Long-acting drug delivery systems: Current landscape and future prospects

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Conventional drug delivery often leads to fluctuating drug levels and reduced efficacy, especially in chronic conditions requiring sustained treatment. Long-acting drug delivery systems (LADDS) offer controlled, extended release, improving efficacy, safety, and patient adherence. This mini review outlines current injectable and implantable LADDS, including approved formulations like nanosuspensions, PLGA microspheres, oil-based injections, *in situ*-forming and preformed implants. Future directions explore thermoresponsive gels, polymer-drug conjugates, prodrugs, 3D printing, and reservoir-type implants using semipermeable membranes. These innovations highlight the need for continued multidisciplinary collaboration to advance next-generation long-acting therapies.

Keywords: long-acting drug delivery systems; chronic conditions; injectables; preformed implants; semi-permeable membranes; drug delivery

Introduction

Conventional medical treatments primarily depend on intermittent dosing, with oral and intravenous administration being the most prevalent.(p1) These methods rapidly introduce high concentrations of drugs into the bloodstream. However, drug levels often diminish below the therapeutic threshold within a short period, resulting in the so-called 'peak-and-trough' effect.(p1) Such fluctuations are far from optimal, as excessively high concentrations can be toxic, whereas sub-therapeutic levels could render the treatment ineffective.(p1)

Oral administration presents further complications. Medications taken orally must survive the harsh conditions of the gastrointestinal tract, including a highly acidic environment and a variety of enzymes capable of degrading active compounds.(p1) Moreover, the liver's first-pass metabolism significantly reduces the bioavailability of many drugs.(p1) To counter these drawbacks, frequent dosing is often required to maintain therapeutic concentrations,(p2) particularly for the management of chronic and long-term illnesses, an increasingly pressing issue given the rising prevalence of chronic diseases caused by an aging global population.

Certain medical conditions necessitate high drug levels at specific target sites. Although increasing the dose could achieve this, it can also lead to systemic toxicity. Hence, there is a growing demand for advanced drug delivery technologies capable of maintaining therapeutic drug levels over extended periods.(p3) LADDS present a compelling solution, aiming to optimise treatment efficacy while minimising side effects and toxicity.(p1)

LADDS encompass a wide array of technologies, including implants, nanoparticle-based formulations, and *in situ*-forming gels.(p4) Their development is inherently multidisciplinary, requiring input from materials science, engineering, pharmaceutical sciences, biology, and medicine. The origins of LADDS can be traced back to the 1930s, when hormone-infused pellets were subcutaneously implanted in livestock to enhance growth rates, an innovation that transformed meat production.(p5) This concept was subsequently adapted for therapeutic use in humans, such as in the treatment of premature menopause.(p6)

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https://doi.org/10.1016/j.drudis.2025.104447

Although LADDS have existed for nearly nine decades, interest in these systems has surged over the past 20 years. Beyond academic research, the pharmaceutical industry is heavily investing in the development of new LADDS products, both as part of lifecycle strategies for existing drugs and in the creation of novel therapeutics. Injectable systems currently dominate the global market for long-acting drug delivery technologies, reflecting their widespread clinical adoption and manufacturing maturity.[p7] As of 2023, the market was valued at $13.7 billion and is projected to grow at a compound annual growth rate of 10.6% between 2025 and 2034.[p7] This growth highlights increasing confidence in LADDS as a viable alternative to conventional delivery approaches for the treatment of long-term conditions.

Current landscape

LADDS have been applied across numerous medical domains, including contraception, oncology, ophthalmology, pain management, and central nervous system disorders. A summary of commercially available LADDS products is presented in Table 1. This table summarises the main approaches used to prepare LADDS products: aqueous suspensions, oil-based injections, preformed implants, *in situ*-forming implants and poly(lactic-co-glycolic) acid (PLGA)-based particulate systems.[p8] Additionally, Figure 1 shows a diagram of different types of LADDS. The table shows some other strategies that do not fall within any of these categories. The focus of this manuscript is injectable and implantable LADDS; therefore we have not included vaginal rings (such as NuvaRing, Figure 1b) in the discussion.

Long-acting suspension and oil-based injections

Apart from the products developed in the 1930s, one of the first LADDS products approved by the FDA, which is still in use, was Bicillin LA. This intramuscular injectable formulation contained an aqueous suspension of penicillin G benzathine and was approved in 1952.[p8] It is used primarily for the treatment of bacterial infections. Since its approval, many more aqueous injectable formulations have been developed, based on suspensions of poorly water-soluble drugs at the nanometric or micrometric scale (Figure 1a). These formulations typically include stabilisers, such as surfactants or polymers, to prevent particle aggregation.[p8] The use of nanosuspensions is not exclusive to LADDS; reducing the particle size of poorly soluble drugs has also been widely applied in oral formulations to enhance dissolution kinetics. These injectable formulations offer significant advantages to patients, providing sustained drug release over periods ranging from 14 days to nearly a year, depending on the drug and formulation.[p8] Additionally, as these formulations consist primarily of the pure drug along with a stabiliser, they tend to have a high drug content, in contrast to other delivery systems that rely on drug encapsulation. However, in LADDS the aim is to obtain suspensions capable of providing slow drug release that can be administered using a conventional intramuscular injection.

Alongside aqueous nanosuspensions, oil-based injections were developed as an alternative formulation. The first commercially available LADDS oil-based injections were introduced in the late 1950s (Table 1). These formulations consist of a lipidic matrix in which a drug, typically lipophilic, is dissolved (Figure 1a).[p8] Administered intramuscularly, the drug is gradually released through slow diffusion from the oily matrix, combined with the degradation and elimination of the lipidic matrix.[p8] It is important to highlight that, to achieve sustained release, hydrophobic prodrugs are commonly used (such as decanoate, enanthate, or propionate esters, among others).

Both injectable suspensions and oily injections have been widely used because of their simplicity and effectiveness. They do not require expensive processes or excipients, and their administration is straightforward, typically delivered via conventional intramuscular injection without the need for specialised training.

Pre-formed implants and in situ-forming implants

The next key area of interest in LADDS is preformed implants.[p3],[p8] Although these devices require a more invasive implantation process than injections, they offer significant advantages, including more controlled drug release kinetics and greater stability. Typically designed as rod-shaped implants for subcutaneous placement, common examples include Implanon, Jadelle, and Norplant, which are contraceptive implants capable of releasing etonogestrel or levonorgestrel over several years (Table 1 and Figure 1b). A more recent blockbuster innovation in this field is Ozurdex, an intraocular implant designed to provide sustained dexamethasone release for up to 180 days (Table 1 and Figure 1b). In addition to contraception and ocular applications, another important area of application for preformed implants is cancer treatment (Table 1). The materials used in implant preparation are highly diverse, ranging from non-degradable materials, such as silicone, to biodegradable polymers, such as PLGA.[p3] Non-degradable polymers require removal once the drug cargo is depleted, whereas biodegradable implants naturally degrade and do not need to be extracted. The former are typically used for the treatment of chronic conditions, whereas the latter are preferred in cases where prolonged treatment is required but the patient is unlikely to need more than one implant. This distinction arises because precisely matching drug release duration with polymer degradation remains highly challenging.

In situ-forming implants offer the possibility of administering implants using conventional needles or syringes.[p8] These liquid formulations solidify or form a semi-solid depot upon injection, utilising mechanisms such as phase separation or thermogelation under physiological conditions (Figure 1a).[p9] These systems have attracted significant interest from researchers and industry professionals since the mid-1990s, leading to the commercial release of products in the late 1990s and early 2000s (Table 1). Most approved products rely on biodegradable hydrophobic polymers, such as PLGA or poly(lactic acid) (PLA), dissolved in a biocompatible organic solvent, such as N-methyl-2-pyrrolidone, which contains the drug.[p10] Upon intramuscular injection, the solvent diffuses into the surrounding tissue, leaving behind a polymer/drug depot.

In situ-forming implants and preformed implants generally offer more prolonged drug release compared with the intramuscular injections discussed in the previous section. *In situ*-forming implants have the advantage of being less invasive,

TABLE 1

Marketed LADDS.[(p8)]

Product type	Product name	Compound	Condition	Duration	Drug content	Excipients	Approval year	Discontinuation year	Route of administration
Aqueous suspension long-acting injection	Abilify Asimtufii	Aripiprazole	Schizophrenia	Every 2 months	300 mg/ml (2.4–3.2 ml)	Water for injection, carboxymethylcellulose sodium (5 mg/ml), povidone (4 mg/ml), polyethylene glycol 400 (1 mg/ml), sodium phosphate monobasic monohydrate (0.74 mg/ml), sodium chloride (6.1 mg/ml), and sodium hydroxide (pH adjustment)	2023		IM
	Abilify Maintena	Aripiprazole	Schizophrenia	Monthly, intramuscular (IM) (0.8–2 ml)	200 mg/ml	Mannitol, carboxymethylcellulose sodium, sodium phosphate monobasic monohydrate, and sodium hydroxide	2013		IM
	Aristada	Aripiprazole lauroxil	Schizophrenia	Monthly to every 8 weeks, IM (1.6–3.2 ml)	275 mg/ml	Water for injection, sodium chloride (0.61%), sodium phosphate monobasic (0.052%), sodium phosphate dibasic anhydrous (0.062%), polysorbate 20 (0.15%), and sorbitan monolaurate (0.38%)	2015		IM
	Aristada Initio	Aripiprazole lauroxil	Schizophrenia	Every 4–8 weeks, IM (up to 3.8 ml)	281 mg/ml	Water for injection, sodium citrate dihydrate (0.81%), sodium chloride (0.33%), polysorbate 20 (0.162%), sodium phosphate monobasic (0.084%), and sodium phosphate dibasic anhydrous (0.074%)	2018		
	Bicillin L-A	Penicillin G benzathine	Antibiotic	Every 2 or 4 weeks, IM (1–4 ml)	262 mg/ml (1.2 M units in 3.5 ml)	Aqueous suspension containing sodium citrate buffer, povidone (∼0.6% w/v), lecithin (∼0.5% w/v), carboxymethylcellulose (∼0.5% w/v), methylparaben (∼0.1% w/v), and propylparaben (∼0.01% w/v)	1952		IM
	Cabenuva	Co-packaging of cabotegravir andrilpivirine	HIV treatment	Monthly		See composition for Vocabria/Apretude and Rekambys/Edurant	2021		IM
	Depo-Medrol	Methylprednisolone acetate	Anti-inflammatory	Once every 1–5 weeks	20, 40, or 80 mg/ml	Aqueous suspension containing sodium citrate buffer, lecithin (∼0.5% w/v), carboxymethylcellulose (∼0.5% w/v), povidone (∼0.6% w/v), methylparaben (∼0.1% w/v), and propylparaben (∼0.01% w/v)	1959		IM, intra-articular, soft tissue or intralesional injection
	Depo-Provera	Medroxyprogesterone acetate	Contraception	Every 3 months	150 or 400 mg/ml	Aqueous suspension containing phosphate buffer, polyethylene glycol 3350 (∼2.95%), polysorbate 80 (∼0.197%), and benzyl alcohol (∼0.93%)	1960		IM
	Depo-subQ Provera 104/ Sayana Press	Medroxyprogesterone acetate	Contraception	Every 3 months	160 mg/ml	Water for injection, polyethylene glycol (2.88%), sodium chloride (0.8%), povidone (0.5%), polysorbate 80 (0.3%), methylparaben (0.16%), sodium phosphate monobasic (0.069%), sodium phosphate dibasic anhydrous (0.059%), and propylparaben (0.015%)	2004		Subcutaneous
	Invega Hafyera	Paliperidone palmitate	Schizophrenia	Every 6 months	312 mg/ml	Water for injection, polysorbate 20 (1%), polyethylene glycol 4000 (7.5%), citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, and sodium hydroxide	2021		IM
	Invega Sustenna	Paliperidone palmitate	Schizophrenia	Monthly	156 mg/ml	Water for injection, polysorbate 20 (1%), polyethylene glycol 4000 (7.5%), citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, and sodium hydroxide	2009		IM
	Invega Trinza	Paliperidone palmitate	Schizophrenia	Every 3 months	312 mg/ml	Water for injection, benzyl alcohol as a preservative (0.99% w/v), polysorbate 20 (0.75%), polyethylene glycol 4000 (7.5%), citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, and sodium hydroxide.	2015		IM
	Kenalog-40	Triamcinolone acetonide	Anti-inflammatory	>3 weeks	40 mg/ml	Polysorbate 80 (0.04%) and carboxymethylcellulose sodium; the pH is adjusted to 5.0–7.5 using either sodium hydroxide or hydrochloric acid as needed	1958		IM or intra-articular
	Rekambys/ Edurant	Rilpivirine	HIV prevention	Monthly	300 mg/ml	Water for injection, poloxamer 338 (50 mg/ml), and citric acid monohydrate (0.1%)	2021		IM
	Ryanodex	Dantrolene sodium	Malignant hyperthermia	N/A	250 mg/5 ml (max)	Mannitol (12.5%), polysorbate 80 (2.5%) and povidone K12 (0.4%)	2014		Intravenous
	Vocabria/ Apretude	Cabotegravir	HIV prevention	Monthly	200 mg/ml	Mannitol (3%), polysorbate 20 (2%), and polyethylene glycol 3350 (2%)	2021		IM
	Zyprexa Relprevv	Olanzapine pamoate	Schizophrenia	Monthly	150 mg/ml	Water for injection, mannitol (5%), carboxymethylcellulose sodium (0.75%), and polysorbate 80 (0.1%); the pH is adjusted using either sodium hydroxide or hydrochloric acid as needed	2009		IM
Oil-based long-acting injection	Clopixol	Zuclopenthixol decanoate	Schizophrenia	2–4 weeks	200 mg/ml	Thin vegetable oil	2011 (Canada)		IM
	Deca-Durabolin	Nandrolone decanoate	Osteoporosis and others	Every 3–4 weeks	25, 50, 100, 200, or 250 mg/ml	100 mg/ml benzyl alcohol in arachis oil	1962	2002	IM
	Depixol	Flupenthixol decanoate	Schizophrenia	2–4 weeks	100 mg/ml	Thin vegetable oil	1970 (EU)		IM
	Depo-Testosterone	Testosterone cypionate	Testosterone replacement	2–4 weeks	100 mg/ml	Benzyl benzoate and benzyl alcohol in cottonseed oil	1974		IM
	Faslodex	Fulvestrant	Metastatic breast cancer	Monthly	50 mg/ml	Benzyl benzoate, benzyl alcohol, ethanol, and refined castor oil	2002		IM
	Gynodian Depot	Estradiol valerate and prasterone enanthate	Menopausal hormone therapy	Every 4–6 weeks	4 mg/ml estradiol valerate and 200 mg/ml prasterone enanthate	Chlorobutanol and sesame oil; or benzyl benzoate, benzyl alcohol, and castor oil	1975 (EU)		IM
	Haldol	Haloperidol decanoate	Schizophrenia	Monthly	70.5 mg/ml	1.2% benzyl alcohol in sesame oil vehicle	1967		IM
	Noristerat	Norethisterone enanthate	Contraception	Every 8 weeks	200 mg/ml	Benzyl benzoate in castor oil	2011 (EU)		IM

(continued on next page)

POST-SCREEN (GREY)

TABLE 1 (*CONTINUED*)

Product type	Product name	Compound	Condition	Duration	Drug content	Excipients	Approval year	Discontinuation year	Route of administration
	Piportil	Pipothiazine palmitate	Schizophrenia	Monthly	50 mg/ml	Butylhydroxyanisole (E320) in sesame oil	1980	2015	IM
	Primobolan Depot	Methenolone enanthate	Anaemia in bone marrow failure	Weekly	100 mg/ml	Benzyl benzoate and benzyl alcohol in grape seed oil	1962	1993	IM
	Primodian Depot	Estradiol valerate and testosterone enanthate	Menopausal hormone therapy	4–6 weeks	4 mg/ml estradiol valerate and 90.3 mg/ml testosterone enanthate	Benzyl benzoate and benzyl alcohol in castor oil	1981		IM
	Prolixin decanoate/ Modecate	Fluphenazine decanoate	Schizophrenia	2–6 weeks	25 mg/ml	Benzyl alcohol in sesame oil	1972	2009	IM
	Proluton Depot	Hydroxyprogesterone caproate	Risk of premature birth	Weekly	250 mg/ml	Benzyl benzoate in castor oil	1955	1999	IM
	Testoviron Depot	Testosterone propionate and testosterone enanthate	Male hypogonadism	Monthly	50 mg/ml testosterone propionate and 200 mg/ml testosterone enanthate	Benzyl alcohol in castor oil	1974		IM
	Trilafon	Perphenazine decanoate	Schizophrenia	Every 2–4 weeks	100 mg/ml	Sesame oil with propyl parahydroxybenzoate	1957		IM
Pre-formed Implant	Dextenza	Dexamethasone	Ocular inflammation and pain following ophthalmic surgery	30 days	0.4 mg (0.5 × 3 mm)	4-arm polyethylene glycol N-hydroxysuccinimidyl glutarate (20 K), trilysine acetate, N-hydroxysuccinimide-fluorescein, sodium phosphate monobasic, and sodium phosphate dibasic	2018		Intracanalicular
	Gliadel wafer	Carmustine	Anticancer (malignant glioma)	2–3 weeks	7.7 mg × 8 (1 mm × 145 mm)	Polifeprosan	1996		Intracranial
	iDose TR	Travoprost	Glaucoma and ocular hypertension	36 months	75 µg (0.5 mm × 1.2 mm)	Titanium	2023		Intracameral
	Iluvien	Fluocinolone acetonide	Diabetic macular oedema	36 months	0.19 mg (0.37 mm × 35 mm)	Water for injection, polyimide tube, polyvinyl alcohol, and silicone adhesive	2014		Intravitreal
	Implanon	Etonogestrel	Contraception	3 years	68 mg	Ethylene vinylacetate	2006		Subdermal
	Jadelle	Levonorgestrel	Contraception	Up to 5 years	75 mg × 2	Silicone	1996		Subdermal
	Norplant	Levonorgestrel	Contraception	Up to 5 years	36 mg × 6 (2.4 mm × 34 mm)	Silicone	1990	2008	Subdermal
	Ozurdex	Dexamethasone	Retinal vein occlusion; posterior segment uveitis; diabetic macular oedema	Up to 6 months	0.7 mg (6 mm × 0.46 mm)	Ester-terminated 50:50 poly D, L-lactide-co-glycolide acid-terminated 50:50 poly D, L-lactide-co-glycolide	2009		Intravitreal
	Probuphine	Buprenorphine hydrochloride	Opioid dependence	6 months	80 mg (2.5 mm × 26 mm)	Ethylene vinyl acetate	2016		Subdermal
	Retisert	Fluocinolone acetonide	Posterior segment uveitis	30 months	0.59 mg (3 mm × 2 mm × 5 mm)	Microcrystalline cellulose, polyvinyl alcohol, and magnesium stearate	2005		Intravitreal
	Supprelin LA	Histrelin acetate	Hormone-dependent advanced carcinoma of the prostate gland	12 months	50 mg (3 mm × 35 mm)	2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, and trimethylolpropane trimethacrylate	2007		Subdermal
	Suprefact Depot	Buserelin acetate	Advanced prostate cancer	2 or 3 months	6.3 or 9.45 mg	Poly D, L-lactide-co-glycolide acid-terminated 75:25	2000		Subdermal
	Vantas	Leuprolide acetate	Advanced prostate cancer	12 months	50 mg (3 mm × 35 mm)	2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, and trimethylolpropane trimethacrylate	2004	2021	Subdermal
	Viadur	Leuprolide acetate	Advanced prostate cancer	12 months	65 mg (4 × 45 mm)	Titanium alloy reservoir	2000	2007	Subdermal
	Vitrasert	Ganciclovir	Cytomegalovirus retinitis	5–8 months	4.5 mg (1 mm × 2.5 mm)	Ethylene vinylacetate (40% hydrolysed), polyvinyl alcohol (98% hydrolysed), and magnesium stearate	1996	2002	Subdermal
	Yutiq	Fluocinolone acetonide	Chronic non-infectious uveitis	36 months	0.18 mg (0.37 mm × 3.5 mm)	Polyimide tube, polyvinyl alcohol and silicone adhesive	2018		Intravitreal
	Zoladex	Goserelin acetate	Prostate cancer	3 months	3.6 and 10.8 mg	Poly(lactic-co-glycolic acid) (PLGA)	1997		Subdermal
In situ-forming implant	Atridox	Doxycycline hyclate	Chronic adult periodontitis	1 week	50 mg	Syringe A: 450 mg of Atrigel® delivery system (36.7% poly(DL-lactide) (PLA) dissolved in 63.3% N-methyl-2-pyrrolidone (NMP)); syringe B: 50 mg of doxycycline hyclate, which is equivalent	1998		Subgingival
	Camcevi	Leuprolide mesylate	Advanced prostatic cancer	6 months	48 mg (42 mg leuprolide equivalents)	Atrigel delivery system –48 mg leuprolide mesylate (48 mg), poly(D. L-lactide) (184 mg) polymer, and N-methyl-2-pyrrolidone (136 mg)	2021		Subcutaneous
	Eligard (Fensolvi)	Leuprolide acetate	Prostate cancer	1, 3, 4, 6 months	7.5, 22.5, 30, 45 mg	Atrigel delivery system	2004		Subcutaneous
	Perseris	Risperidone	Schizophrenia	Monthly	90 mg in 0.6 ml	Atrigel® delivery system with poly D, L-lactide-co-glycolide 80:20	2018		Subcutaneous
	Sublocade	Buprenorphine	Severe opioid use disorder	Monthly	300 mg in 1.5 ml or 120 mg in 0.8 ml	Atrigel® delivery system with poly D,L-lactide-co-glycolide 80:20	2017		Subcutaneous
	Uzedy	Risperidone	Schizophrenia	1 or 2 months	357.1 mg/ml	Steady Teq system: dimethyl sulfoxide (45% w/w), methoxy-poly(ethylene glycol)-co-poly(D,L-lactide) (15% w/w), and poly(D.L-lactide)-co-poly(ethylene glycol)-co-poly(D.L-lactide) (10% w/w)	2023		Subcutaneous
PLGA microsphere	Arestin	Minocycline HCl	Adult periodontitis	14 days	1 mg	50:50 poly(D,L-lactide-co-glycolide) polymer (37.2 mg per dose) and sucrose (0.8 mg per dose)	2001		Subgingival
	Bydureon	Exenatide	Type 2 diabetes	Weekly	2 mg	50:50 poly(D,L-lactide-co-glycolide) polymer (37.2 mg per dose) and sucrose (0.8 mg per dose)	2012	2021	Subcutaneous

TABLE 1 (*CONTINUED*)

Product type	Product name	Compound	Condition	Duration	Drug content	Excipients	Approval year	Discontinuation year	Route of administration
long-acting injectable	Lupron Depot	Leuprolide acetate	Advanced prostatic cancer	Every 1, 3, 4, and 6 months	3.75, 11.25, 22.5, or 45 mg	Polylactide-co-glycolide (1 mg drug in 3 mg polymer), polylactic acid (11% leuprolide acetate encapsulation in microspheres), and mannitol; diluent: polysorbate 80, sodium carboxymethyl cellulose, and water for injection	1998	2022	IM and subcutaneous
	Nutropin Depot	Somatotropin	Long-term treatment of growth failure	Once or twice monthly	13.5, 18, or 22.5 mg	Microparticles: 13.5 mg somatotropin, 1.2 mg zinc acetate, 0.8 mg zinc carbonate, and 68.9 mg PLG; 18 mg somatotropin, 1.6 mg zinc acetate, 1.1 mg zinc carbonate, and 91.8 mg PLG; 22.5 mg somatotropin, 2.0 mg zine acetate, 1.4 mg zinc carbonate, and 114.8 mg PLG; diluent: 30 mg/ml carboxymethylcellulose sodium salt, 1 mg/ml polysorbate 20, 9 mg/ml sodium chloride, and sterile water for injection	1999	2004	Subcutaneous
	Risperdal Consta	Risperidone	Schizophrenia	Every 2 weeks	25, 37.5, or 50 mg	75:25 polylactide-co-glycolide (PLG) (38% risperidone encapsulation in microspheres); diluent: water for injection, sodium carboxymethyl cellulose (2.25%), sodium chloride (0.6%), polysorbate 20 (0.1%), citric acid (0.1%), disodium hydrogen phosphate dihydrate (0.127%), and sodium hydroxide (0.054%)	2003		IM
	Sandostatin LAR	Octreotide acetate	Metastatic carcinoid tumours	Every 4 weeks	11.2, 22.4, or 33.6 mg	Mannitol, poly-dl-lactide-coglycolide and carboxymethylcellulose sodium	1998		IM
	Signifor LAR	Pasireotide pamoate	Acromegaly	Every 4 weeks	10, 20, 30, 40,or 60 mg	Polylactide co-glycolide (50–60:40–50), polylactide-co-glycolide (50:50); prefilled syringe: water for injection, mannitol, poloxamer 188, and carboxymethylcellulose sodium	2012		IM
	Trelstar Depot	Triptorelin pamoate	Advanced prostate cancer	Every 4 weeks	3.75 or 22.5 mg	Mannitol, poly-dl-lactide-coglycolide, polysorbate 80, and carboxymethylcellulose sodium	2000		IM
	Vivitrol	Naltrexone	Prevention of relapse to opioid dependence	Monthly	380 mg	75:25 polylactide-co-glycolide (PLG) (33.7% naltrexone encapsulation in microspheres); diluent: water for injection, polysorbate 20, carboxymethylcellulose sodium, and sodium chloride	2006		IM
Other types of long-acting platforms	Somatuline depot	Lanreotide acetate	Acromegaly	Every 4 weeks	60 mg/0.2 ml, 90 mg/0.3 ml, or 120 mg/0.5 ml	Liquid crystal formulation ~24.6%, lanreotide in water for injection	2007		Subcutaneous
	Plenaxis	Abarelix	Advanced prostatic cancer	Every 4 weeks	113 mg	Self-assembly peptide into nanotubes; complex with carboxymethylcellulose and 0.9% sodium chloride	2003	2005	IM
	Sunlencal	Lenacapavir sodium	HIV treatment	Every 6 months	473.1 mg in 1.5 ml	Aqueous solution in 896.3 mg of polyethylene glycol 300 (as solvent) and water for injection	2022		Subcutaneous

whereas preformed implants typically provide more predictable and sustained release kinetics.

PLGA-based injectable microparticles

The use of PLGA extends beyond the manufacture of solid implants and *in situ*-forming implants; it has been widely utilised in the production of microparticles for drug encapsulation (Figure 1a).[p8] These formulations can be administered intramuscularly, enabling sustained drug release through drug diffusion from the particles and PLGA degradation. Most of these products gained regulatory approval in the early 2000s (Table 1). One particularly well-known example is Risperdal Consta, a formulation containing PLGA microspheres loaded with risperidone for the treatment of schizophrenia.[p8] A single injection provides up to 28 days of drug release.[p8]

Challenges for current LADDS

Current LADDS have demonstrated clear success in specific therapeutic areas, as outlined in the previous sections and Table 1. However, several challenges remain in broadening their application to a wider range of conditions. A key limitation is their suitability primarily for potent drugs, as the volume of injectables or the size of implants restricts the total dose that can be delivered.

Drug release kinetics are a key consideration. Most formulations discussed earlier rely on diffusion and dissolution, offering sustained but uncontrolled release, with faster rates in the initial stages.[p11] For controlled, zero-order release, reservoir implants are preferred, as drug permeation through rate-controlling membranes enables a more consistent release profile.[p11] This factor is critical to avoid potential toxicity issues in the early stages caused by burst drug release.

Additionally, most LADDS are designed for single-drug delivery, limiting their effectiveness in patients who require combination therapies.[p12] Patient acceptability is also critical; formulations must be well tolerated. For instance, syringeability issues with *in situ*-forming gels or viscous injectables can cause pain during administration,[p12] and some formulations have been reported to cause adverse effects at the injection site, further impacting patient acceptance.[p13] Depot shape and size can also influence performance.[p14] Although preformed implants offer greater consistency, they often involve more invasive and painful procedures.

Finally, these formulations must be sterile because of their injectable or implantable nature. This can be achieved either through terminal sterilisation, which is more cost-effective but might alter product properties, or via aseptic manufacturing, which maintains product integrity but significantly increases production costs.

Future perspectives

Researchers are currently developing new types of LADDS. Although most of these emerging technologies align with previously discussed categories, they introduce innovations across various domains. The literature highlights a broad range of applications for these novel systems, with key areas including cancer treatment, particularly intratumoral drug delivery, as well as ocular diseases and chronic conditions such as HIV. This mini review

will focus on newly developed strategies rather than specific applications of the materials and technologies.

As highlighted earlier, progress in LADDS demands a multidisciplinary approach. The following subsections will examine how various fields are contributing to the advancement of next-generation LADDS.

Chemistry-based approaches for development of LADDS

Chemistry plays a central role, particularly in the synthesis of new polymers and drug complexes that enable sustained release. These can be formulated into nanoparticles, *in situ*-forming gels, or solid implants.

One common strategy involves thermoresponsive gels, liquids at ambient temperature that solidify into gels at body temperature. To this end, new materials such as peptide-like hydrogels have been developed.[p15],[p16] These materials offer excellent biocompatibility and biodegradability, and their properties can be easily tailored by modifying the amino acid sequence. Drugs are conjugated within the hydrogel backbone. These peptide-like hydrogels contain a phosphate group that renders the compounds soluble.[p15],[p16] However, upon injection, phosphatase enzymes trigger gelation, and the resulting depot relies on hydrolysis to release the drug in a sustained manner.[p15],[p16] Figure 2a shows a diagram of this type of injectable LADDS and how they work. This technology shows promise for the treatment of chronic conditions such as HIV.[p15],[p16]

Another approach involves the covalent attachment of drugs to synthetic polymers using ester bonds, allowing for slow release via hydrolysis. These types of compounds are known as 'drugamers' and have shown great promise to deliver HIV pre-exposure prophylaxis (Figure 2b).[p17] These types of polymeric-prodrugs do not only offer the possibility of long-acting drug delivery but they can be adapted to offer alternative properties, such as macrophage or dendritic cell targeting.[p18],[p19]

As an alternative to injectable depots, prodrugs have been synthesised to develop new types of nanoparticle formulations. This strategy involves converting hydrophilic parent molecules into hydrophobic prodrugs.[p20],[p21] These hydrophobic prodrugs can then be nanomilled to produce long-acting injectable suspensions. The approach has shown promise in the delivery of HIV therapies.[p20],[p21] This strategy has also been applied to create solid implants using hydrophobic prodrugs derived from hydrophilic HIV drugs (e.g. emtricitabine).[p22] As alternatives, solid implants have been developed using dexamethasone drug dimers (Figure 2c).[p23] In this way, solid devices can be manufactured with high drug loading, as the drug itself constitutes the main component of the device.[p23] Natural compounds have also been explored for the preparation of solid implants, such as silk fibroin or starch,[p24],[p25] which offer excellent mechanical properties while also being biocompatible and biodegradable.

In addition to the approaches previously discussed, emerging hydrogels show promise not only for injectable LADDS but also for the development of stimuli-responsive systems. Material properties such as surface charge,[p26] thermoresponsiveness, and magnetic sensitivity can be harnessed to control drug release.[p27] External stimuli, such as electrical voltage, ultrasound, and magnetic fields, have been shown to trigger drug release. However, this strategy is generally more suitable for potent drugs, as it currently lacks the capacity to deliver high doses effectively.

Although these approaches offer significant potential and versatility, there are outstanding regulatory challenges, as the creation of new chemical entities can complicate approval processes. Combining known drugs with already-approved polymers could provide a more efficient route to market.

Engineering-based approaches for development of LADDS

Engineers have also developed devices that regulate drug release over extended durations. A simple technique involves embedding drugs in polymer matrices via hot-melt extrusion,[p28],[p29] but this often requires optimisation of factors like crystallinity and drug-polymer interactions. However, optimise process parameters could be somewhat challenging. Additionally, pilot studies normally require large amounts of drugs and excipients, making the development expensive. Recently, vacuum compression moulding has shown promise for formulation development, using smaller material quantities and thus accelerating early-stage research.[p30],[p31]

Also, researchers have explored the use of advanced manufacturing techniques such as 3D printing, allowing fast implant customisation.[p32],[p33],[p34],[p35],[p36],[p37] This allows the preparation of implants adapted to the patient's needs, customising drug loading and dose and release profiles. The technology is promising but before it can be applied there are still many unanswered regulatory questions.[p38]

In addition to advancements in manufacturing techniques, implant geometry can be optimised to enhance drug release characteristics. Semipermeable membranes offer a greater degree of control over drug release.[p11] Monolithic implants often exhibit an initial burst release because of the high concentration of drug on the surface of the device.[p11] In contrast, reservoir-type implants incorporate rate-controlling membranes, providing more precise regulation of the release process.

These membranes have been developed using a diverse range of polymers, including biodegradable materials such as poly(caprolactone) (Figure 3a) and silk fibroin.[p39],[p40],[p41],[p42],[p43],[p44] Their porosity can be tailored by adjusting parameters such as material composition and processing conditions.[p39],[p40],[p41] Porous membranes have demonstrated significant potential in *in vivo* experiments, particularly in the delivery of risperidone for schizophrenia treatment.[p41] Additionally, drugs can be incorporated into the membrane. A good example of this is the use of lidocaine loaded into the membrane to reduce pain associated with implant administration.[p42]

More advanced porous membranes, featuring nanoscale pores, have also been developed.[p45],[p46] These membranes have been integrated into subcutaneous implants designed to be refillable through the skin (Figure 3b). These devices facilitate sustained drug release through passive permeation via nanometric channels. The technology has demonstrated its effectiveness in delivering HIV treatments in animal models (Figure 3b),[p47],[p48] maintaining consistent testosterone replacement therapy,[p49] and enabling intratumoral sustained drug delivery for cancer treatment.[p50] Additionally, the implant design can be modified to enable refilling with solid therapeutics, to extend the duration of drug release.[p51]

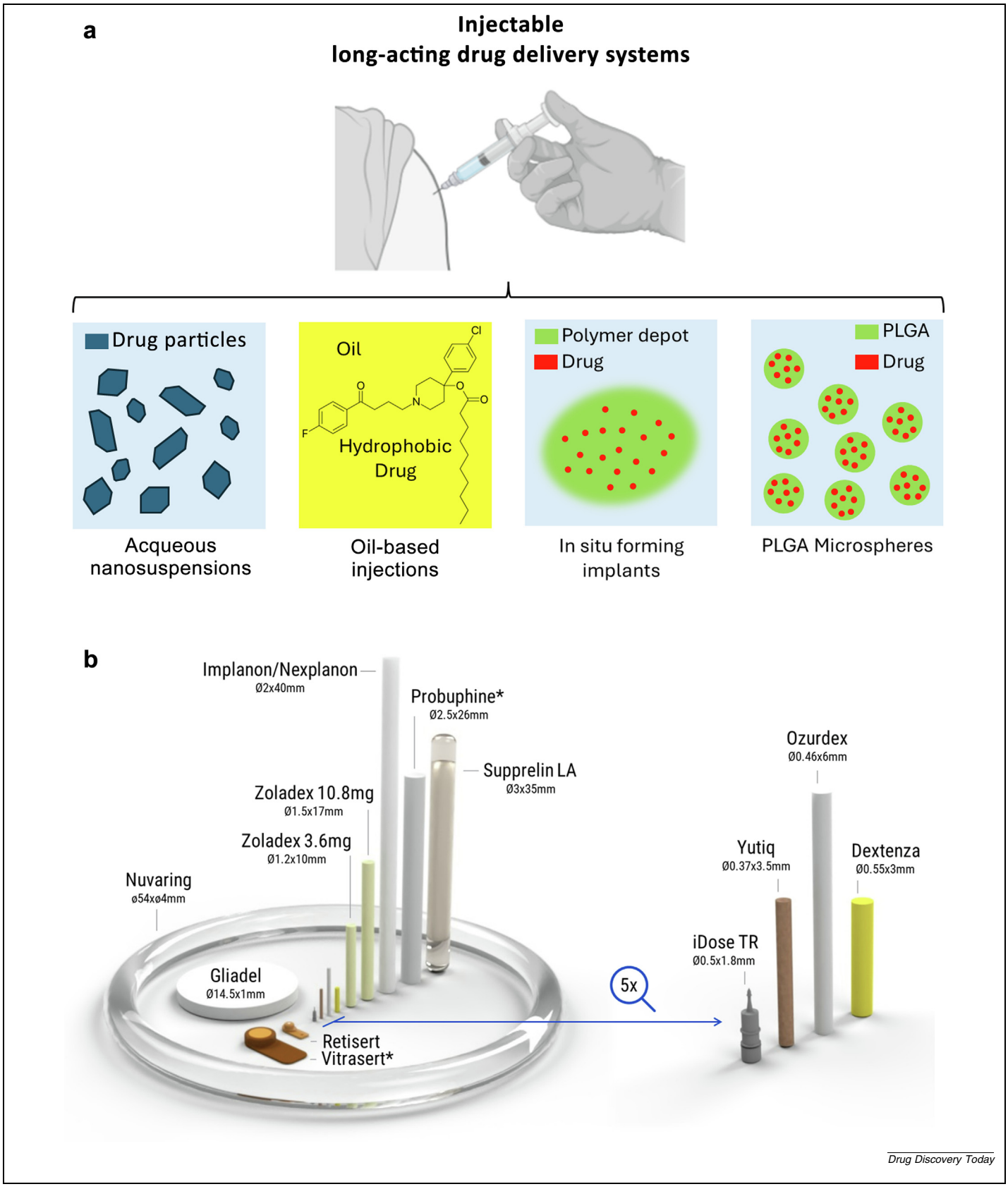

FIGURE 1

Diagram showing different types of injectable **(a)** and implantable **(b)** LADDS. Panel b image was provided by MeltPrep®.

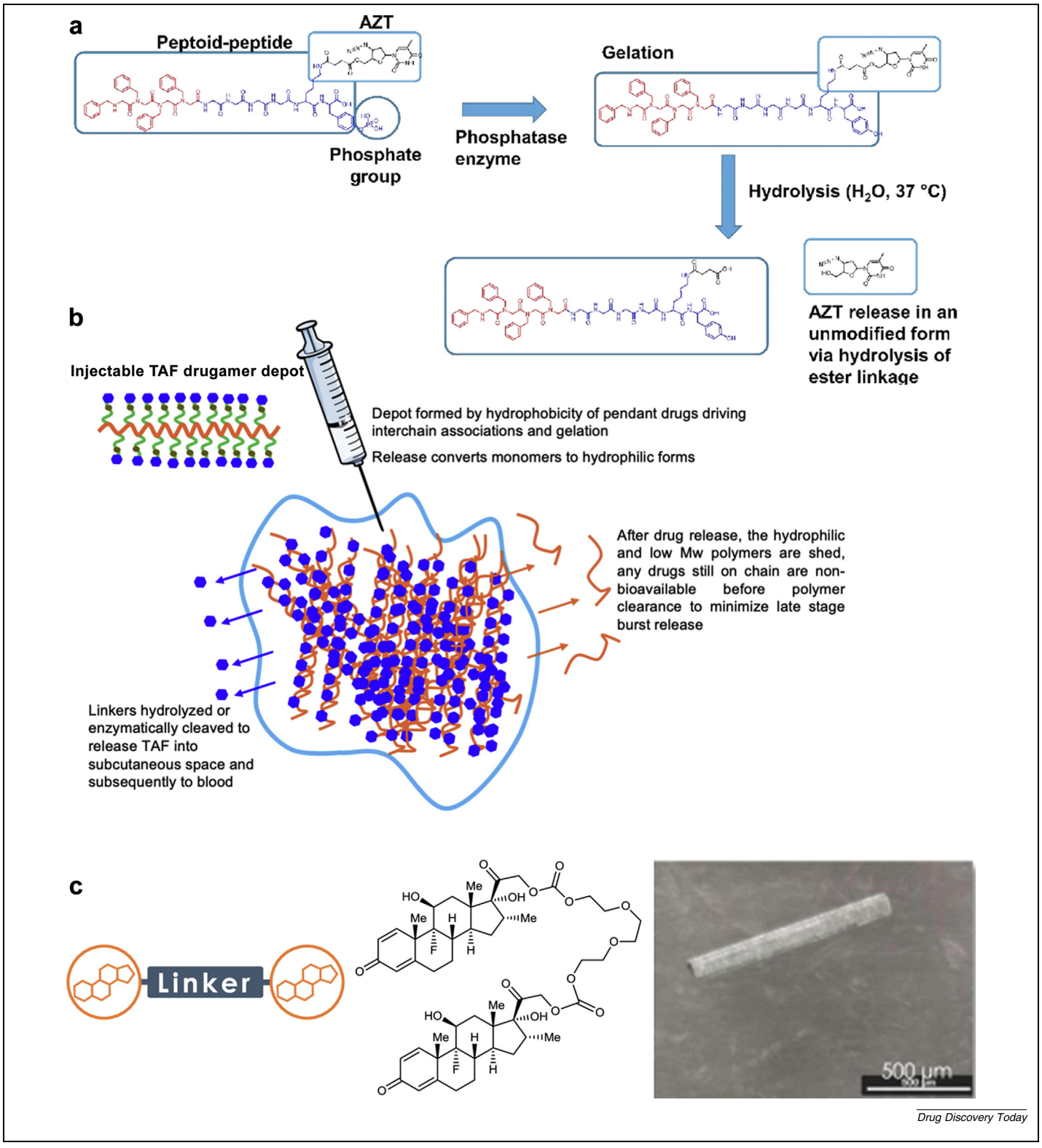

FIGURE 2

Diagram showing **(a)** the behaviour of peptide-like (peptoid) hydrogels containing zidovudine (AZT) and **(b)** polymeric 'drugamers' after injection. **(c)** Diagram of dexamethasone dimers and image of a solid implant using this compound. Reproduced with permission from (p16),(p17),(p23).

Engineers are advancing this field not only through improved manufacturing techniques but also via the development of active implantable devices for on-demand drug delivery. Actuation can be achieved using stimuli-responsive materials that react to external triggers such as magnetic fields or ultrasound.[p27],[p52] A common method involves reservoir-type implants with a responsive barrier that controls drug release. Upon stimulation, such as localised heating from magnetic fields or ultrasound, the barrier melts or opens, allowing the drug to be released. Magnetic nanoparticles embedded in lipids have been used for this purpose.[p52]

Implantable electronics now allow external control by clinicians and patients,[p53],[p54] with some systems designed as closed-loop devices requiring no intervention.[p55] These devices employ a variety of approaches to deliver both liquids[p56] and solid particulates,[p57] with solids favoured for their improved stability. Although highly promising, these implants are better suited to potent drugs because of the limited loading capacity. Traditional electronics use non-biodegradable metals and plastics, but recent research into biodegradable components is paving the way for more sustainable and adaptable devices.

Innovative active implants that do not rely on electronics have also emerged, enabling programmable or triggered drug release via mechanisms such as clock actuators[p58] or refillable osmotic pumps that propel gas-actuated pistons for subcutaneous infusion.[p59]

Although highly promising, these implants are generally more suited to potent drugs, as their compact design often limits drug-loading capacity. Additionally, most electronic components are traditionally composed of metals and plastics, making them non-biodegradable. However, in recent years, a growing body of research has explored the development of biodegradable electronic components, paving the way for more sustainable and versatile implantable devices.

Engineering approaches are not only focused on adapting drug release rates but also improving the LADDS administration. Although LADDS offer advantages over traditional drug administration, including sustained release and improved compliance, they often require invasive procedures such as surgery or the use of a trocar. Injectable systems, although less invasive, still pose risks such as needlestick injuries and require healthcare professionals for administration.

To overcome these limitations, research has turned toward minimally invasive solutions. One such innovation is the microarray patch (MAP), a device with microneedles (MNs) that painlessly penetrate the skin and deliver long-acting formulations via water-soluble polymers (Figure 3c).[p60],[p61],[p62] These patches can be self-administered, enhancing accessibility to treatment. Although they might not deliver high drug volumes, they offer promise for applications like long-acting HIV treatments. Hybrid MAPs, containing implantable biodegradable tips, have recently been developed to provide sustained intradermal drug release post-application.[p63],[p64],[p65]

Biodegradable microimplants, longer, needle-like devices made from degradable polymers, represent another alternative.[p66],[p67] These systems resemble MAPs in function but are intended for biologic drugs.

Pharmacy-based approaches for development of LADDS

The development of LADDS requires the input of pharmaceutical scientists. The success of LADDS is heavily influenced by parameters such as drug solubility, stability, and crystallinity, among others. Pharmacists and pharmaceutical scientists have extensive experience in this area. Formulation strategies can be used to modify drug performance and achieve sustained drug release. Also, combining drugs with established excipients or polymers can simplify development while facilitating regulatory approval. This strategy applies across LADDS technologies, such as nanoparticle encapsulation using pharmaceutical-grade materials or combining drugs with thermoresponsive agents like poloxamers. In solid implants, selecting appropriate excipients can drastically influence drug release profiles. In reservoir-type devices, excipients within the core can improve solubility and release rates. Cyclodextrins or other solubility enhancers have been used to enhance hydrophobic drug delivery in core–shell systems.[p41],[p42],[p68],[p69] These approaches have been applied to the delivery of HIV drugs or antipsychotics.[p41],[p68] However, solubility can also be controlled by using other strategies such as reducing the pH. Biodegradable polymers capable of providing a micro-acidic environment inside implants will increase the solubility of certain drugs, such as antipsychotics.[p70] This technology can be used to enhance hydrophobic drug release from reservoir-type implants.

Key challenges in advancing future LADDS

The development of the new strategies presented here demonstrates limitations similar to those of current approaches. A common issue is the requirement for sterile systems; therefore the sterilisation methodology should be carefully considered when designing new LADDS, as conventional sterilisation techniques can impact both performance and material properties. This is particularly important for new polymer- or peptide-based strategies.

Moreover, achieving a sustained drug release profile that maintains therapeutic drug levels is typically only feasible for potent drugs. Repeated injections are often necessary for injectable systems. An alternative to overcome these limitations of implantable systems could be the use of novel strategies such as the aforementioned transcutaneous refillable systems. Additionally, relying on chemically labile bonds can delay drug release from formulations, rather than depending solely on passive diffusion. Ultimately, the highest degree of control can be achieved through actuated devices that precisely regulate drug release.

Another key aspect, often overlooked, is the foreign body reaction to LADDS following administration. Tuning material properties is critical to avoid such reactions, which can lead to the formation of a fibrous capsule around the LADDS, thereby preventing effective drug release.[p71],[p72] Minimising foreign body response requires a multidisciplinary approach, as various LADDS-related parameters are involved such as surface roughness and charge, chemical composition, material type, and the size and shape of the formulation once administered.[p71] The implementation of these technologies requires regulatory clearance and clinical trials. Regulatory approval can be particularly

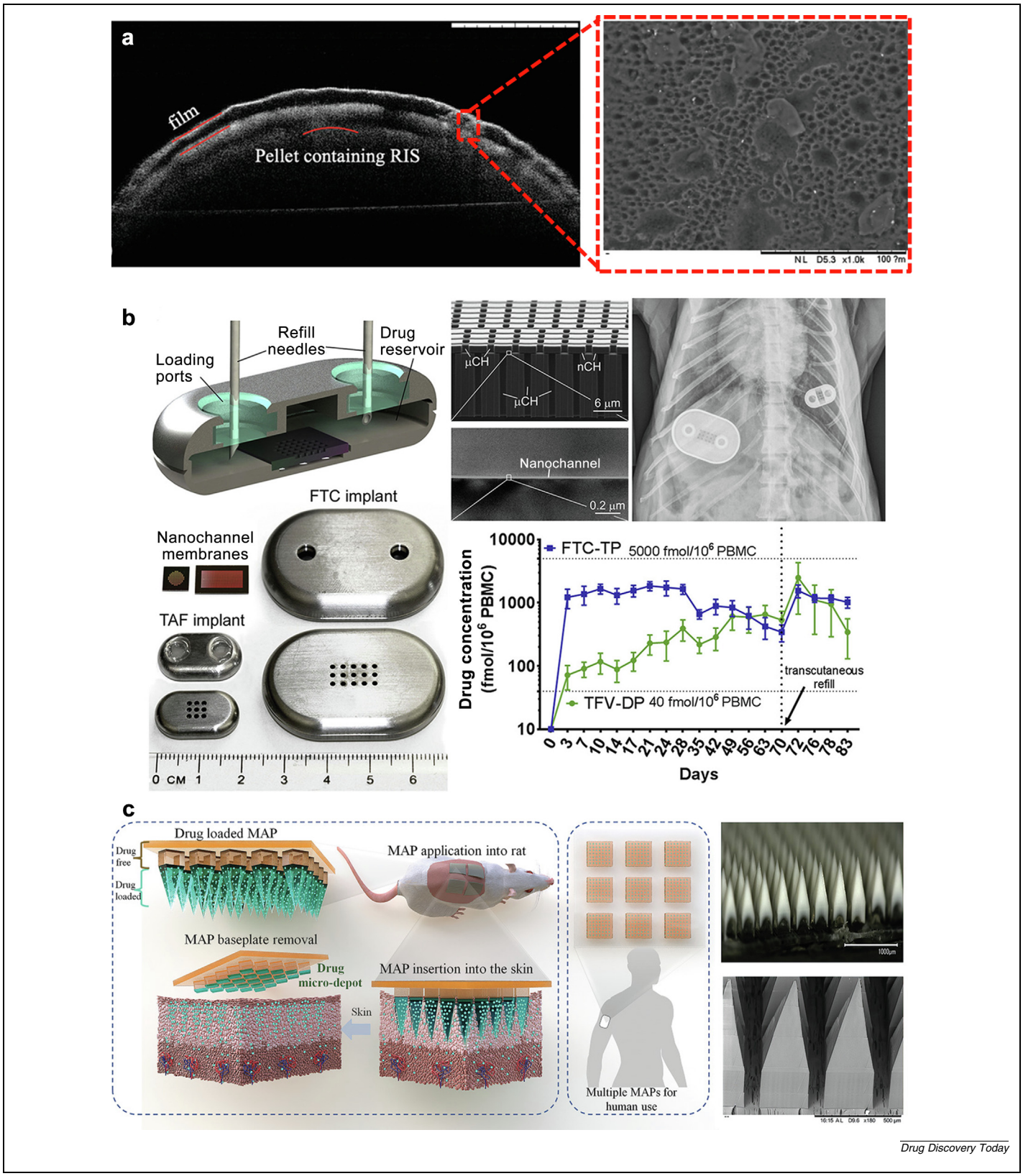

FIGURE 3

(a) Cross section of an implant coated with a poly(caprolactone) porous membrane and scanning electron microscopy (SEM) image of the membrane. **(b)** Reservoir implant containing nanochannels. Top right panels show SEM images of the structure of the channels and an X-ray image of the implants in a monkey animal model. Bottom right panel shows drug pharmacokinetics profiles for the delivery of tenofovir alafenamide–diphosphate (TFV-DP) and emtricitabine (FTC). **(c)** Diagram of microneedle (MN) arrays loaded with long-acting suspensions. Right panel shows an optical microscopy image and an SEM image of the MN arrays loaded with cabotegravir nanosuspensions. Reproduced, with permission, from (p41),(p48),(p60).

challenging for some of these novel strategies, as they often involve new chemical entities or unregulated approaches. To facilitate faster regulatory clearance, the use of already-approved materials in the development of new LADDS is highly recommended.

In addition to technical challenges, patient-centred design should be a priority. Co-design strategies that involve patients in the design and development process are preferred, as this approach maximises patient acceptability and adoption of the technology.

Concluding remarks

LADDS have evolved considerably from their early forms, offering more precise control over drug release, improved patient adherence, and potential reductions in systemic side effects. The current landscape shows a robust pipeline of innovations spanning various technological platforms, including injectables (aqueous nanosuspensions, PLGA-based particulate systems, oil-based injections, and *in situ*-forming depots) and implantables such as the preformed implants, many of which are already in clinical use. Emerging materials, advanced manufacturing techniques such as 3D printing, and minimally invasive delivery platforms such as MAPs and microimplants further expand the potential of LADDS and represent promising future directions, especially in global health settings.

Still, key challenges remain. These include improving drug-loading efficiency, achieving precise release kinetics, simplifying manufacturing, and addressing regulatory uncertainties, particularly for systems involving new chemical entities. Continued multidisciplinary collaboration between chemists, biologists, engineers, and pharmaceutical scientists will be essential to drive innovation and translation in this rapidly evolving field.

CRediT authorship contribution statement

Eneko Larrañeta: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Juan Domínguez-Robles:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization.

Acknowledgments

E.L. would like to acknowledge the Academy of Medical Sciences (SBF005\1011) for their financial support for this work. J.D.R. acknowledges the project PID2023-149078OA-I00 funded by MICIU/AEI/10.13039/501100011033, FEDER, EU; and the project RYC-2021 034357-I, funded by MICIU/AEI/10.13039/501100011033 and the European Union NextGenerationEU/PRTR.

Declaration of interests

No interests are declared.

Data availability

No data was used for the research described in the article.

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