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Challenges and innovations in long-acting injectable formulations: can formulation design space be rationalized?

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Abstract

Objectives: To date, ∼70 long-acting injectable (LAI) formulations have been developed. More than half of these formulations consist of oily solutions and suspensions containing poorly water-soluble drugs. However, numerous drugs do not fall into the category of poor solubility, such as hydrophilic small molecules, nucleic acids, peptides, and proteins. These drugs are typically formulated using biodegradable poly(lactide-co-glycolide) polymers. An important question to consider is whether there are guiding principles for selecting appropriate drugs for LAI formulations. The historical advancements and challenges associated with LAI formulations were examined to identify indicators that may predict effective drug candidates for this type of delivery system.

Key findings: Several properties of drugs, including water solubility, lipophilicity, tissue permeability, half-life ($t_{1/2}$), and effective dosage, were analysed in relation to the development of LAIs. This study investigated several parameters to forecast formulation success, with a focus on achieving an optimal balance between the drug's partition coefficient (logP), which reflects both water solubility and cellular permeability, and the effective dose.

Summary: The current overview of recent innovations and formulation considerations indicates that a systematic approach, integrating two key parameters, logP and the effective dose of a drug, may be employed for the preliminary screening of drugs that have the potential to be formulated into LAIs with a higher probability of success in clinical applications.

Keywords: long-acting injectables (LAIs); PLGA; oily solutions; partition coefficients; logP; tissue permeability; target specificity

Development of drug delivery systems

The field of drug delivery has developed a range of new technologies over the past several decades. While we appreciate the progress that new technologies have brought, we recognize that the speed of technological advancements in the pharmaceutical industry is lagging behind the rapid changes in other fields, such as electronic systems like computers and smartphones. The critical difference between the drug delivery field and others is that safety and efficacy must be demonstrated in humans through highly controlled clinical studies, which often take years and decades.

The introduction of a new drug delivery technology is often followed by a wave of products for various drugs and variations of the technology. As long as the safety and efficacy criteria for new drugs are met, the same technology can be applied to other drugs. At the beginning of controlled drug delivery technologies, dissolution-controlled technology in oral formulations was followed by diffusion-controlled, osmosis-controlled, and ion-exchange-controlled technologies. The availability of similar technologies has led to the development of hundreds of new once-a-day formulations. There is no need to make a formulation unnecessarily complex. In fact, simpler formulations are typically better suited for clinical translation. Progress in drug delivery technologies must consider the transition from laboratory to clinical applications. A summary of new drug delivery technologies introduced over the past seven decades is provided in Table 1.

Understanding the mechanism is the fundamental requirement for developing effective treatments. A good example of this is oral controlled-release formulations, which are produced even today using the same drug-release mechanisms. This is largely due to the simplicity of the formulations. Oral drug delivery, however, is limited to the delivery of small molecules only up to 24 h. Recent advances have demonstrated that certain peptide drugs can be formulated into oral preparations, as seen in Rybelsus (Table 1). While oral delivery of peptide drugs using absorption enhancers provides convenience to patients, the high cost of making synthetic peptides presents a considerable challenge in manufacturing cost due to poor oral bioavailability (usually ∼1% or less) and a ∼100-fold increase in weekly dose requirements when switching from the typical dose of subcutaneous (SQ) administration (1 mg) to oral (98 mg) [1–4]. A recent article reviewed the current status, challenges, and translational considerations of the oral delivery of biologics, including nucleic acid and protein therapeutics [5]. Despite significant advances in

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Table 1. The first formulations approved by the US FDA introducing new technologies.

Formulation	Product	Year
Dissolution-controlled oral formulation	Spansule®	1952
Oil-based long-acting injectable	Prolixin®	1972
Diffusion-controlled ocular formulation	Ocusert®	1974
Osmosis-controlled oral formulation	OROS®	1975
Ion exchange-controlled oral formulation	Delsym®	1982
PLGA-based long-acting injectable	Lupron Depot®	1989
PEGylated protein	Adagen®	1990
PEGylated caster oil micelle	Taxol®	1994
PEGylated liposome	Doxil®	1995
Ab-drug conjugate	Mylotarg™	2000
Nanocrystals	Rapamune®	2000
Amorphous solid dispersion	Kaletra®	2000
Albumin–drug complex	Abraxane®	2005
PEGylated small molecule	Movantik®	2014
CAR-T gene therapy	Kymriah®	2017
PEGylated lipid nanoparticle	Onpattro®	2018
Oral peptide delivery	Rybelsus®	2019

oral drug delivery systems, the oral delivery of biologics still requires a series of new scientific breakthroughs [5].

Table 1 also highlights the significance of introducing new technologies, such as PEGylation. Once PEGylation [the grafting of poly(ethylene glycol) (PEG) to drugs] was introduced as a safe and effective method, it was applied to various formulations. One notable formulation was Onpattro, which used PEGylated lipid nanoparticles for the delivery of small interfering RNA (siRNA). The same formulation was used to develop the COVID-19 vaccine in 2021. Imagine a situation where no formulation was available to deliver the messenger RNA (mRNA) used for making the vaccine. The availability of drug delivery vehicles approved by the US Food and Drug Administration (FDA) accelerated the clinical application.

Of the formulations listed in Table 1, this article focuses on long-acting injectables, such as Lupron Depot. The long duration, ranging from a week up to 6 months, requires time-consuming studies to establish the safety and efficacy of the formulations. It is reported that >200 long-acting injectable (LAI) formulations are in clinical use [6]. The development of LAI formulations requires ensuring enhanced therapeutic outcomes by controlling drug release kinetics and stability, thereby achieving both safety and efficacy [6]. The goal of this article is to explore a system that can enable the efficient development of LAI formulations, achieving a higher success rate and lower failure rate in clinical studies through the judicious selection of a drug and formulation based on *in vitro* studies.

Long-acting injectable formulations

A brief history

Two pillar excipients for the fabrication of LAI formulations are lipids (or oils) and polymers, which play various roles ranging from support vehicles to release rate modifiers, stabilizers, solubilizers, permeation enhancers, and transfection agents [7]. Oil-based solutions include oily solutions with dissolved drugs and oily suspensions with solid drugs. The drugs are dissolved in pharmaceutical oils, such as sesame seed oil or middle-chain triglycerides [8]. Upon intramuscular (IM) or subcutaneous (SQ) injection, drug transfer from the oil phase into the tissue fluid represents the main release-limiting factor [8]. The spreading of the oil solution along the muscle fibres can occur, increasing the surface area and thereby accelerating drug release [9, 10]. Key advantages of oil-based solutions include uncomplicated manufacture (including terminal sterilization) and feasible long-term stability [9]. Despite their cost-effectiveness and simple manufacturing processes, oil-based depot formulations have not been widely used recently, likely due to difficulties in tuning drug release kinetics [11].

The first LAI oily solution formulation approved by the FDA is Proluton Depot, which delivers hydroxyprogesterone caproate for a week [12]. It was approved in 1956 but subsequently withdrawn from the market in 2000. Makena, which delivers the same drug, was approved in 2011 but was also withdrawn in 2023 [13]. Makena was not shown to be effective in a confirmatory clinical trial for reducing the risk of preterm birth in women with a singleton pregnancy, and the benefits were not shown to outweigh the risks [13, 14]. The fluphenazine enanthate formulation was developed by G.R. Daniels at E.R. Squibb & Sons Ltd in 1966, followed by the development of fluphenazine decanoate [15]. It was the fluphenazine decanoate formulation that exhibited an extended duration of action with potentially lower side effects [16], which was approved by the US FDA in 1972 (Prolixin decanoate) [17].

Aqueous suspension formulations are also widely used for LAI formulations. Submicron-size drug crystals are suspended in aqueous media and generally administered via the IM route [10]. A common method of preparing oil-based LAI formulations involves the covalent attachment of a fatty acid chain to drugs, forming prodrugs that are then placed in the oil phase. Decanoate, enanthate, and caproate are often used to construct an ester bond with the parent drug, increasing its solubility in the oil phase and enhancing its partitioning into fatty tissues [8]. Drugs deposited in fatty tissues can form a reservoir for sustained release into the surrounding blood. The drug release rate depends on the slow release of prodrugs from fatty tissues into the circulation, as well as the sustained hydrolysis of ester bonds to release the parent drug [11]. The parameters affecting the drug release include the drug

concentration in the oil phase, the surface area of the oil depot, and the partition coefficient between the tissue fluid and the oil depot.

Current long-acting injectable formulations approved by the Food and Drug Administration

Over the years, numerous LAI formulations have been developed. Different types of LAIs include oily solutions, suspended solids, microparticles, solid implants, and *in situ* forming (ISF) implants, as listed in Table 2. ISF implants are distinguished from oleogels, which are semisolid systems consisting of oil as a liquid constituent, immobilized by the gelator into a continuous phase [18]. Oleogels are also structurally distinct from oily solutions or suspensions. ISF implants are based on dissolving a drug and PLGA in an organic solvent, e.g. N-methyl-2-pyrrolidone (NMP). NMP dissolves in water in all proportions, i.e. completely miscible with water. Thus, upon injection, NMP is diluted with body fluid, causing the precipitation of PLGA polymers to form a gel, which then solidifies into a solid implant. In addition to widely used PLGA polymers, there are LAI formulations that were not based on other biodegradable polymers. For example, Zynrelef and Sustol use tri(ethylene glycol)-poly(orthoester), and Gliadel is based on poly[bis(*p*-carboxyphenoxy)propane]:sebacic acid, both of which are biodegradable. The use of nonbiodegradable polymers includes poly(ethylene-co-vinyl acetate) (Probuphine and Implanon) and poly(2-hydroxyethyl methacrylate)/poly(2-hydroxypropyl methacrylate) (Vantas and Supprelin LA) [12]. Since the formulations of nonbiodegradable polymers require surgical removal at the end of their use, they are limited to drug delivery for at least a few years.

Table 2: Formulations in this table were collected from [9, 12, 17–23]. LogP values were mostly obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and DrugBank (https://go.drugbank.com/). Many logP values on websites are known to be calculated using XLOGP3 (http://www.sioc-ccbg.ac.cn/skins/ccbgwebsite/software/xlogp3/), an atom-additive method that calculates logP (the octanol–water partition coefficient) by summing the contributions from each atom in the given molecule, and a method for the fast calculation of logP [24].

In Table 2, the drug release from oily solutions and suspension formulations is primarily attributed to the poor solubility of the drug. On the other hand, microparticles, ISF implants, and solid implants are based on PLGA polymers to control the release of the drug. Thus, the PLGA-based formulations can deliver both poorly soluble drugs and water-soluble drugs, including peptides and proteins. Despite the versatility of the PLGA formulations, Table 2 indicates that >60% (41/66) of the total LAI formulations are oily solutions and suspension formulations. This may be partly due to the earlier approval of the oily solution formulation (Prolixin in 1972) compared with the first PLGA formulation, approved in 1989 (Lupron Depot) by the FDA.

Analysis of the data in Table 2 reveals several interesting observations. The products in Table 2 were plotted against the normalized monthly dose (dose/month) of each product in Fig. 1. The first apparent general correlation is that the normalized monthly dose decreases in the order of LAI types: oily solutions, suspensions, microparticles, ISF implants, and solid implants. Oily solution and suspension formulations can deliver 1000 mg/month because they do not need PLGA polymers, which can occupy a substantial weight fraction of the formulations. The highest dose for PLGA microparticle formulations is 380 mg/month for Vivitrol, delivering naltrexone. For ISF implants, Sublocade has the highest dose of 300 mg/month. Conversely, solid implants are used to produce only up to 10 mg/month maximum.

Oral formulations vs. long-acting injectable formulations

The original biopharmaceutics classification system (BCS) for orally delivered drugs is constructed on solubility and permeability. Here, the permeability means the membrane permeation of the drug into the intestinal mucosa of the gastrointestinal (GI) tract, which results in its absorption [25]. For oral drug delivery, high solubility means that the highest dose of a drug recommended for human use is soluble in 250 ml or less in aqueous media throughout the pH range of 1.2–6.8, and high permeability means ≥90% of a dissolved drug is absorbed from the GI tract [26]. The BCS has made a far-reaching impact in drug discovery, development, and delivery, recognizing the importance of water solubility and permeability of a drug [25]. It established an *in vitro–in vivo* correlation for immediate release oral products by allowing product dissolution data as a surrogate for costly and time-consuming *in vivo* bioavailability studies [27]. Thus, the BCS has been highly useful in obtaining bioavailability waivers for immediate-release formulations of generic drugs that belong to class I, characterized by high solubility and permeability.

The question for LAI formulations is whether the same two parameters, solubility and permeability (representing absorption), used in oral formulations can be applied to drugs for LAI formulation development. Drug solubility and permeability may not be suitable for designing LAI formulations for drugs. The permeability of a drug from the LAI formulation through the surrounding tissues at the injection site differs from its permeability through the GI tract. LAI formulations have different design criteria than other types of injectables or oral drug products, as their target product profiles are drastically different [28].

There is no doubt that more LAI formulations will be developed in the future. One question facing formulation scientists is whether there are any principles that determine which drugs can be good candidates for preparing LAI formulations. Oily solution and suspension formulations account for >60% of the total LAI formulations on the market, primarily due to their ease of manufacture. However, such formulations cannot be used for most drugs, especially hydrophilic small molecules, nucleic acids, peptides, and protein drugs. The physicochemical properties critical for *in vivo* release and absorption kinetics include water solubility, hydrophobicity (or partition coefficient), pKa, intrinsic dissolution rate, and molecular weight [28]. It is generally understood that the upper molecular weight for oral delivery is around 500 g/mol. The average molecular weight of all drugs in Table 2 is 865 g/mol. If peptide drugs are excluded, the average molecular weight of the remaining small molecules is 499 g/mol, with a range of 293–981 g/mol. The doses for peptide drugs are typically 100 mg or less, whereas the doses for small molecules can range up to 1000 mg. Since Nutropin Depot

Table 2. Examples of various types of long-acting injectables (LAIs).

	Product	LAI type	Drug	Mol. wt. (g/mol)	LogP	Water solubility (mg/ml)	Dose
1	Faslodex	Oily solution	Fulvestrant	293.4	2.10	0.5000	500 mg/month
2	Androcur Depot	Oily solution	Cyproterone acetate	416.9	3.81	0.0001	300 mg/2 weeks
3	Haldol Depot	Oily solution	Haloperidol decanoate	530.1	4.30	0.0001	140, 400 mg/month
4	Testoviron Depot	Oily solution	Testosterone propionate	344.5	4.40	0.0001	50 mg/month
5	Cisordinol-Acutard	Oily solution	Zuclopenthixol acetate	443.0	4.79	0.0006	200, 500 mg/month
6	Proluton Depot	Oily solution	Hydroxyprogesterone caproate	428.6	4.81	0.0009	250 mg/week
7	Naldebain ER	Oily solution	Dinalbuphine sebacate	881.1	5.34	0.0003	20 mg/week
8	Makena	Oily solution	Hydroxyprogesterone caproate	428.6	5.88	0.0065	250 mg/week
9	Delestrogen	Oily solution	Estradiol valerate	356.5	6.00	0.0001	10–20 mg/month
10	Noristerat	Oily solution	Norethisterone enantate	410.6	6.00	0.0010	100, 200 mg/2 months
11	Gynodian Depot	Oily solution	Estradiol valerate	356.5	6.00	0.0001	4 mg/month
12	Depo-Testosterone	Oily solution	Testosterone cypionate	412.6	6.11	0.0001	400 mg/month
13	Gynodian Depot	Oily solution	Prasterone enanthate	400.6	6.28	0.0001	200 mg/month
14	Testoviron Depot	Oily solution	Testosterone enanthate	400.6	6.30	0.0001	200 mg/month
15	Primobolan Depot	Oily solution	Methenolone enanthate	414.6	6.90	0.0001	200, 400 mg/week
16	Deca-Durabolin	Oily solution	Nandrolone decanoate	428.6	7.30	0.0561	50 mg/3 weeks
17	Fluanxol Depot	Oily solution	Fluphenazine decanoate	591.8	8.22	0.0002	5 mg/2 weeks
18	Lyogen Depot	Oily solution	Fluphenazine decanoate	591.8	8.22	0.0002	45 mg/6 month
19	Prolixin Decanoate	Oily solution	Fluphenazine decanoate	591.8	8.22	0.0002	12.5–100 mg/month
20	Nebido	Oily solution	Testosterone Undecanoate	456.7	8.50	0.0001	1000 mg/3 months
21	Depixol	Oily solution	Flupentixol decanoate	588.8	8.80	0.0001	50 mg/month
22	Clopixol Depot	Oily solution	Zuclopenthixol decanoate	555.2	9.00	0.0001	200, 500 mg/month
23	Piportil	Oily solution	Pipotiazine palmitate	714.1	10.50	0.0001	50–100 mg/month
24	Apretude	Suspension	Cabotegravir	405.4	1.04	0.0001	600 mg/2 months
25	Bicillin L-A	Suspension	Penicillin G benzathine	981.2	1.92	0.2850	917 mg/month
26	Kenalog (IM)	Suspension	Triamcinolone acetonide	434.5	1.94	0.0210	60 mg/1.5 months
27	Xipere (eye)	Suspension	Triamcinolone acetonide	434.5	1.94	0.0210	4 mg/3 months
28	Depo-Medrol	Suspension	Methylprednisolone acetate	416.5	2.58	0.0193	40 mg/2 weeks
29	Depo-Provera	Suspension	Medroxyprogesterone acetate	386.5	4.10	0.0001	150, 400 mg/3 months
30	Depo-SubQ Provera	Suspension	Medroxyprogesterone acetate	386.5	4.10	0.0001	104 mg/3 months
31	Zyprexa Relprevv	Suspension	Olanzapine pamoate	718.8	4.58	0.0042	300–405 mg/month
32	Abilify Maintena	Suspension	Aripiprazole	448.4	4.60	0.0078	300–400 mg/month
33	Abilify Asimtufii	Suspension	Aripiprazole	448.4	4.60	0.0078	720, 960 mg/2 months
34	Aristada	Suspension	Aripiprazole lauroxil	660.7	4.70	0.0002	880 mg/2 months
35	Aristada Initio	Suspension	Aripiprazole lauroxil	660.7	4.70	0.0002	880 mg/1.5 months
36	Cabenuva	Suspension	(Cabotegravir &) rilpivirine	366.4	4.86	0.0185	600, 900 mg/month
37	Sunlenca	Suspension	Lenacapavir	968.3	6.47	0.0036	927 mg/6 months
38	Invega Sustenna	Suspension	Paliperidone palmitate	664.9	10.10	0.0070	234 mg/month
39	Invega Trinza	Suspension	Paliperidone palmitate	664.9	10.10	0.0070	819 mg/3 months
40	Invega Hafyera	Suspension	Paliperidone palmitate	664.9	10.10	0.0070	1092, 1560 mg/6 months
41	Bydureon	Microparticle	Exenatide	4187.0	−21.00	25.0000	2 mg/week
42	Triptodur	Microparticle	Triptorelin	1311.5	−0.41	0.0305	22.5 mg/6 months
43	Arestin	Microparticle	Minocycline HCl	493.9	−0.03	3.0700	1 mg/2 weeks
44	Sandostatin LAR	Microparticle	Octreotide acetate	1139.3	0.42	0.0122	20 mg/month
45	Lupron Depot	Microparticle	Leuprolide acetate	1209.4	1.07	0.0354	45 mg/6 months
46	Lutrate Depot	Microparticle	Leuprolide acetate	1209.4	1.07	0.0354	67.5 mg/3 months
47	Trelstar	Microparticle	Triptorelin pamoate	1699.8	1.73	0.0337	22.5 mg/6 months
48	Vivitrol	Microparticle	Naltrexone	341.4	1.92	3.0700	380 mg/month
49	Zilretta	Microparticle	Triamcinolone acetonide	434.5	1.94	0.0210	32 mg/3 months
50	Somatuline Depot	Microparticle	Lanreotide acetate	1156.4	0.91	0.0050	60, 120 mg/month
51	Signifor LAR	Microparticle	Pasireotide	1313.4	3.03	0.0020	20–60 mg/month
52	Risperdal Consta	Microparticle	Risperidone	410.5	3.27	0.1700	50 mg/2 weeks
53	Rykindo	Microparticle	Risperidone	410.5	3.27	0.1700	25, 50 mg/2 weeks
54	Nutropin Depot	Microparticle	Somatropin	22125.0		10.0000	13.5 mg/month
55	Atridox	ISF implant	Doxycycline hyclate	460.4	−0.06	0.0641	50 mg/month
56	Camcevi	ISF implant	Leuprorelin mesilate	1305.5	1.04	0.0338	42 mg/6 months
57	Eligard	ISF implant	Leuprolide acetate	1209.4	1.07	0.0354	45 mg/6 months
58	Fensolvi	ISF implant	Leuprolide acetate	1209.4	1.07	0.0354	45 mg/6 months
59	Perseris	ISF implant	Risperidone	410.5	3.27	0.1700	90, 120 mg/month
60	Uzedy	ISF implant	Risperidone	410.5	3.27	0.1700	250 mg/2 months
61	Sublocade	ISF implant	Buprenorphine	467.6	3.55	0.0168	100, 300 mg/month
62	Scenesse	Solid implant	Afamelanotide	1646.8	−1.40	0.0230	16 mg/2 months
63	Zoladex	Solid implant	Goserelin acetate	1329.5	1.55	0.0493	10.8 mg/3 months
64	Ozurdex	Solid Implant	Dexamethasone	392.5	1.90	0.1000	0.7 mg/3 months
65	Durysta	Solid implant	Bimatoprost	415.6	3.41	0.0187	10 μg/6 months
66	Propel	Solid implant	Mometasone furoate	539.5	4.27	0.0108	0.37 mg/month

Formulations in this table were collected from [9, 12, 17–23]. Trademark symbols of the products are omitted. LogP values were mostly obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and DrugBank (https://go.drugbank.com/). Many logP values on websites are known to be calculated using XLOGP3 (http://www.sioc-ccbg.ac.cn/skins/ccbgwebsite/software/xlogp3/), an atom-additive method that calculates logP (the octanol–water partition coefficient) by summing the contributions from each atom in the given molecule, and a method for the fast calculation of logP [24].

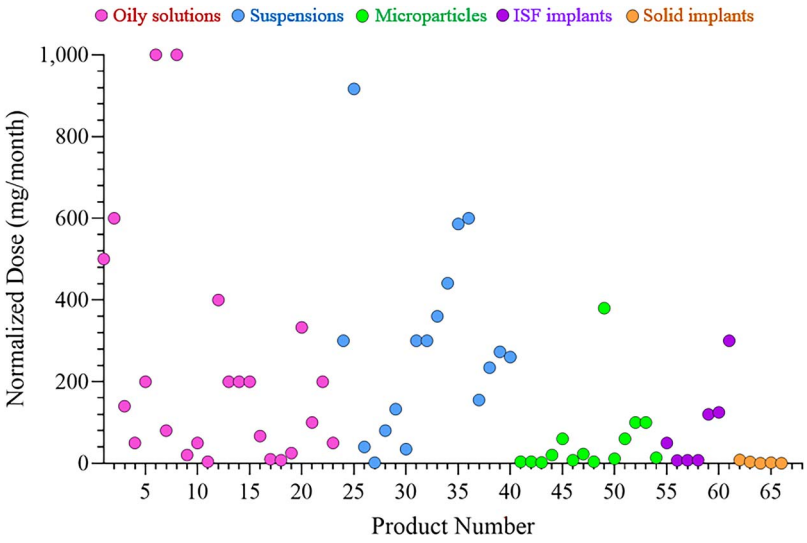

Figure 1. Normalized doses of LAI products categorized into five LAI types: oily solution, suspension, microparticle, ISF implant, and solid implant.

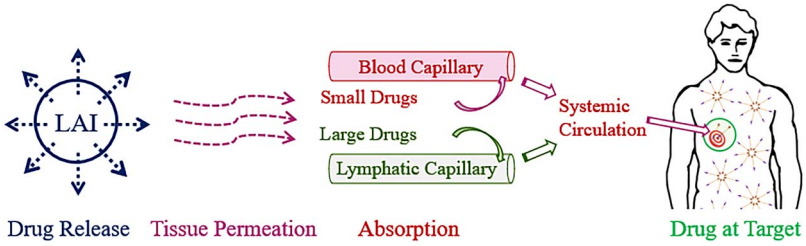

Figure 2. Simplified steps of drug release from an LAI formulation to reach the target site (Modified from [32]).

delivers somatropin with a molecular weight of 22,125 g/mol, the LAI formulation can potentially deliver various large molecular drugs, as long as the total dose is limited to 100 mg or less. The stability of the drug during the manufacturing process, including sterilization, is also a critical property for LAI formulations.

A model for studying the drug efficacy of long-acting injectable formulations

Drug molecules released from LAI formulations undergo a complex series of steps from release until they reach the target site. Different drugs undergo various processes due to their unique physicochemical properties. Nevertheless, we can divide the multi-step processes into simpler steps, as shown in Fig. 2. The release of the drug from the formulation into the surrounding tissue requires a first partition process, followed by permeation through the surrounding tissue. Once the drug reaches the blood vessel, another partition process may be required. During the process, the drug may have to undergo multiple partitioning steps, and thus, it needs to have an optimal solubility–permeability balance for maximizing the overall absorption [29]. Such a solubility–permeability balance, affecting tissue permeation and absorption, may be represented by a single parameter, the logarithm of the drug partition coefficient (logP). LogP collectively characterizes the water solubility, multiple partitioning between aqueous solution and cell membranes, and permeation through tissues, which are mostly composed of water, regarding LAI local absorption.

Molecules <16–20 kDa are mostly absorbed via blood capillaries into the systemic circulation, while large proteins such as monoclonal antibodies (mAbs) are usually absorbed by lymphatics, followed by transport through the lymphatic circulation before entering the systemic circulation [30]. Many LAI products for peptides have been available for several decades; however, developing LAIs for proteins remains highly challenging and is still far from the market. One exception was Nutropin Depot, which delivered somatropin and was withdrawn from the market due to a complicated manufacturing process. Issues related to the manufacturing and sterilization of protein LAI products still need to be overcome [31].

Another parameter to consider is the target-binding specificity of a drug, which can be measured by the affinity to target receptors. It can be assumed from the drug dose, which is clinically determined, because potent drugs (i.e. having high affinity) require only small doses. Thus, one way to examine drug properties related to the efficacy of LAI formulations is through logP and dose. These two parameters are used as the initial design parameters to evaluate drugs and determine their suitability for LAI formulations.

Drug partition coefficient

The partition coefficient (P) is the ratio of the concentration of a drug in the water-saturated 1-octanol phase (O) to its concentration in the 1-octanol-saturated aqueous phase (W) at equilibrium. The logarithm of P (logP) is commonly used to quantify a drug's hydrophobicity (or lipophilicity). The logP of the drug became an important parameter when it was found to represent the extent of partitioning of a drug from

an aqueous environment into the cell membrane and drug absorption from the GI tract [33]. The lipophilicity of octanol was found to be comparable to that of a cell membrane [34].

The higher the logP value, the more hydrophobic the drug is, making it easier to pass through cell membranes (i.e. absorption), but its water solubility is decreased. Drugs with high lipophilicity (high logP) can become poorly water-soluble, thereby reducing absorption and bioavailability. On the other hand, highly hydrophilic drugs (with low logP) may not pass through biological membranes easily. According to the well-known Lipinski rule of 5, 90% of FDA-approved oral drugs have logP values of $<\sim 5$ [35, 36]. It is noted that the rule of 5 is mainly for developing orally active drugs. While such a general property is appreciated, the logP value alone may not have any predictability of the drug penetration through biological barriers, e.g. the blood–brain barrier [37]. In addition, the curation of experimental values of logP is not trivial, in the sense that the experimental conditions used to measure logP may differ, e.g. pH for ionizable drugs [38].

As found in Table 2, logP values of drugs range from 2.10 to 10.50 for oily solutions and 1.04 to 10.10 for suspensions. On the other hand, PLGA formulations loaded with various drugs have logP values from −0.41 to 3.27 for microparticles (excluding −21.00 of exenatide), −1.60 to 3.55 for ISF implants, and − 1.40 to 4.27 for solid implants. Overall, the drugs loaded in PLGA polymers include hydrophilic drugs and peptides that cannot be formulated into oily solutions or suspensions. The PLGA formulations offer greater versatility in terms of drug types. Additionally, salts of poorly soluble drugs have been formulated as LAI microparticles, seemingly creating a locally saturated depot for long-term absorption.

Drug tissue permeability

For LAIs, drug absorption represents the permeation of the drug into the surrounding tissue and blood and lymphatic vessels. Most released drugs diffuse through the extracellular matrix (ECM), which is a water-rich and hydrophilic environment. Thus, the tissue can be considered a porous medium, and the drug's diffusivity in water can be utilized.

Upon SQ or IM injection, the released drug goes through a transition from the formulation environment to the homeostatic environment of the surrounding tissue, and this process may vary for different formulations and various injection sites of the body [39–41]. Each injection site has varying compositions of the extracellular matrix formed by collagen, hyaluronic acid, and chondroitin sulphate, the interstitial fluid, the temperature of the tissue, and hydrostatic and osmotic pressure, all of which may result in varying degrees of bioavailability [39]. Furthermore, different injection sites have different presystemic catabolism, local SQ blood flow, local lymphatic flow, and interactions with ECM materials [42].

The drug fate at the injection site, which could dictate these pharmacokinetic outcomes, is poorly understood [43]. It is challenging to investigate how drugs released from a formulation at an injection site in the body diffuse through surrounding tissues into the systemic circulation. The ECM is an immensely complicated and heterogeneous environment. Thus, the tissue permeation process in humans is also difficult to reproduce in preclinical *in vivo* models, let alone *in vitro* models. A recent study examined the parameters that might affect the fate of drugs released at the injection site to provide reliable *in vitro* models [43].

The effects of injection conditions (such as needle length, injection volume, viscosity, and flow rate on depot formation and pain) on the drug permeation in tissues (e.g. the shape and concentration distribution of the injected drug solution) are not clearly understood, which may affect the predictability of drug effect [44]. There is considerable variation in the absorption and action of the drug from patient to patient but, more importantly, from injection to injection for the same patient [44]. Based on the real-time X-ray imaging, the permeability of the drug solution through the tissues was estimated according to the permeation direction, injection speed, and tissue [44]. Integrating various formulation attributes, injection conditions, and local physiological features, multiphysics simulations of LAI's drug release and absorption kinetics at the local injection site may offer a solution to predict the systemic exposure of LAIs [45].

Dose for pharmacokinetics and target specificity

While some instruments can provide temporal variations of the permeation and diffusion phenomena, as described in the preceding section, they are not available in most laboratories. One way to assess the tissue permeation of the injected drug is to measure its pharmacokinetic profile, which enables the determination of the time of drug appearance in the blood. *In vitro* dissolution tests play a critical role in estimating the *in vivo* performance of a drug formulation. *In vitro–in vivo* correlation (IVIVC) provides additional information on how a LAI formulation functions in the body [46].

The target binding specificity partially determines the dose. The higher the target binding specificity, the lower dose required. Thus, the total dose (mg/month) in Table 2, which is generally measured in human trials, can be used conversely to represent the target binding specificity.

The potency of a drug against a target indication should be high because of maximum dose and volume limitations per injection site, $\leq$2 ml for SQ injection and $\leq$5 ml for IM injection [47]. Such limitations require a low total clearance of the drug to achieve sufficiently high concentrations for therapeutic efficacy. The drug also needs to be metabolically stable at the injection site and provide safety and local tolerability at the injection site [28]. Peptide molecules have low oral bioavailability, but they are very potent molecules with low doses, which makes them good candidates for LAIs [18].

Drugs with a short half-life ($t_{1/2}$) require repeated administration to maintain the plasma concentration even after dosing with conventional parenteral forms, i.e. intravenous (IV) route. A drug with a longer half-life is preferred for developing LAI formulations, as it will maintain therapeutic concentrations for a longer time. Drugs with an ultra-short half-life need to be made into analogues with a longer half-life. For example, unlike native glucagon-like peptide 1 (GLP 1) with a $t_{1/2}$ of $1\sim 2$ min after IV administration, its analogue, exenatide, has a $t_{1/2}$ of 2.5 h after subcutaneous administration, leading to the development of a once-a-week microparticle formulation (Bydureon) [18]. Formulations that deliver GLP-1 analogues for a month or longer have yet to be developed, and analogues with longer half-lives may be a key factor.

While logP may infer water solubility, tissue permeability, and membrane permeability, the drug dose can reflect the potency, target specificity, and metabolism. The dose necessary for efficacy can be estimated from *in vitro* and animal studies, as well as clinical trials of non-LAI formulations.

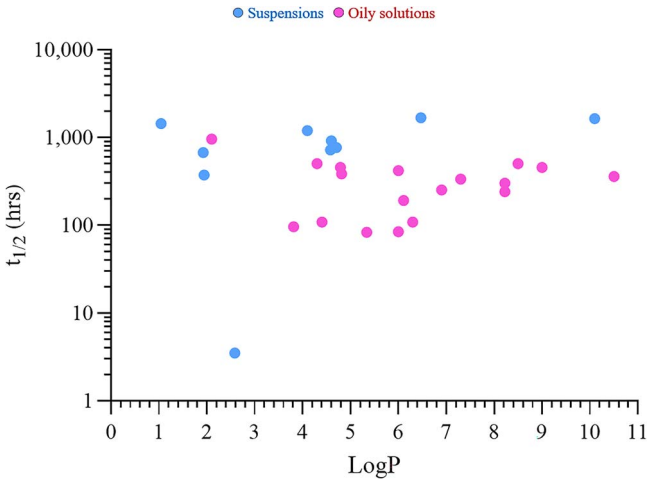

Figure 3. $t_{1/2}$ vs LogP of oily solution and suspension products listed in Table 2 (the information on half-lives presented in this table was primarily gathered from DrugBank (https://go.drugbank.com/), the US FDA (https://www.accessdata.fda.gov/media/), the UK Electronic Medicines Compendium (https://www.medicines.org.uk/emc), guidance on long-acting antipsychotic injections [48], and individual drug websites).

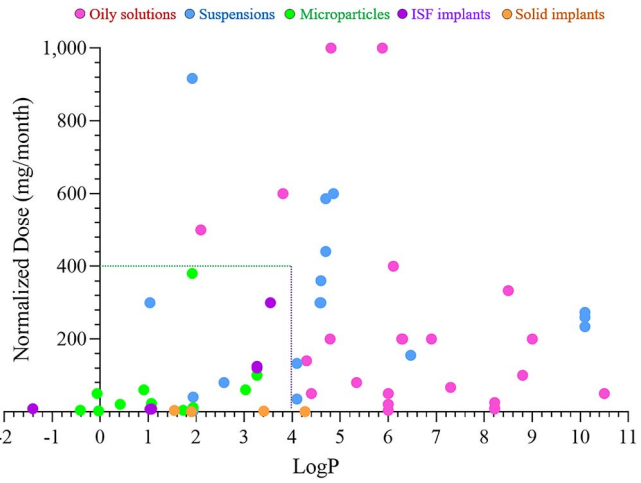

Figure 4. Normalized dose of LAI products in Table 2 as a function of logP of the drugs (in the figure, the logP value of −21.00 for exenatide with an 8 mg/month dose (#41 in Table 2) was omitted).

Figure 3 presents the half-life plotted against the corresponding logP values for oily solution and suspension formulations in Table 2. Microparticles, ISF implants, and solid implants were excluded from this analysis due to the significant influence of the controlled release matrix and their respective manufacturing processes on the $t_{1/2}$. The steroid backbone confers substantial lipophilicity to nearly all oily solution formulations, potentially enhancing the extent to which the compound partitions into tissue. Additionally, esterification with fatty acids, as noted in Table 2, is frequently employed to both augment solubility in the oil vehicle and modulate the release kinetics from this vehicle [49]. Generally, the clearance rate of the oily vehicle is independent of the injection volume [50, 51], and the rate of disappearance tends to increase with decreasing viscosity [51]. Oils intended for injection typically possess half-lives on the order of days to weeks, further impacting drug absorption. For drug suspensions, the low aqueous solubility and low intrinsic dissolution rate are essential parameters governing controlled release. The formation of hydrophobic salts (e.g. pamoic acid) or the esterification process is often utilized to modify solubility or dissolution rates. A general trend observed is that the $t_{1/2}$ increases in correlation with logP. However, half-lives can exhibit substantial variability due to differences within the patient population.

Long-acting injectable formulation development dimension

Various properties can be considered when selecting suitable candidate drugs for LAI formulations. However, as the first line of screening criteria, the two parameters, logP and dose, may be used. How well the two parameters can screen candidate drugs remains to be seen, as more data on these parameters are necessary. The most useful data would be the pharmacokinetic profiles of each formulation, describing the bioavailability (as compared with the IV administration), the time to reach the initial burst peak or the time to get the initial steady-state drug concentration in the blood (representing cell and tissue permeation), and the drug dose–efficacy relationship (representing target specificity). The two-parameter model provides a tool for examining the drug properties that can adequately describe the overall properties of a drug for developing LAI formulations.

Figure 4 shows the LAI products in Table 2 plotted against their respective normalized doses and logP values. The overall observation is that many formulations have the drugs with logP of around 5 (4 ~ 6). However, it appears that the drugs with logP higher than 4 can be formulated into oily solutions or suspensions. This is understandable, as the two formulations prefer drugs with poor water solubility or a slow intrinsic dissolution rate. The two formulations are also ideal for the drugs requiring high doses, e.g. 1000 mg/month. For these drugs, the particle size of the drug is an important parameter. Many hydrophilic drugs were modified into prodrugs or different forms to develop LAI formulations [18]. If the drug's water solubility is too low, however, there is a danger of precipitation of the released drug in an aqueous environment [41].

In Fig. 4, the logP values of the drugs used in the microparticles, ISF implants, and solid implants are all <4. The logP values for LAI formulations play a slightly different role than for oral formulations, as the poor water solubility of drugs does not seem to limit the development of effective LAI formulations. Figure 3 also indicates that for oily solution formulations, the dose tends to decrease as the drug logP value increases. The opposite behaviour is observed for suspension, microparticle, and ISF implant formulations. In general, PLGA-based formulations are suitable for drugs with a logP value <4 and a total dose of <400 mg/month, as indicated by the dotted lines in Fig. 4.

The simplified approach of utilizing logP and dose may be beneficial for the initial screening of candidate drugs for LAI formulations. However, a comprehensive analysis of existing data, such as the information presented in Table 2 with additional drug properties and pharmacokinetic profiles, is essential for rational formulation design. This in-depth analysis can be facilitated by recent advancements in artificial intelligence and machine learning (AI/ML), as well as model-informed drug development [52], through the collection and

analysis of more evidence. The initial and crucial step in AI and machine learning is ensuring high-quality data, as the quality of the input directly influences the model's efficacy [53]. AI and ML technologies are designed to analyse large datasets to uncover complex patterns, thereby enhancing the discovery of new chemical entities or the repurposing of existing drugs more efficiently than traditional trial-and-error methods [53]. However, when the training dataset is limited and lacks diversity or high quality, AI-based models may fit the training data well but fail to capture the underlying reality, leading to discrepancies, or "hallucinations," from verified, real-world data. One of the essential criteria for ensuring data quality is reproducibility, both within one's own laboratory and across different research groups. A key statistical indicator used to assess this is the variance of experimental measurements. When considering the roles of AI/ML in formulation design, one area that stands to gain significantly from a data-driven approach is the inference or establishment of predictive functional mappings between the design space and the critical quality attributes of an LAI formulation. ML techniques, such as manifold learning, can effectively capture nonlinear relationships between these two data domains. To achieve meaningful analysis through AI/ML and pharmacokinetic modeling, it is imperative to have access to a substantial volume of high-quality data. Ultimately, human expertise remains a critical factor in generating such data.

Conclusion

The currently available LAI formulations were examined with a focus on identifying guiding principles for selecting drugs suitable for the future development of LAI formulations. In contrast to oral delivery systems, LAI formulations are capable of delivering larger molecules, such as peptides and proteins. While advances have been made in oral delivery technologies (e.g. Rybelsus for peptides), challenges related to bioavailability and manufacturing costs persist. Until further breakthroughs are made in the oral delivery of biologics, LAI formulations, particularly those utilizing PLGA polymers, will remain a promising and practical option.

Key properties that determine drug suitability for LAI formulation development include water solubility, logP, $t_{1/2}$, effective dose, and stability during manufacturing. Understanding these parameters helps rationalize formulation design space and enables more efficient LAI development by integrating historical insights with modern formulation advances. Furthermore, the incorporation of AI/ML holds considerable promise for advancing the science of LAI formulation. However, the future success of AI/ML-based approaches in LAI development hinges on access to high-quality, diverse datasets, highlighting the ongoing need for human expertise in generating, curating, and interpreting these datasets. Looking forward, the integration of empirical knowledge and computational techniques could significantly accelerate the development and optimization of future LAI therapeutics.

Author contributions

Andrew Otte conceptualized the manuscript contents, wrote a portion of the draft, reviewed it, and edited it. Tonglei Li conceptualized the manuscript contents, wrote a portion of the draft, reviewed it, and edited it. Kinam Park conceptualized the manuscript contents, wrote a portion of the draft, reviewed it, edited it, and finalized the manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

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Data availability

The data underlying this article are available in the article.

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