivery systems such as light-triggered insulin depots to facilitate real-time clinical monitoring and precision dosing. By minimizing the dependence on daily adherence, these advancements aim to alleviate "pill fatigue" and promote global health equity through simplified, highly accessible treatment protocols.

Key words: Long-acting therapeutics, Antiretroviral Therapy (ART), Diabetes management, Medication adherence, Drug delivery systems.

1. Introduction

1.1. The Global Burden of Chronic and Infectious Diseases

The global health landscape faces severe pressure from chronic and infectious diseases, driving the urgent need for future therapeutic innovations. Diabetes mellitus affects over 415 million adults, costing over one trillion USD annually, with cases projected to exceed 850 million by 2050. Concurrently, HIV/AIDS

requires lifelong antiretroviral therapy (ART) for nearly 40 million individuals globally [1]. Despite scientific advances, HIV still causes over 600,000 annual deaths, while the escalating diabetes epidemic severely strains global health systems, highlighting the critical need to evolve management strategies for both conditions.

1.2. Medication Adherence Challenges in Long-Term Care

Sustaining daily medication regimens for these lifelong conditions is exceptionally difficult. Patients frequently experience "pill fatigue" and struggle with complex dosing schedules. Physical obstacles like swallowing difficulties (dysphagia) and polypharmacy heavily impact elderly diabetic patients, while the social stigma surrounding HIV often leads to intentional ART dose-skipping to protect privacy[2]. These adherence challenges are further compounded by economic burdens, systemic inequalities, and supply chain inconsistencies, demonstrating exactly why the future of long-term care must pivot away from a reliance on daily oral medications.

1.3. The Clinical Importance of Long-Acting Therapeutics

Long-acting (LA) medicines represent the future of chronic disease management, transforming care from antiretroviral therapy to diabetes treatment. By replacing daily pills with advanced injectables, implants, or patches, LA therapies drastically reduce pill fatigue. For HIV, infrequent LA ART maintains viral suppression and diminishes daily illness reminders; for diabetes, extended-release treatments offer improved, highly convenient glycaemic control. Clinically, LA systems maintain consistent drug concentrations and provide a "pharmacokinetic tail" that acts as a safety buffer for delayed doses. While challenges like cold-chain storage and professional administration remain, LA therapeutics mark a revolutionary step toward sustained treatment success and enhanced patient quality of life.[3]

2. Overview of Long-Acting Drug Delivery Systems

2.1. Core Principles of Sustained and Controlled Drug Release

The fundamental objective of sustained and controlled drug delivery is to extend the release rate of active pharmaceutical ingredients, thereby prolonging effective half-life and ensuring stable plasma concentrations. This is achieved through specific release kinetics; while the idealized goal remains zero-order releaseproviding constant drug delivery regardless of concentration,most clinical systems follow models such as the Higuchi model or demonstrate triphasic release patterns. Triphasic patterns typically involve an initial surface burst release, followed by a steady diffusion-governed phase through the

polymer matrix, and concluding with a final accelerated phase driven by bulk polymer erosion or degradation.[4]

Key mechanisms driving these processes include Fickian diffusion through rate-controlling membranes and the controlled biodegradation of polymeric materials, wherein factors such as molecular weight, crystallinity, and hydrophobicity of vehicles such as PLGA determine drug depot longevity. Advanced optimization strategies employ complexation techniques to mitigate initial "burst effects," while porogens such as PEG ensure complete late-stage drug release. Chemical modifications into lipophilic prodrugs further facilitate targeted delivery to sanctuary sites.[5]

These principles have catalysed paradigm shifts across chronic disease management. Within HIV therapy, LA injectables such as cabotegravir and rilpivirine have successfully transitioned patients from daily oral regimens to as few as six annual treatments, utilizing nanocrystal technology to establish secondary intracellular depots ensuring sustained viral suppression. Similarly, in diabetes management, ultra-long-acting insulin analogues and thermosensitive hydrogels for peptides such as exenatide provide flat, predictable pharmacodynamic profiles that minimize hypoglycemia risk and enhance treatment persistence.

2.2. Pharmacokinetic and Pharmacodynamic Advantages

The integration of LA drug delivery platforms into chronic condition management particularly HIV and diabetes marks a fundamental shift toward superior therapeutic stability and adherence. By decoupling clinical success from the burden of daily self-administration, these technologies alleviate the psychological pill fatigue inherent in traditional oral regimens.

Within HIV treatment, transition to injectable combinations such as cabotegravir and rilpivirine replaces hundreds of annual daily doses with six to twelve injections. This shift is supported by extended terminal half-lives and advanced methodologies such as Long-Acting Slow Effective Release ART (LASER ART), which utilizes macrophage-sequestered nanocrystals to establish intracellular reservoirs within viral sanctuary sites, ensuring continuous suppression while minimizing drug resistance risk.

Concurrently, diabetes treatment has evolved through the implementation of ultra-long-acting insulin analogues and specialized hydrogels that replicate natural basal secretion patterns. Innovations such as onceweekly exenatide delivery via thermosensitive block copolymer hydrogels provide predictable, stable glucose regulation while significantly reducing adverse event risks such as nocturnal hypoglycaemia. Ultimately, transition to depot-mediated sustained-release formulations ensures more consistent drug exposure and improved pharmacodynamic efficacy, substantially enhancing quality of life for patients navigating long-term metabolic and infectious disease management.

2.3. Major Types of Long-Acting Delivery Systems

Advanced LA drug delivery systems utilize diverse technological platforms to extend drug release from days to several months, significantly enhancing patient adherence and therapeutic outcomes in chronic disease management.

2.3.1. Injectable Depot Formulations

Injectable depots maintain therapeutic concentrations through a single administration into intramuscular or subcutaneous spaces. In-Situ Forming Implants (ISFIs) utilize solvent-induced phase inversion, where water-miscible solvents diffuse outward as interstitial fluid infiltrates to solidify polymer-drug matrices into stable depots. Aqueous Nanocrystal Suspensions leverage surfactant-stabilized, water-insoluble drug particles to establish dissolution-controlled reservoirs, exemplified by contemporary antiretroviral therapies such as Cabenuva. Oil-Based Solutions continue to serve hydrophobic agents, providing steady release from oily vehicles over extended durations.

2.3.2. Implantable Polymeric Systems

Subdermal implants provide ultra-long-term release, frequently exceeding six months, through preformed solid devices. Non-Biodegradable Implants (e.g., silicone or ethylene-vinyl acetate) offer highly predictable zero-order release kinetics but necessitate surgical removal following depletion. Conversely, Biodegradable Implants constructed from polymers such as PLA, PCL, or PLGA eliminate explanation requirements through degradation into non-toxic metabolic byproducts such as lactic acid. These systems employ either reservoir designs withrate-controlling polymer membranes encasing drug cores or matrix designs wherein therapeutic agents are uniformly dispersed throughout the polymer.

2.3.3. Nanoparticle and Microparticle Carriers

Particulate systems encapsulate active pharmaceutical ingredients within microscopic matrices to modulate pharmacokinetics and protect against degradation. Polymeric Microparticles,particularly PLGA-based formulations,account for significant proportions of clinically approved LA injectables due to tunable release properties and established safety profiles. Lipid-based nanocarriers, including Solid Lipid Nanoparticles (SLNs) and vesicular structures such as liposomes or noisome, enhance drug loading and permeability by mimicking biological membranes.[6] Specialized applications such as LASER ART utilize prodrug nanocrystals sequestered by tissue macrophages to establish secondary intracellular depots within viral sanctuary sites, ensuring prolonged therapeutic suppression.

2.3.4. Microneedle and Transdermal Technologies

Advancements in transdermal delivery provide minimally invasive alternatives that bypass hepatic first-pass metabolism and gastrointestinal degradation. Microneedle Array Patches (MAPs) utilize micron-scale projections to deliver drugs directly into vascularized dermis. Dissolving MAPs comprise biocompatible hydrophilic polymers that release encapsulated drug depots upon dissolution in biological fluids. Hydrogel-forming MAPs employ super-swelling cross-linked polymers to create aqueous channels for continuous systemic diffusion from attached reservoirs. [7]These platforms enable highly customized therapeutic regimens addressing diverse patient needs while enhancing privacy and psychological normalcy.

3. Long-Acting Antiretroviral Therapy

3.1. The Evolution of HIV Treatment Strategies

The trajectory of HIV therapeutics represents one of the most significant achievements in modern medicine, evolving from the era of "monotherapy failure" to the current paradigm of long-acting (LA) suppression. The journey began in 1987 with zidovudine (AZT), a drug characterized by high toxicity and the rapid emergence of viral resistance. The true revolution occurred in 1996 with the introduction of triple-drug Highly Active Antiretroviral Therapy (HAART). While HAART transformed HIV from a death sentence into a manageable chronic condition, early regimens were clinically burdensome, requiring dozens of pills daily, strict dietary timing, and severe side effects.

The mid-2000s and 2010s saw the rise of Single tablet Regimens (STRs), which condensed therapy into one daily pill. However, even with STRs, the requirement of 365 doses per year remained a significant hurdle. For many, the daily pill served as a constant psychological reminder of their infection, fueling "pill fatigue" and increasing the risk of accidental status disclosure. The 2021 regulatory approval of the first complete long-acting injectable regimen. Cabotegravir and Rilpivirinemarked the dawn of a new era. This transition from daily oral intake to monthly or bimonthly injections is not merely a change in delivery; it is a fundamental shift that addresses the social, psychological, and systemic barriers that have historically hindered the global goal of ending the HIV epidemic.

3.2. Mechanisms of Action for Long-Acting Antiretroviral Drugs

The effectiveness of LA HIV medications relies on their ability to target diverse stages of the viral life cycle while maintaining stable plasma concentrations over extended periods*(figure 1)*

Entry and Fusion Inhibitors: Agents like Ibalizumab (a monoclonal antibody) and Fostemsavir prevent the virus from attaching to or entering CD4+ T-cells. By blocking the initial "handshake" between the virus and the host cell, these drugs prevent the cellular machinery from being hijacked.

Broadly Neutralizing Antibodies (bNAbs): These represent a cutting-edge frontier in LA therapy. bNAbs target highly conserved regions of the HIV envelope, not only blocking entry but also flagging infected cells for destruction by the host's own immune system[8].

Capsid Inhibitors: Lenacapavir, a firstinclass agent, disrupts the HIV capsidthe protein shell protecting the viral genome. Unlike traditional drugs that target a single enzyme, lenacapavir interferes with multiple stages, including capsid assembly, nuclear transport of the viral genome, and virus production.[9]

Integrase and Reverse Transcriptase Inhibitors: The foundation of current LA therapy relies on Cabotegravir (an integrase strand transfer inhibitor) and Rilpivirine (a non-nucleoside reverse transcriptase inhibitor). These drugs prevent the virus from converting its RNA into DNA and subsequently integrating that DNA into the host genome.

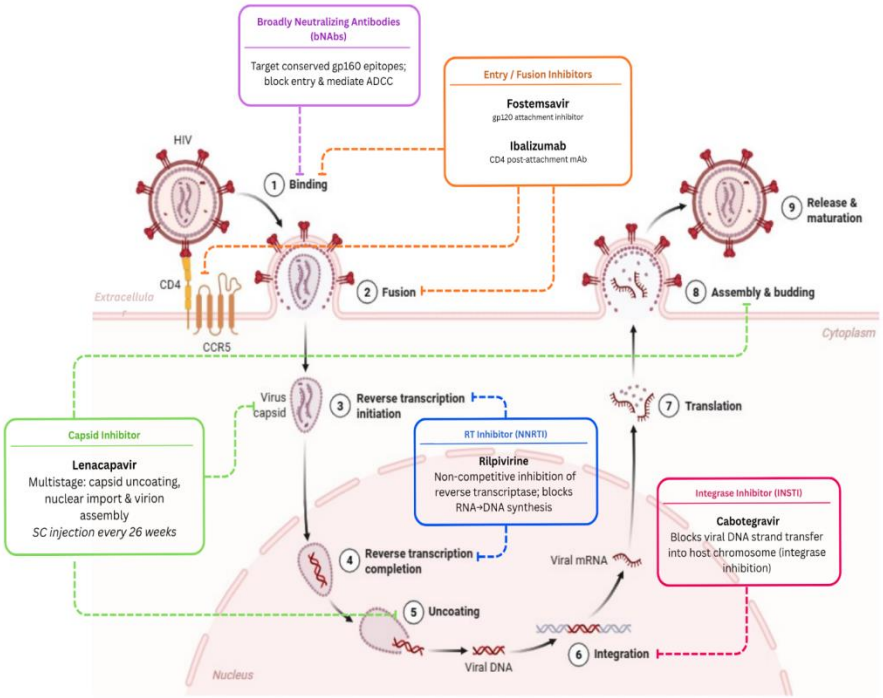

Figure:1. Long-Acting Medicine in HIV Therapy

Schematic representation of the HIV-1 replication cycle showing sites of action of long-acting antiretroviral agents. Entry/fusion inhibitors (fostemsavir, ibalizumab) and broadly neutralizing antibodies act at viral binding and fusion (Steps 1–2). Rilpivirine (NNRTI) inhibits reverse transcription (Step 4), while cabotegravir (INSTI) blocks integration of viral DNA (Step 6). Lenacapavir (capsid inhibitor) targets multiple stages, including uncoating, nuclear import, and assembly (Steps 3, 5, 8). Long-acting formulations administered at extended intervals enable sustained viral suppression.

3.3. RealWorld Therapies and Approvals

Several landmark agents have moved from the laboratory to clinical reality, providing patients with unprecedented freedom.

Cabotegravir (Integrase Inhibitor): Specifically formulated as an aqueous nanosuspension, Cabotegravir is designed for intramuscular injection. Once injected, it creates a "depot" that slowly releases the active drug into the bloodstream. In the HPTN-083 and HPTN-084 trials, LA Cabotegravir was evaluated for Pre-Exposure Prophylaxis (PrEP). The results were staggering: the long-acting injection was up to 89% more effective than daily oral Truvada in preventing infection, primarily because it eliminated the "human error" factor of missed daily doses.[10]

Rilpivirine (NNRTI): When paired with Cabotegravir (marketed together as Cabenuva), Rilpivirine provides a complete, twodrug LA regimen. The ATLAS and FLAIR Phase III trials established that monthly injections were noninferior to traditional three-drug oral regimens.[11] Subsequent studies, such as ATLAS-2M, confirmed that bimonthly (every eight weeks) dosing was equally effective, further reducing the clinical burden on the patient.

Lenacapavir (Capsid Inhibitor): Marketed as Sun Lenca, this agent is a breakthrough for "heavily treatmentexperienced" (HTE) patients who have developed resistance to multiple drug classes. Its unique pharmacokinetic profile allows for subcutaneous injections just twice a year (every 26 weeks). The CAPELLA trial showed that even in patients with highly resistant virus, 83% achieved virologic suppression at one year. More recently, the PURPOSE 1 trial demonstrated 100% efficacy in preventing HIV among cisgender women, a milestone that could redefine global prevention strategies.

Table:1. *Comparison of pharmacokinetic properties such as safety profile, efficacy, and duration of action among different long-acting ART drugs.*

Drug	Safety Profile	Efficacy	Duration	Half-Life	Onset of Action
Cabotegravir	Well tolerated	89% more effective than daily oral PrEP	Monthly to bimonthly	Not specified	Slow release with IM depot
Rilpivirine (NNRTI)	Safe when used with cabotegravir	Non-inferior to standard three-drug oral regimens	Monthly to bimonthly	Not specified	Slow release with cabotegravir
Lenacapavir (Capsid Inhibitor)	Safe in highly treatment experienced patient	83% virologic suppression at 1 year; 100% prevention efficacy in cisgender women	Twice a year	Not specified	Slow release with SC depot

IM – Intramuscular; *SC – Subcutaneous*; *NNRTI – Non-Nucleoside Reverse Transcriptase Inhibitor*; *PrEP – Pre-Exposure Prophylaxis*; *HIV – Human Immunodeficiency Virus*

3.4. Key Clinical Trials and Efficacy Outcomes

The evidence for LA therapeutics is rooted in rigorous clinical investigation. For patients who are already virologically suppressed, the transition to LA injectables have consistently shown "non-inferiority" meaning they are just as safe and effective as oral pills. However, in "real-world" settingswhere patients may struggle with housing instability, mental health issues, or substance use LA therapies often show *superior* outcomes. This is because the "pharmacokinetic tail" of LA drugs provides a "forgiving window"; if a patient is a few days late for an injection, the drug levels often remain high enough to prevent viral rebound, whereas missing a few days of oral pills could lead to immediate treatment failure and the emergence of drug resistance.

3.5. Impact on Patient Adherence, Stigma Reduction, and Viral Suppression

The impact of LA therapy extends far beyond biology; it fundamentally alters the lived experience of HIV. Clinical trials consistently report adherence rates exceeding 95% for injection visits. This high level of engagement is driven by immense patient preference; in most studies, over 90% of participants prefer the injection over daily pills.

The psychosocial benefits are perhaps the most profound. For many individuals living with HIV, the act of taking a pill every morning is a "daily trauma" that

reinforces the stigma associated with the virus.[12] LA therapy allows for "treatment by stealth"patients can maintain total viral suppression without keeping pill bottles in their homes or taking medication in front of others. This privacy reduces the anxiety of accidental disclosure and allows individuals to reclaim a sense of "normalcy." By decoupling the lifesaving necessity of medication from the daily behaviour of pill taking, LA therapeutics provide a bridge to a future where HIV is not just a manageable condition, but one that no longer defines the daily rhythm of a patient's life.[13]

4. Translation of Long-Acting Technologies to Diabetes Management

4.1. Long-Acting Insulin Analogues

From Daily to Weekly Control the management of diabetes has historically been defined by the relentless necessity of daily injections, a requirement that often led to "injection distress" and suboptimal adherence. The evolution of basal insulin analogues has sought to flatten the pharmacokinetic profile of insulin, extending its duration of action to provide a steady "background" level of glucose suppression.

Insulin Degludec: As an ultra-long acting basal insulin, Degludec currently serves as the gold standard comparator in clinical trials. Its unique mechanism involves the formation of multi hexamers at the subcutaneous injection site, which slowly dissociate into monomers for absorption into the circulation. While its 42-hour half-life allows for some dosing flexibility, it still necessitates a daily commitment. Emerging data from trials evaluating even longer acting alternatives suggest that while Degludec is highly effective, the transition to once-weekly regimens may yield superior HbA1c reductions by significantly lowering the psychological and physical barrier to treatment initiation.

Insulin Glargine: For decades, Insulin Glargine (U100 and U300) has been the bedrock of basal therapy. However, daily administration is prone to "glycaemic variability" the fluctuations in blood sugar that occur as the drug's effect wanes toward the end of a 24-hour cycle. In landmark trials such as ONWARDS 1 and 4, Glargine served as the benchmark against which once-weekly Insulin Icodec was measured. These studies revealed that moving from 365 injections a year to just 52 not only improves patient satisfaction but can achieve more pronounced reductions in mean glucose levels, likely due to more consistent plasma concentrations.

4.2. Long-Acting GLP-1 Receptor Agonists and Dual Agonists

The most significant commercial and clinical success in long-acting diabetes technology has occurred within the GLP-1 receptor agonist (GLP-1 RA) class.

These medications mimic the incretin hormones that stimulate insulin secretion in a glucose dependent manner, meaning they carry a lower risk of hypoglycaemia compared to traditional insulin.

Semaglutide: Semaglutide was engineered with a specific fatty acid chain that allows it to bind to albumin, shielding it from rapid degradation by the enzyme DPP-4. This engineering extends its half-life to approximately seven days, enabling a once-weekly subcutaneous delivery. Beyond glycaemic control, Semaglutide has set new benchmarks in Type 2 diabetes care by providing significant weight reduction and documented cardiovascular protection, fundamentally changing the goal of therapy from simple "sugar control" to comprehensive metabolic health.[14]

Dulaglutide: Addressing the physical barriers of needle phobia, Dulaglutide utilizes a human GLP-1 analogue linked to an IgG4 Fc fragment. This large molecular structure prevents renal filtration and extends its presence in the body. More importantly, it is delivered via a sophisticated, single dose pen with a concealed needle, specifically designed to reduce the "medicalized" feel of the treatment. This focus on the user interface has made it a favourite for patients transitioning from oral meds to injectables.

Tirzepatide: Representing the cutting edge of sustained release innovation, Tirzepatide is a "Tw incretin" a single molecule that activates both GLP-1 and Glucose-dependent Insulinotropic Polypeptide (GIP) receptors. By targeting two pathways simultaneously, it achieves weight loss and HbA1c reductions that were previously only seen with bariatric surgery. Its once-weekly dosing schedule, enabled by similar albumin binding technology, demonstrates how molecular engineering can produce "long-acting" effects while simultaneously increasing therapeutic potency.[14]

4.3. Emerging Depot and Implantable Diabetes Therapies: The "Set and Forget" Era

The future of diabetes management is rapidly moving beyond the needle toward "set and forget" models that mimic the autonomy provided by the healthy pancreas. This evolution is driven by advances in material science and bioengineering.

Injectable Biomimetic Hydrogels: Researchers are developing biochemical depots that can be injected once every several months. These hydrogels are composed of biodegradable polymers that respond to the body's internal environment (such as pH or temperature) to release insulin or GLP-1 analogues at a constant, controlled rate. Unlike traditional injections, these depots maintain a "steady state," eliminating the peaks and troughs that lead to hyperglycaemic or hypoglycaemic events.[15]

Insulin Icodec and Albumin Binding Depots: Specifically for insulin, the move toward a once-weekly profile relies on a high affinity for circulating albumin.

Once injected, the vast majority of the Icodec molecules bind to albumin, forming an inactive circulating depot that slowly releases active insulin over seven days. This effectively turns the patient's own blood into a slow-release reservoir.

Implantable Rods and Microchips: Adapted from long-acting contraceptive technology, implantable rods placed under the skin can provide automated dosing of GLP-1 RAs for six months to a year. Even more futuristic are "smart" implantable microchips that contain thousands of tiny drug reservoirs, which can be programmed to open at specific intervals or in response to a digital signal from a continuous glucose monitor (CGM).

Sustainability and Digital Integration: The next generation of these therapies will prioritize biocompatibility and environmental sustainability, utilizing naturally absorbable, eco-friendly polymers that disappear once the medication is spent. Furthermore, the integration of digital health sensors will allow these long-acting systems to communicate directly with clinical teams, providing real-time data on treatment efficacy without the patient ever needing to log a dose.[16] By moving toward these ultra-long-acting systems, the medical community aims to decouple the management of diabetes from the daily behaviour of the patient, moving closer to a "functional cure" for millions.

Table: 2. *Comparison of pharmacokinetic properties such as safety profile, efficacy, and duration of action among different long-acting antidiabetic drugs.*

Drug/Technology	Safety Profile	Efficacy	Duration of Action	Half Life	Onset of Action
Insulin Degludec	Well tolerated but daily dose is needed	Highly effective	42hrs	42hrs	Slow absorption
Insulin Glargine (U100, U300	risk of glycaemic variability	Effective basal insulin	24hrs	Not specified	Gradual onset
Semaglutide (GLP-1 RA)	Lower hypoglycaemia risk	High efficacy in glucose lowering and weight reduction	Once weekly	7days	Gradual onset
Dulaglutide (GLP-1 RA)	Safe with low hypoglycaemia risk	Effective glucose control	Once weekly (~5 days)	Extended by IgG4 Fc fragment	Gradual onset
Tirzepatide (Dual GLP-1/GIP RA)	Safe with enhanced efficacy profile	Superior HbA1c and weight loss effects	Once weekly (~7 days)	~7 days (albumin binding)	Gradual onset

GLP-1 RA– Glucagon like peptide-1 receptor agonist;GIP- Glucose-dependentinsulinotropic polypeptide; IgG4 – Immunoglobulin G4; HbA1c – Glycated Haemoglobin

5. Emerging Technologies in Long-Acting Medicine

The landscape of long-acting (LA) therapeutics is undergoing a radical transformation, driven by breakthroughs in materials science and digital integration. These innovations aim to move beyond simple "slow-release" mechanisms toward "intelligent" delivery systems that respond to the body's physiological needs.

5.1. Nanotechnology-Based and Lipid-Based Delivery Systems

Nanotechnology has redefined the precision of drug kinetics. By utilizing nano formulation and microencapsulation, researchers can now shield active pharmaceutical ingredients (APIs) from premature degradation, ensuring a gradual and highly predictable release profile. Liposome based carriers have become a cornerstone of modern oncology; by encapsulating potent chemotherapeutics, these lipid bilayers increase drug stability and bioavailability while significantly reducing systemic toxicity through "enhanced permeability and retention" (EPR) effects.[17] Furthermore, lipid-based suspensions often enhanced with hydrophobic modifications like decanoate or palmitate esters create a prodrug depot that dissolves slowly in the muscle or subcutaneous tissue, extending therapeutic windows from days to several weeks or even months.[16]

5.2. Advanced Biodegradable Polymer Depots

The development of poly (lactic-co-glycolic acid) (PLGA) and similar copolymers has revolutionized the treatment of chronic conditions such as schizophrenia and hormone-dependent cancers. These biodegradable depots act as a matrix; as the polymer chains undergo hydrolysis, the medication is released at a constant rate (zero-order kinetics). Modern innovations in this space are focusing on "tuneable" degradation adjusting the ratio of monomers to precisely dictate the lifespan of the depot. Additionally, there is a burgeoning shift toward "green" polymer chemistry, utilizing sustainable manufacturing processes and bio-derived materials to ensure that the environmental footprint of long-term care is minimized without compromising clinical efficacy.

5.3. Next Generation Implantable Drug Delivery Devices

Implantable technology has evolved from passive rods to active, "smart" systems. Subcutaneous implants, such as those used in long-term contraception (e.g., etonogestrel) or opioid use disorder treatment (e.g., buprenorphine), provide years of protection from a single clinical intervention. The next frontier involves microchip-based implants capable of storing hundreds of individual doses in separate reservoirs. When integrated with digital health sensors, these devices can monitor physiological markers in real-time and trigger the release

of a dose via a wireless command or a pre-programmed algorithm, allowing clinicians to adjust therapy remotely based on continuous patient data.

6.4. Smart Microneedle and Responsive Transdermal Platforms

Transdermal delivery is moving beyond the simple nicotine patch. Microneedle arrays provide a painless, "dissolvable" route for biologics and vaccines that were previously restricted to cold-chain injections. Furthermore, "responsive" platforms are emerging such as glucose responsive insulin patches or light activated depots. These systems utilize bio-sensing elements that trigger drug release only when specific physiological thresholds are met (e.g., high blood sugar). By fusing digital monitoring with these responsive materials, the industry is moving toward a "closed loop" model of personalized therapy, effectively eliminating the adherence risks associated with daily oral or self-injected regimens

6. Clinical Advantages and Therapeutic Challenges

6.1. Adherence Improvements and Quality of Life

LA drugs alleviate daily oral therapy burdens, reducing pill fatigue while enhancing patient confidentiality by minimizing inadvertent status disclosure risks. Clinical trials demonstrate strong patient preference for injectable regimens, with satisfaction rates frequently between 90% and 100%. Instruments such as the HIV Treatment Satisfaction Questionnaire confirm elevated treatment satisfaction following transition to LA injectables.

6.2. Pharmacokinetic Considerations

A defining feature of LA drugs is the prolonged "pharmacokinetic tail," wherein drug levels decline slowly over weeks to months following final administration. Cabotegravir, for example, demonstrates half-lives ranging from 5.6 to 11.5 weeks, with detectable plasma levels persisting up to one year. While injectable routes bypass absorption issues common to oral medications, LA drugs remain vulnerable to metabolic interactions, particularly with enzyme inducers such as CYP3A4 or UGT1A1, potentially reducing drug efficacy.

6.3. Risks of Drug Resistance and Systemic Safety

Extended tail phases increase drug resistance risks if viral suppression is inadequately maintained, necessitating prompt transition to oral therapy within one-month post-injection. Injection site reactions represent the most common adverse events, generally mild and decreasing over time. Rare but serious side effects include hepatotoxicity, depression, and weight gain.[18]

6.4. Health Economics and Global Accessibility

Elevated manufacturing costs, complex logistics, and infrastructure requirements limit LA drug availability primarily to resourcerich settings. Challenges include specialized staffing, private clinical spaces, strict dosing schedules, and cold-chain storage for certain agents [19]. Expanding access in resource limited regions remains a critical public health priority.

7. Regulatory and Development Considerations

7.1. Navigating Drug Approval Pathways for Novel Delivery Systems

The regulatory environment for long-acting (LA) drugs is undergoing a paradigm shift to accommodate unique pharmacokinetic (PK) profiles. Traditional bioequivalence studies, which often require extended washout periods in crossover designs, are increasingly impractical due to the prolonged half-lives of LA agents.[13] Consequently, regulatory bodies like the FDA are moving toward Model-Integrated Evidence (MIE) frameworks. These frameworks use physiologically based pharmacokinetic (PBPK) modelling and virtual bioequivalence to predict long-term drug behaviour, enabling streamlined approvals without compromising clinical safety standards.

7.2. Scale Up and Sterile Manufacturing Challenges

Transitioning LA formulations from the laboratory to commercial scale presents formidable technical hurdles. These medications often rely on sophisticated nanosuspensions or lipid nanoparticles that require precise, sterile manufacturing environments to ensure consistent release profiles and prevent batch to batch variability. Furthermore, the high degree of specialized expertise and stringent intellectual property protections surrounding these delivery platforms can restrict generic market entry. This highlights an urgent need for public-private partnerships to diversify manufacturing capabilities and ensure global equitable access.[20]

7.3. Requirements for Long-Term Safety and Pharmacovigilance Monitoring

The "pharmacokinetic tail" the period where drug levels slowly decline necessitates rigorous long-term surveillance. A primary concern is the emergence of drug resistance if patients disengage from therapy during sub-therapeutic phases. To mitigate this, regulators often mandate robust clinical protocols, such as "oral bridging" for missed doses. Continuous post-marketing pharmacovigilance is also essential to monitor for delayed systemic toxicities, including potential hepatotoxicity or neuropsychiatric effects, ensuring that the

long-term benefits of these transformative therapies consistently outweigh their risks.[20, 21]

8. Future Perspectives in Long-Acting Therapeutics

8.1. Horizon Scanning for Next-Generation Drug Delivery Technologies

The future of LA medicines aims toward longerduration therapies with minimally invasive delivery, ultimately reducing daily management burdens of chronic diseases. Next-generation systems include ultralong-acting implants, such as in situ forming implants and subcutaneous rods, capable of providing multiyear therapeutic coverage from a single administration.[22] Microarray patches emerge as needlefree, non-invasive alternatives, potentially enhancing self-administration and accessibility, particularly in resourcelimited settings.

8.2. Integration with Precision Medicine and Pharmacogenomics

Future LA platforms are expected to integrate with precision medicine approaches, tailoring drug release to individual metabolic and genetic profiles to maximize efficacy while reducing adverse effects. This will likely involve digital health technologies such as embedded sensors or responsive transdermal systems activated by physiological signals or light, enabling real-time monitoring and personalized dosing adjustments.[5]

8.3. Expansion of Long-Acting Paradigms to Other Chronic Diseases

The proven success of LA drugs in HIV and psychiatric care is driving application to other chronic diseases. Within tuberculosis, LA injectable formulations are under development to improve adherence during lengthy treatment courses. [23]Hepatitis C treatment is progressing toward singledose particle suspensions to facilitate global eradication efforts. Long-acting injectable antipsychotics, such as biannually administered paliperidone palmitate, continue to reduce relapse rates and establish standards in psychiatric disorder management.[16]

10. Conclusion

Long-acting drug delivery systems represent a transformative paradigm in chronic disease management, effectively addressing the adherence challenges that undermine therapeutic outcomes in conditions such as HIV and diabetes. By decoupling clinical efficacy from daily patient behaviour through innovative platforms including injectable depots, polymeric implants, nanoparticle carriers, and transdermal technologiesthese systems enhance treatment persistence, reduce psychosocial burdens, and improve quality of life.[24] The

documented success of agents such as cabotegravir, rilpivirine, and ultralong-acting insulin analogues demonstrates superior adherence and patient satisfaction compared to conventional oral regimens. While challenges persist regarding pharmacokinetic tail risks, drug resistance, manufacturing complexity, and global accessibility, ongoing advances in biodegradable materials, smart responsive platforms, and precision medicine integration promise to expand therapeutic applications.

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