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Review

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Making the Leap from Daily Oral Dosing to Long-Acting Injectables: Lessons from the Antipsychotics

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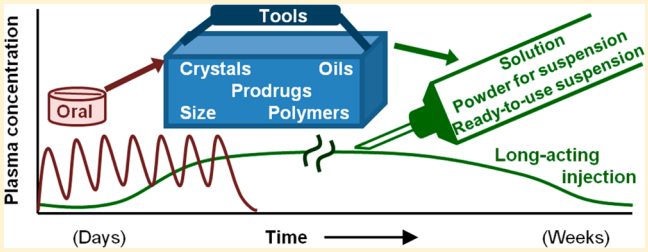
ABSTRACT: There are now long-acting versions of six antipsychotic drugs on the U.S. market, and with them, five unique combinations of molecular form and delivery strategy long-acting-injectable-antipsychotics (LAIAs) show evidence of reduced relapses of schizophrenia, but their introduction has been slow, taking at least nine years after the approval of each oral drug. Oily solutions of lipophilic prodrugs were the first to enter the LAIA market, but they relied on esterification of a hydroxyl handle that was lost with the emergence of the atypical antipsychotics. A review of the literature and patents shows that companies tested many different approaches before reaching the currently marketed versions, including aqueous suspensions of poorly soluble salts, polymeric microspheres, and new approaches to making prodrugs. Yet, very little has been published to support faster development of safe long-acting injectables (LAIs). This review introduces some of the critical considerations in creating an LAI; then it analyzes the existing products and discusses areas where further research is needed. The available literature suggests that lipophilic prodrugs may be inherently safer than poorly soluble salts as LAIs. Other areas needing additional study include (1) the range of physical properties acceptable for LAIs and the effect of prodrug tail length in achieving them, and (2) the role of physiological responses at the injection site in the release of drug from a depot.



KEYWORDS: *long-acting injectable, prodrug, aqueous suspension, safety, lag phase, burst, physical properties*

A. INTRODUCTION

Long-acting injectable (LAI) medicines have been used to treat several diseases, including schizophrenia, bacterial infections, prostate cancer, and diabetes, with recent papers highlighting efforts to apply LAI technology to the treatment of HIV.[1,2] The hallmark application of LAI formulations in the 20th century was the treatment of schizophrenia, a devastating psychiatric condition associated with frequent relapse, loss of function, and low compliance to oral therapy. A recent review detailed the impact of LAI therapy on clinical, functional, and economic outcomes of schizophrenic patients, including the emerging understanding of benefits from introducing LAIs early in the treatment of disease.[3] Despite evidence of improvement in patient outcomes, there have also been issues with some LAIs, including cases of "Post-Injection Delirium Sedation Syndrome" (PDSS) caused by the sudden release of olanzapine from Zyprexa Relprevv. An LAI for treating bacterial infections, penicillin benzathine, carries a label warning of deaths from inadvertent intravenous injection and of severe neurological damage from injections too close to nerves. Such incidents should not distract from the positive patient outcomes, but they do highlight the need for improved understanding of the technologies employed to ensure safe and effective release of drug.

The history of delivery technologies used in marketed LAIA's in the U.S. is shown in Figure 1, where it appears as an evolution from solutions in oil to aqueous suspensions.[4] The LAIAs were introduced beginning in the 1960s as solutions of simple ester prodrugs in sesame oil, and these remained the only option for more than three decades. A second generation of safer oral antipsychotics with lower incidence of side effects emerged in the 1990s, and their LAI versions slowly entered the U.S. market as listed in Table 1. The first of the atypical antipsychotics to be approved as an LAI was risperidone (RISP) in polymeric microspheres, where the polymer controls the rate of drug release after injection in aqueous suspension. Since 2009, all newly approved LAIAs have been formulated for

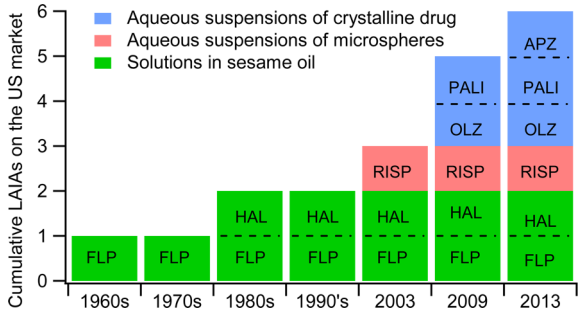


Figure 1. Number of LAIA Drugs on the U.S. Market Based on Delivery Strategy.

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Table 1. FDA Approval Dates for Antipsychotic Drugs with LAI Versions in the U.S.

active drug (abbrev[a])	type[b]	FDA approval	form of drug in product (abbrev[a])	formulation
Fluphenazine (FLP)	oral	1959	HCl salt (FLP·HCl)	tablet
	LAI	1967	enanthate prodrug (FLP-C7)	solution in sesame oil
	LAI	1972	decanoate prodrug (FLP-C10)	solution in sesame oil
Haloperidol (HAL)	oral	1967	free base (HAL)	tablet
	LAI	1986	decanoate prodrug (HAL-C10)	solution in sesame oil
Risperidone (RISP)	oral	1993	free base (RISP)	tablet
	LAI	2003	free base (RISP)	polymeric microspheres
Olanzapine (OLZ)	oral	1996	free base (OLZ)	tablet
	LAI	2009	pamoate salt (OLZ·pamoate)	powder for aqueous suspension
Paliperidone (PALI)	oral	2006	free base (PALI)	tablet
	LAI	2009	palmitate prodrug (PALI-C16)	nanocrystals in aqueous suspension
Aripiprazole (APZ)	oral	2002	free base (APZ)	tablet
	LAI	2013	monohydrate (APZ·H_2O)	powder for aqueous suspension
	LAI	phase 3	lauroxil ester prodrug (APZ-CH_2O-C12)	ready-to-use aqueous suspension

[a]Abbrev denotes the abbreviations that will be used for each compound within the text. [b]Type refers to the type of product, either oral or LAI.

injection as aqueous suspensions of crystalline drug forms, where the low solubility and slow dissolution rate of the crystalline solid controls the rate of absorption. Nine years passed between the approval of oral risperidone and the LAI Risperdal Consta. Making the transition for olanzapine and aripiprazole took 10 and 13 years, respectively. Considering the clear benefits of LAIA therapy, the long delay between oral and LAI may seem surprising. However, closer examination reveals the difficulty in delivering these molecules as LAIs and that the technology evolved in response to the changing physicochemical properties of the new drug molecules.

This review grew from efforts to select an optimum prodrug and delivery strategy for aripiprazole (APZ) after discovering a series of prodrugs where esters are reversibly linked to the lactam of APZ through a hydrolytically labile hydroxymethyl group. The approach yielded a large number of prodrug candidates with different physical properties, but little guidance could be found for selecting one to take forward into development as an LAI. Here, data from journal articles and patents are gathered and interpreted in order to explain the last half-century of LAI development, particularly antipsychotics. Additionally, the data have been analyzed to identify areas that are poorly understood and in need of additional research.

The goal is to enable researchers to quickly transition important oral therapies to safe and effective LAIs by helping them to understand the interplay between molecular properties and existing delivery strategies. The remaining sections are structured as follows: section B introduces subjects that are applicable to multiple delivery strategies, such as prodrugs and particle size control; section C is primarily a review of the literature and patents associated with currently marketed LAIAs, but organized by delivery technology and including examples of failures as well as successes; finally, section D provides an analysis of areas in need of further research, including prodrugs for aqueous suspension, the "lag phase" after injection of aqueous suspensions and the safety of poorly soluble salts relative to lipophilic prodrugs.

B. GENERAL CONSIDERATIONS FOR TRANSITIONING FROM ORAL TO LAI

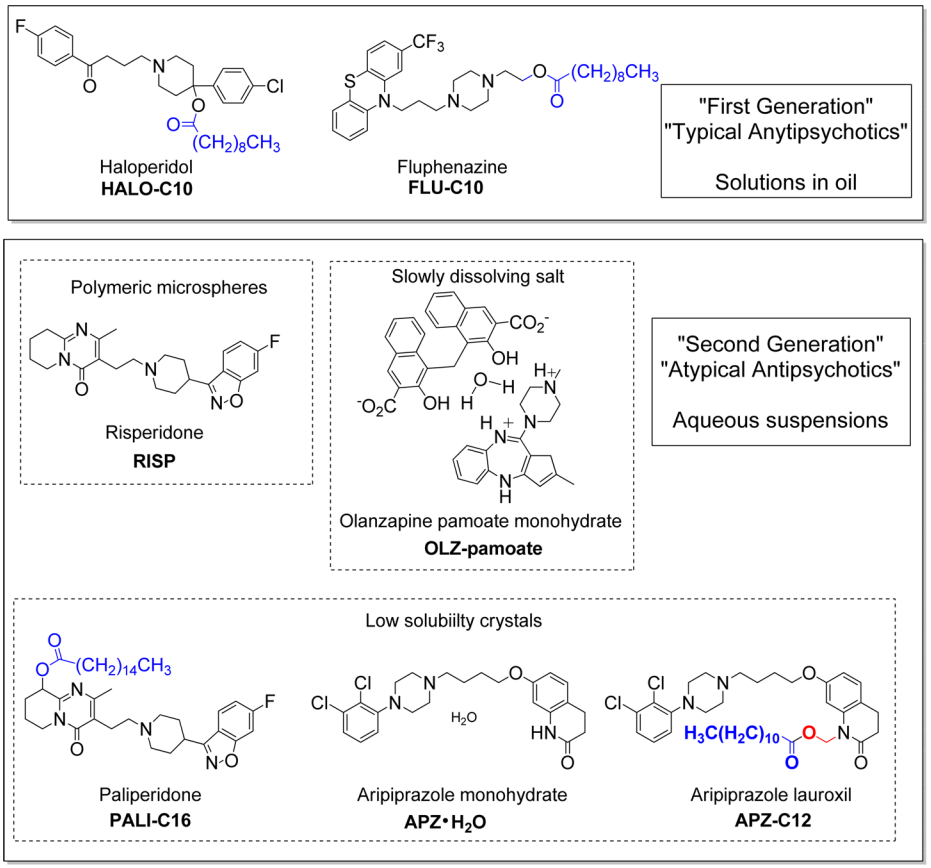
The pharmaceutical industry is geared toward making relatively small molecules that will dissolve and permeate through membranes to allow for good oral absorption and daily dosing. LAI technology aims to maintain safe and effective levels of those active drugs, typically for at least 2 weeks following the injection; this requires dosing a large amount of drug. A quick scan of package inserts for the oral antipsychotics show that most of these products have serious side effects, such as sedation or coma, at higher blood concentrations. Sudden release of too much drug is often referred to as "dose dumping" and causes a "spike" in the plasma concentrations. Evaluating the possibility and consequences of dose dumping is a critical activity in the selection of delivery technology for a given molecule.

B1. Local Effects on the Release of Antipsychotics.

The intramuscular injection site is approximated by buffered saline at pH 7.4–7.6 in the laboratory, but events such as the "Post-injection Delerium/Sedation Syndrome (PDSS)" that occurs in 0.07% of patients receiving OLZ-pamoate serve as reminders that there are differences that must be considered.[5] In a small number of injections, it is believed that either (1) a small amount of drug is injected directly into a vein and/or (2) a vein is punctured by the needle, causing blood to leak into the injection site. The solubility of OLZ-pamoate is on the order of 15-fold higher in plasma than in pH 7.6 buffer, allowing for a rapid solubilization of drug when blood leaks into the site. However, an increased solubility in plasma should not necessarily be used as an exclusion test when assessing a candidate, since some compounds with extremely low aqueous solubility (<10 ng/mL) may rely on components native to serum such as albumin and lipoproteins for solubilization. The key is to determine the extent of the solubilization during an event such as accidental infiltration of blood to the injection site, and the consequences of a high plasma level if this is a possibility.

The pH of tissue can drop as low as pH 6.5 for several hours[6] in response to trauma, such as a cut, and this can affect the solubility of some antipsychotics. All of the known antipsychotic molecules in LAI formulations contain a piperidine or piperazine ring with an acid dissociation constant, or pK_a, between 7 and 9. The higher the pK_a, the larger the thermodynamic drive to ionize if the pH drops. Since ionization typically increases aqueous solubility, this is especially important to understand for suspensions of crystalline drug where the formulation provides no physical barriers to ionization. The solubility of RISP (pK_a = 8.2), for example, is relatively low at 0.028 mg/mL in deionized water at room temperature (native pH = 8.9), but it increases 10-fold to 0.29

Scheme I. Structures of Antipsychotic Drug Molecules Used in LAI Products



mg/mL in pH 7.6 buffer, and >100-fold to 4.4 mg/mL at pH 6.6.[7] APZ has a lower pK_a value of 7.4 and estimates of solubility in water are around 10 ug/mL[8] while its solubility remains low in buffer at pH 6.8.[9] The solubility of OLZ-pamoate is known to be about four times lower at pH 6.8 than at pH 7.4 while crystalline OLZ free base is likely to increase in this range. It is also important to remember that ionization could change the relationship between the drug and excipients within oil depots or polymeric microspheres.

B2. Prodrugs. Prodrugs have been widely used to address drug delivery problems,[10,11] and they have been a central strategy in the transition from oral drugs to LAIs. Esterification of alcohols with fatty acids can drastically reduce the aqueous solubility and increase solubility in oils for injection. Since the fatty acids are endogenous and most commonly occur with even-numbered tails of four to 28 carbons,[12] there exists the ability to tune the physical properties of the molecule, including melting point, solubility, and partition coefficient. Most esters are efficiently cleaved to the active by esterases, which exist throughout the body. Furthermore, simple ester prodrugs are typically considered to be safe and are no longer considered to be new chemical entities (NCEs) by the FDA for purposes of regulatory exclusivity.[13]

Despite the wide acceptance of ester prodrugs, risk reduction strategies dictate selection of prodrugs that cleave rapidly after release from the injection site whenever possible. With this philosophy, the prodrug is used primarily to regulate the rate of dissolution for a crystalline entity, or the rate of diffusion or partitioning out of a controlled-release depot. Alternative degradation/elimination pathways could also begin to play a role if the ester was slow to hydrolyze, thereby reducing potency and increasing the risk of failure in toxicity studies. However, there are certainly cases where a slow hydrolysis rate has been beneficial: HALO-C10 is a case where the ester cleavage is unusually slow in blood and plasma; Nambu, et al, have suggested that the slow conversion in blood increases the safety of the prodrug by giving it time to redistribute into tissue rather than causing a spike in active HAL concentration.[14]

Easy access to handles for prodrugs ended with the emergence of the atypical antipsychotics RISP, OLZ, and APZ which lack -OH groups.

Scheme I shows the structures of the antipsychotics that are available as LAIs in the U.S., showing active parent moiety and highlighting molecular level modifications used in the extended release versions (blue for esters, red for nonester covalent linkers). The first-generation antipsychotics HALO and FLU, along with others outside of the U.S., contained -OH groups that were easily esterified to provide prodrugs with conveniently high solubility and partitioning into sesame oil. RISP, OLZ, and APZ have all been developed using other delivery strategies. High loads of RISP were successfully incorporated into poly(lactic-*co*-glycolic) acid (PLGA) microspheres that slowly release the drug to allow biweekly dosing. OLZ was recrystallized as a salt of pamoic acid having lower aqueous solubility and is injected as an aqueous suspension. Micron-sized APZ·H_2O was suspended in aqueous media and lyophilized to await reconstitution immediately prior to dosing.

Despite having marketed LAI versions of the second generation antipsychotics, prodrug versions of each have been created, all for different purposes. PALI, the active metabolite of RISP, was developed as PALI-C16 and is marketed as Invega Sustenna. The prodrug allows monthly dosing as a ready-to-

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inject, room temperature stable suspension. The microsphere version of RISP (Riperdal Consta) remains highly effective, but requires refrigeration, reconstitution, and biweekly dosing. However, PALI is an active metabolite of RISP, so there can be differences in activity that make one more appropriate for a given patient. APZ-C12 is in phase 3 trials and has a unique chemistry using a hydroxy-methyl linker to allow reversible attachment of an ester to the lactam. Attaching the acyl chain directly onto the lactam −NH would yield a relatively stable molecule rather than a prodrug, but the hydroxymethyl group is a hydrolytically reversible moiety that remains stable as long as it is esterified. The resulting prodrug is sufficiently stable to be stored as a ready-to-use suspension. Finally, a recent paper reported on carbamate linked esters of OLZ,[15] intended as a strategy to reduce the differences in solubility between buffer and plasma, and thereby potentially reduce or eliminate incidents of PDSS resulting from rapid release of drug. More detail on the selection of prodrugs for use in different delivery strategies will be included in later sections.

B3. Particle Size. Particle size must be controlled in order to make sure the solid particles fit through the supplied needle without clogging and that the drug releases at the proper rate. The solubility and intrinsic dissolution rate are inherent properties of a crystalline molecule, but the actual rate of dissolution is expected to increase at smaller particle sizes (higher surface area). In oral drug delivery, the physical form of a compound is often changed to improve dissolution rate, but this can lead to instability in an LAI. For example, APZ has many polymorphs, solvates and salts, but will recrystallize to the thermodynamic APZ·H_2O[8,16] form in the aqueous environment of tissue for days, weeks or months after injection. Without a polymer-based formulation or a prodrug to control the release, the only means to fine-tune the dissolution rate is through particle size. For PALI and APZ prodrugs, different tail lengths could be expected to provide different solubility and dissolution rates, but the particle size remains an essential parameter for optimizing the release and ensuring reproducibility. Fortunately, the technologies and understanding needed for precise milling and stabilizing small crystals after milling have grown tremendously through research into improving the oral bioavailability of poorly soluble drug molecules.

The late 1990s through the early 2000s saw the emergence of the first "nanomilled" drug products, where particles are wet milled in the presence of polymers or surfactants to provide submicrometer particles, and these have been reviewed previously.[17,18] Suspensions of crystalline drugs in aqueous vehicles containing dissolved stabilizing excipients are milled by stirring at high energy with solid milling media (typically polystyrene or ceramic beads). The resulting colloidal dispersions can be stable, or the particles can grow through flocculation to give agglomerates, or through "Ostwald ripening" where the larger crystals grow as smaller ones dissolve. Molecules with higher aqueous solubility, or suspensions stabilized by excipients that can solubilize the drug, are likely to see higher growth rates. Since tablets are the most sought-after dosage form for oral delivery, there has also been a large body of research into drying the milled solids while ensuring that critical attributes remain upon reconstitution when the tablet disintegrates. These same principles can be applied to aqueous suspensions for injection. If the milled crystals are physically or chemically too unstable for storage in the aqueous medium, then the water can be lyophilized to leave a cake for reconstitution in the clinic. There are two added difficulties when milling for intramuscular (IM) use: the first is the need for sterility and the second is the limited set of stabilizers that are approved for the IM route. If an excipient that is novel to IM administration is required to maintain the desired particle size during storage in aqueous suspension, then the team must either deliver particles for resuspension or accept the challenges and risks associated with gaining approval for the new excipient.

B4. Excipients. The number of acceptable excipients currently approved for IM dosing is extremely limited compared to oral dosing.[19] Introducing a new route of administration to an existing excipient brings additional costs and uncertainty to a program.[20] The excipients used in LAIAs that are delivered as aqueous suspensions are shown in Table 2.

Table 2. Excipients in LAIs for Aqueous Suspension

	viscosity modifier	surfactant	other
RISP	Na-CMC	PS20	PLGA[a]
OLZ-PAM	Na-CMC	PS20	
PALI-C16	--	PS20	PEG4000[b]
APZ·H_2O	Na-CMC		

[a]PLGA is a polymer that controls the release of RISP from the depot. [b]PEG4000 will increase viscosity very little compared to Na-CMC, but it can be present as a steric stabilizer for the nanomilled PALI-C16 crystals.

Sodium carboxymethyl cellulose (Na-CMC) and polysorbate 20 (PS20) are each present in three of the atypical antipsychotic products, and PEG4000 is present in the formulation of PALI-C16. Buffers and tonicity agents used in intravenous (IV) injections are also typically acceptable. These vehicles will wet and suspend most hydrophobic solids, but they do not always prevent formation of dense, difficult-to-resuspend sediments or to stabilize crystals toward growth after milling to a fine particle size.

B5. Intellectual Property and Market Considerations. While the main focus of this review is scientific, the product will never be developed if it is destined to lose money. The concept must at the very least have "freedom to operate," but patent protection is almost essential in order to recoup development costs. The boilerplate language of many patents on new drugs will include claims to "prodrugs thereof," which could block any competitor from using any prodrug until that patent expires. However, such broad claims do not make all prodrugs of the compound obvious, and a novel prodrug can be patented and developed to enter the market upon expiration of the blocking patent. In some cases, patent law has established that a simple straight chain ester of a molecule that contains an alcohol or carboxylic acid could be considered obvious to one of ordinary skill in the relevant art and therefore, not patentable. Unique or less common prodrugs, or those that have unpredictable benefits, can still be considered novel.

There are typically hundreds if not thousands of patents relating to any drug that is approved and profitable, especially if it is marketed in the U.S.. A SciFinder search conducted in October 2013 found 306 patents including PALI, 538 for APZ, 993 for RISP, and 1022 for OLZ. While the majority of these patents do not relate directly to LAIs, there is clearly a large volume of material to navigate. Transitioning an orally administered molecule to an LAI is an expensive process involving toxicity studies and clinical trials, and the costs must be recovered before exclusivity expires and generic competitors

are allowed to compete. If there is another LAI version of the drug on the market, or the possibility that one could be introduced, then the analysis must also consider what competitive advantages the new concept could provide over the other product(s). It is difficult to overstate the importance of consulting experts in patent law, regulatory exclusivity, and market research from the point of conception through the full development of an LAI.

C. DELIVERY TECHNOLOGIES

The following sections will take a deeper look at four different delivery strategies: solutions in oil, polymeric microspheres, crystalline solids for aqueous suspension, and ready-to-use aqueous suspensions. The latter three are all aqueous-suspension technologies, but they have significant difference in ease of use. Polymeric microspheres are based on PLGA, which has a low glass transition temperature, especially with drugs encapsulated. To remain stable on storage, they must be refrigerated until mixed with diluent immediately prior to injection. Solids for aqueous suspension require mixing immediately prior to injection because of poor chemical stability of the drug, poor control of particle growth or aggregation when in suspension. Each has its own directions-for-use for addition of diluent, wetting of particles and achieving a uniform suspension that ensures accurate delivery of the solids. Premade suspensions, especially when preloaded into a syringe, are the simplest for use in small practices without a separate lab room for mixing, though even these will typically require a protocol of tapping or shaking to ensure successful injection.

C1. Solutions in Oil. The majority of marketed antipsychotics have a maximum dosing volume of no more than 3 mL per injection site.[9,21] In determining whether a solution in oil is appropriate, one must first know the solubility of the drug within the oil and the highest dose that patients will need. Clearly, an antipsychotic like APZ with a solubility of <1 mg/mL in oils and a daily dose of >5 mg would not work. HALO-C10, FLU-C10 and the other first-generation antipsychotics are all soluble to >100 mg/mL in sesame oil. Suspensions of crystalline prodrugs in oil do occasionally appear in patents; for example PALI-C10 and PALI-C16 suspended in sesame oil were both evaluated alongside the now-marketed nanocrystal aqueous suspension of PALI-C16, with the oil suspensions providing lower exposure.[22] A RISP-pamoate salt was also dosed as a suspension in sesame oil and found to be active for up to 3 weeks,[23] but the authors observed burst effects when using this strategy. To date, no LAIA suspensions in oil have made it to market.[22]

Many vegetable and synthetic oils have been tested as depots for antipsychotics as well as steroids, but sesame oil has become the oil of choice for LAIAs. Sesame oil (SO) has a high viscosity and is generally well-tolerated. High viscosity provides a longer half-life for clearance from both muscle and the subcutaneous (*s.c.*) space. In a study of radiolabeled oils in rabbit, it was found that 300 μL injections of peanut oil (viscosity = 39 cps), have $t_{1/2}$ of 22−26 days following subcutaneous and IM injections.[24] The lower viscosity oil ethyl oleate (EO, viscosity =3.9 cps) is cleared much faster, with $t_{1/2}$ of only 9−11 days. The effect of viscosity on release rate vanished at low injection volumes (50 uL) when the release of small molecules was only monitored for 6 h.[25]

Lymphatic uptake is considered important in the absorption of FLU-C10 and HAL-C10 from oil depots,[26−29] though this is at odds with the literature on clearance of oils from tissue. Neat oils are not readily taken up lymphatically when injected as pure substances.[30] Howard and Hadgraft looked for radio-activity in lymph after dosing radio-labeled EO and Arachis oil (peanut oil) and found that no more than 5% of oil was absorbed lymphatically.[24] It is believed that lymphatic uptake requires spreading of the oil along the fascial planes of the muscle toward lymphatic vessels; high viscosity retards spreading and flow while small droplets flow more easily.[31] If correct, reducing viscosity, emulsifying the oil or adding a component that would reduce interfacial tension between the oil and aqueous environments could all lead to faster uptake with a larger lymphatic component. An example from a patent on APZ prodrugs demonstrates the increase in area under the plasma concentration versus time curve, AUC, available from emulsifying the oil phase.[32] Here, the prodrug APZ-C10 dissolved in EO was injected into rat either neat or pre-emulsified in water with glycerol and the surfactant dipalmitoylphosphatidylcholine (DPPC). The 0−14 day AUC increased from 67 to 1490 ng*ml/day when emulsified. FLU-C10 and HALO-C10 both have pK_a's of 8.1−8.2, and therefore, some degree of ionization is to be expected in tissue with a pH of 7.4. The charged species are amphiphilic, having long fatty tails, and could reasonably be expected to have an influence on the properties of the sesame oil and its interaction with water, though no data have been published. Regardless of the mechanism of release from the oil, Oh-E, et al. demonstrated that HAL-C10 is primarily absorbed into the lymphatic system and that the ester is most likely cleaved by esterases within lymphocytes.[33]

C1a. Modifying Molecules for Oil Depots. The three primary drug characteristics to consider for developing a solution in oil are solubility, partition coefficient and chemical stability. Ester prodrugs offer a means to tailor the solubility and logP of a drug by changing the length of the tail. The ester bond is known to be stable in oils and is unlikely to add any new stability liabilities to a parent drug. Beyond the need to have suitable solubility in oil, the partition coefficient appears to be a critical parameter for achieving sustained release, though it can be difficult to measure for highly lipophilic compounds. A molecule with high aqueous solubility and hydrophilicity will partition out of oil and be released too quickly; a molecule with high affinity for the oil phase may release too slowly. Based on evaluation of successful LAIs, the decanoate tail (C10) appears to have the best release rate for many molecules.

The effect of ester tail length on the release of fluphenazine from oil depots has been reported by Florence and Vezin.[34] The shorter tail FLU-enanthate(C7) was the first LAIA to reach the market. It was a solution in sesame oil that required dosing every 2 weeks. FLU-C10 replaced FLU-C7 due to its slower release from oil, which reduced the dosing frequency to once per 3 weeks. Release from oils was slower for longer chain esters. In a functional assay where fluphenazine is used to suppress apomorphine-induced retching in dogs, FLU-C10 showed activity for 30 days with a 50% reduction in retching versus the control group. FLU-C16 showed a peak reduction of approximately 35% with activity observed up to 20 days, while FLU-C18 showed activity for a relatively narrow window of only 10 days. An aqueous suspension of FLU-C18 gave improved activity comparable to the solution of FLU-C16 in oil, showing that the lower activity of the FLU-C18 oil depot stems from slower release of prodrug from the depot rather than from failure to cleave the prodrug after release. Since the

pure oils can have half-lives exceeding 30 days, release from the depot relies on the partitioning of drug out of the oil. While the partition coefficient of FLU-C16 and FLU-C18 could not be measured (presumably due to the limitation of low aqueous solubility), there is a 30-fold increase in partition coefficient just from increasing the tail length by three carbon atoms from C7 to C10.

A further comparison of "drug/prodrug in oil strategies" comes from the patent describing aqueous suspensions of PALI-C16.[22] Here, pharmacokinetic studies compared PALI-C10 and PALI-C16 in sesame oil or Miglyol to aqueous suspensions of PALI-C16. From the data provided, PALI-C10 released faster from sesame oil than PALI-C16 and provided higher exposure to drug even at the four-week time point. Dosing the PALI-C16 from Miglyol, a mixture of medium chain triglycerides with lower viscosity than sesame oil, provided higher exposure and faster release, but low levels at the four-week time point. The authors stated that the Miglyol formulations "exhibited considerably less systemic and local tolerance than the sesame oil based formulations", but those formulations provided higher initial exposure to the prodrugs, so without further information, it is not clear whether the excipient or high drug levels were to blame. Just as for FLU-C18, the aqueous suspension of crystalline PALI-C16 also provided higher exposure to drug than the sesame oil formulation. A note of caution on this experiment is that the full details of the oil-based formulations were not disclosed in the examples, and the language in the examples suggests that the PALI-C10, and possibly others, may have been suspensions of crystals in oil, not solutions.

C2. Polymeric Microspheres. Polylactic acid (PLA) and PLGA polymers have been considered the most desirable of the synthetic and naturally occurring polymers that have been tested for controlled-release delivery systems.[35] PLGA is used in surgical sutures and is known to be biocompatible. The degradation rate of the polymer can be controlled with the lactide/glycolide ratio and molecular weight. Higher molecular weight (mw) polymers will typically have a slightly higher glass transition temperature (Tg) and a longer period of slow release after initial dosing. PLGA has been used to make various types of drug-eluting systems, including microspheres, implants, and *in situ* formed gels. The manufacturing of these delivery systems has been previously reviewed by Petersen.[36] Okada and Tagouchi provided evidence for organization of free carboxylate terminals toward pockets of charged drug molecules with the hydrophobic polymer chains left to form a more rigid matrix between pockets of drugs as one possible mechanism for retaining higher drug loads.[35]

The ability of PLGA to meter the release of small molecules allowed RISP to become the first LAI of an atypical antipsychotic, Risperdal Consta, which remains the only antipsychotic delivered as a polymeric microsphere for aqueous suspension and injection. RISP has relatively low solubility in its nonionized state, but with a pK_a of 8.2, the solubility increases rapidly with decreasing pH.[7] As previously stated, the pH at injection sites can drop in response to trauma, including potentially the deposition of a large mass of foreign solids. A polymeric barrier that slows the rate of diffusion can protect against rapid release during brief periods of pH change at an injection site.

Risperdal Consta is manufactured using an oil/water (o/w) emulsion process. PLGA and RISP are dissolved in ethyl acetate and benzyl alcohol to form the oil phase and then emulsified with water containing polyvinyl alcohol. The emulsion is diluted into water to extract the majority of the organic solvent and the microspheres are collected.[37] The microspheres are then suspended using water with added ethanol to further extract the solvents from the microsphere. The Tg of PLGA in the microspheres can be below room temperature until the solvent content gets low. Therefore, the temperature is maintained below 10 °C during the first steps of the extraction and wash process. A benefit of the water/ethanol wash process is the removal of any water-soluble drug from the surface of microspheres, which greatly reduces the burst effect and prevents a spike in plasma concentrations of drug in the hours after injection. The most complete reduction in initial burst is obtained by drying the microspheres to <0.2% moisture content prior to a final resuspension step.[38] The final microspheres contain >30% RISP by weight.

The mw of the PLGA is a major factor in the rate of drug release, but the mw decreases during the manufacturing process and during release. Tertiary amines, including FLU and RISP are among the drugs that are known to catalyze the degradation of PLGA.[39] Microspheres of PLGA 50:50 were prepared either as placebos or with drug loaded up to 16.6% FLU-HCl in an oil/water emulsion process.[40] The PLGA in the resulting microspheres decreased from approximately 43 kDa in the placebo, to 30, 27, and 23 kDa with drug loads of 4.2%, 8.2% and 16.6%. Figure 2 shows an overlay of data from the work of Dunne et al.[40] Here, the decrease in polymer molecular weight and the cumulative release of drug are plotted as a function of time during a dissolution study of the microspheres containing 4.2% and 8.2% FLU-HCl. Both samples show an initial release of drug in the first day followed by a lag period where little drug release is observed. The polymer continues to degrade throughout the lag phase, with drug release accelerating as the polymer mw falls further below ~10 kDa. A similar correlation between PLGA mw and release was observed for dexamethasone/PLGA microspheres as reported by Zolnik and Burgess.[41] There is also a lag phase in the release of RISP from Risperdal Consta, and a separately published report on the RISP catalyzed hydrolysis of PLGA.[39]

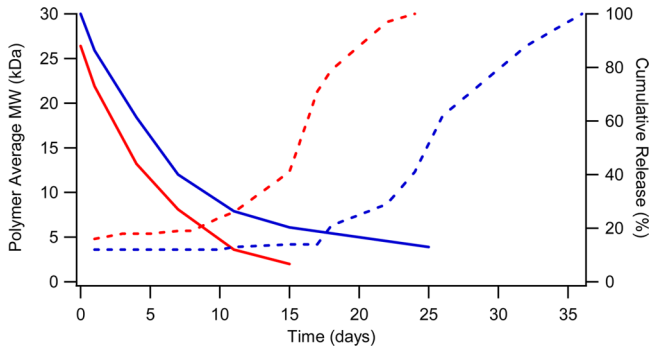

Figure 2. Overlay showing the degradation of PLGA (solid lines) and the cumulative *in vitro* release of FLU (dotted lines) as a function of time from microspheres having 4.2% (blue) or 8.2% (red) FLU in 50/50 PLGA.

Nahata and Saini published a detailed account of studies aimed at optimizing OLZ-PLGA microspheres, and they were able to provide 14-day release.[42] Their work included several variables, including solvent evaporation method, choice and concentration of surfactant during the o/w emulsion step, volume and content of the external aqueous phase during the

Table 3. Data from a Dog Study Comparing IM Injections of 2.5 mg/kg of PALI as a PALI-C16 Aqueous Suspension, a PALI-C16 Suspension in Sesame Oil, or a PALI-C10 Suspension in Sesame Oil

compd	formulation	C_{max} (ng/mL)	needle	T_{max} (d)	AUC_{0-28d} (ng·h/mL)	C_{4wks} (ng/mL)
PALI-C16[22]	15.6% aq susp	54.6 ± 7.3	21G	11.5	18 210	8.8
PALI-C16[22]	sesame oil	21.9 ± 9.4	19G	8.8	7054	4.2
PALI-C10[22]	sesame oil	33.1 ± 18.2	19G	5.5	13 875	12.0

solvent extraction and drying methodology. Importantly, they monitored encapsulation efficiency and initial burst as a function of target drug load. The term "initial burst" refers to the percentage of the total drug load that dissolves and is released from the formulation in the first hours after dosing. While it was possible to get high encapsulation and relatively low initial burst at low drug loading, the burst was not brought below 20% at more realistic drug loads of 25−30% in the microspheres. They also explored PLGA with monomer ratios of 50:50, 75:25 and 85:15, but the burst remained above 20%. Unfortunately, high plasma concentrations of OLZ bring unacceptable side effects (PDSS) that would not be solved by the microspheres in this study.

Despite the success of Risperdal Consta, there are disadvantages to developing microsphere-based products. The relatively low Tg of PLGA and the susceptibility of the polymer toward hydrolytic degradation necessitates refrigerated storage to ensure the physical stability of, and proper release from, the microspheres. The process requires specialized expertise, especially for scaling-up and production of sterile microspheres. Though no study on the subject has been published, high costs of manufacturing and production were cited as a reason for Genentech's withdrawal of Nutropin Depot in PLGA microspheres from the market.[43] Likewise, the expense of making PLGA microspheres was listed in one of the patents protecting Abilify Maintena as a reason for injecting suspensions of crystalline APZ.[44] In contrast, the experience and equipment to develop products involving synthesis of prodrugs, dissolution into oils, crystallization and/or milling are well established within most pharmaceutical companies.

C3. Crystals for Aqueous Suspension. A ready-to-use aqueous suspension would be the most convenient formulation for a physician by which to inject a crystalline compound. However, the compound must be stable against chemical degradation in water, the particle size must remain in a usable range until injected, and the particles must not form a dense sediment that is too difficult to resuspend after shipping or storage.[45] If these criteria cannot be met, then the crystals must be supplied as a powder for suspension. This may be the fastest way to get a new compound into development with a switch to ready-to-use suspension later in development or postmarket approval.

Zyprexa Relprevv (OLZ-pamoate) and Abilify Maintena (APZ·H_2O) are currently marketed as powders for reconstitution, where the product contains a sterile vial of powder and a sterile diluent along with appropriate syringes and needles. Both of these compounds have solubilities in the range of 0.1−10 μg/mL, while the compounds formulated as ready-to-use suspensions, APZ-C12 and PALI-C16, have solubilities below 0.1 μg/mL. (APZ-C12 and PAL-C16 have been synthesized at Alkermes and the solubility in 50 mM phosphate buffered saline (studied over the pH range of 6.0−8.0) was below the limit of detection in HPLC-UV methods that could detect the compounds down to ∼0.1 μg/mL.) This higher solubility may actually be one of the limiting factors; chemical degradation typically occurs much faster for dissolved compounds than for molecules that are locked into a stable crystal lattice. Therefore, the rate of degradation that is so often measured in solution stability studies during development is really only applicable to the dissolved fraction.

One patent protecting the Abilify Maintena product claims a freeze-dried cake containing APZ with a particle size in the range of 1−10 μm and all of the excipients so that only sterile water is required to reconstitute the formulation for injection.[46] The patent provides two examples for preparing crystals of the proper particle size. The first example employs a DYNO-MILL with high density zirconium oxide beads to reduce the particle size of crystalline APZ·H_2O in suspension with all of the excipients at about 10% solids load. The resulting suspension is ready for lyophilization. The second example uses the impinging jet method where a fine stream of APZ/ethanol solution is impinged with a fine stream of water. The resulting crystals are filtered, dried, and resuspended into an aqueous vehicle with all of the excipients and then freeze-dried in vials to give the final product. Both examples produced very similar particle-size distributions with a mean particle size of 2.5 μm. The available literature does not disclose the reason for lyophilizing rather than packaging as a ready-to-use suspension. However, an injectable aqueous solution of APZ is marketed for immediate release to treat acute agitation, which suggests that the molecule is chemically stable in water and that the bigger difficulty may be related to the physical behavior of the suspended crystals on storage or shipping.

C4. Ready-to-Use Aqueous Suspension. The only ready-to-use LAIA on the market as of 2013 was PALI-C16, and the trial of patents shows this product to be the culmination of over a decade of work to go from oral risperidone to a once-monthly injection. It was described as an improvement upon injections of a RISP-pamoate salt in the patent where it was first disclosed, since suspensions of RISP-pamoate provided extended release, but with high initial plasma concentrations, i.e., a burst effect.[22] The innovator provided results from pharmacokinetic (PK) studies in dogs that compared PALI-C10 as a suspension in oil to PALI-C16 suspensions in oil and in water as shown in Table 3. The description of the study suggests that the decanoate was a solid that was not completely soluble in oil, but it does not state whether the solid was crystalline. It is clear that the PALI-C16 aqueous suspension gives higher plasma exposure and C_{max} than either of the suspensions in sesame oil. The lower viscosity of the aqueous suspension also allows for injection through a narrower 21-gauge needle.

The patents for paliperidone palmitate demonstrate the quick evaluation of delivery technologies with a convergence on nanomilling to reach submicrometer particles.[22,47] The use of wet-media milling was of growing interest in the late 1990s, with the company NanoSystems (later Elan Drug Technologies and now part of Alkermes plc) leading the technology development, and Janssen Pharmaceutica applied the technique to esters of paliperidone.[18]

Table 4 shows PK data from dogs dosed with suspensions containing 7% Pali-C16 milled to give specific surface area ranging from 1.3 to >15 m^2/g, as included in a patent from 1999.[47] There is a clear trend of C_{max} and AUC increases as well as T_{max} decreases with growing surface area and shrinking particle size, though the smallest particle size broke from the trend in C_{max} and T_{max}. Interestingly, the body of the patent states the drug is cleared particularly fast in dog compared to human and that the PK data in humans accordingly showed a much larger effect on particle size than had been predicted, though no data are provided.

Table 4. Particle Size Dependence on PK in Dog after IM Injection of PALI-C16 in Aqueous Suspension[a]

particle size[b] (μm)	specific surface area (m^2/g)	C_{max} (ng/mL)	T_{max} (days)	$AUC_{0\text{-}t}$ (ng·h/mL)
6.03	1.3	41.2 (±22.1)	12 (±5)	19487 (±7697)
1.38	6.5	86.4 (±30.5)	7 (±3)	25769 (±9782)
0.74	13.5	139 (±33)	1.8 (±1.5)	28603 (±4305)
0.52	>15	132 (±60)	6.3 (±1.5)	34852 (±14055)

[a]7.02% PALI-C16 in aqueous suspension dosed IM to dog in the left hind paw at 2.5 mg/kg using a 21 G 1.5″ BD microlance needle. [b]50% of particles in the sample are smaller than the value in this column, based on data reported from a Mastersizer X light scattering particle size analyzer.

D. EMERGING WORK AND AREAS FOR FURTHER RESEARCH

The literature and patents describe the currently marketed LAIAs, but they offer little guidance for selecting prodrugs or delivery options when assessing a new molecule. Two of the current LAIAs could potentially be improved through the use of prodrug-based delivery; the market desire for ready-to-use aqueous suspensions provides opportunities for both APZ and OLZ. Any strategy to improve OLZ should also seek to eliminate the possibility of PDSS. HALO and FLU have been on the market for decades, but one might question whether there is any benefit of switching to aqueous suspensions of a new crystal form. Prodrug strategies for OLZ and APZ have recently been disclosed along with physical data for fatty tails ranging in length from 2 to 18 carbons.[15,48] The data show that a large variability in properties such as melting point can be expected within a series and that the trends are largely unpredictable without actually synthesizing and characterizing all molecules within the target series.

D1. Selecting Prodrugs for Aqueous Suspension. Florence and Vezin published the first study comparing the activities of two long chain fatty acids of a single prodrug as aqueous suspensions in 1982.[34] The study showed that FLU-C16 is more active than FLU-C18, that the activity is particle-size dependent, and that aqueous suspensions of long-chain analogues can outperform their respective solutions in oil. In this early paper, the aqueous suspensions are described as "solidified emulsions" that are available because the prodrugs melt around 50 °C. (We prepared and confirmed these compounds are crystalline with the melting points reported.) One of the patents for PALI-C16 states that other esters were prepared and tested in oils and aqueous suspensions.[22] The text concluded that PALI-C16 aqueous suspensions were most favorable, but no data have been published, so the criteria remain unclear. The melting point of PALI-C16 is reported to be 118 °C,[49] which is clearly high enough to make stable aqueous suspensions. Perhaps FLU-C18 with its lower melting point (mp) would also have shelf-stable suspensions, but one might expect a melting point depression in water that is uncomfortably close to body temperature. Unfortunately, there are too few studies published to help researchers decide on a minimally acceptable mp for crystalline prodrugs in aqueous suspension.

A recently published study on carbamate linked esters of OLZ (CLEOs) demonstrated a trend in mp change with tail length. This prodrug series was shown to have a single crystal packing motif with layers of parent separated by layers of lipid tail. The trends of tail length versus mp have also been recently disclosed for hydroxymethyl linked esters of APZ and pioglitazone (not an antipsychotic).[48] An overlay of these data is shown in Figure 3. The data for the APZ esters stand out in that there are two maxima in the mp trend at APZ-C6 and APZ-C12 with a minimum in between. In the abstract, the authors relate the behavior to changes in crystal packing. With melting points near 100 and 80 °C, both of these molecules were tested in human phase 1 clinical trials as aqueous suspensions, and APZ-C12 continued into a phase 3 pivotal trial that was recently completed with positive results.

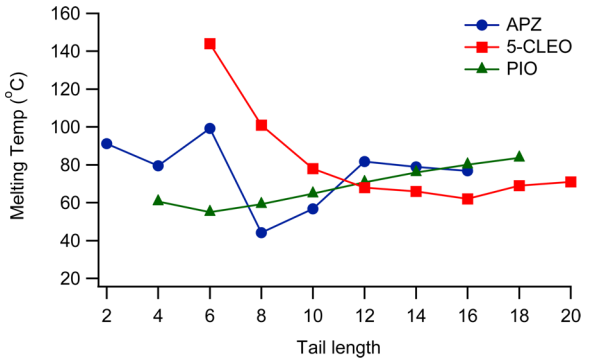

Figure 3. Overlay of melting point vs tail length (total carbon atoms) for APZ, 5-CLEO, and pioglitazone (PIO) linked esters.

D2. Understanding the Lag Phase in LAI Aqueous Suspension. There is a lag period where little drug is absorbed after injections of LAI depots of RISP, PALI-C16, and APZ·H_2O, which necessitates continuing oral therapy after the initial injection. After the second or third dose, drug still being released from earlier injections provides coverage during the subsequent lag periods, and oral augmentation is withdrawn. The lag, as seen in Figure 2 for Risperdal Consta, has been explained as a need for polymer to degrade sufficiently to allow for faster diffusion of the drug.[39] A 1−3 week lag period for crystalline drugs cannot be so easily explained, since the crystal does not become more soluble by virtue of sitting longer in the injection site. The body responds to all foreign materials shortly after they are injected, and the impact of this response as it evolves in the weeks following injection is just beginning to receive attention. A poster presented at the Controlled Release Society meeting in 2013 addressed this issue and described the immune response at the injection site, but did not make a conclusive link between the response and the lag period for an undisclosed lipophilic prodrug injected as an aqueous suspension.[50] Paquette et al. recently reported on the local tissue response to suspensions of APZ·H_2O and OLZ-pamoate.[51] These crystalline drugs were both shown to induce

foreign body responses where the drug became encapsulated following injection, but the paper did not provide PK data. Further work is needed to explain not only the lag phase but also the physiological components responsible for dissolution and mobilization of molecules with nanogram per milliliter level aqueous solubility from depots.

D3. Potential Safety Advantage of Lipophilic Prodrugs over Poorly Soluble Salts. Most of the parent antipsychotics are capable of inducing sedation at sufficiently high plasma concentrations, but only OLZ-pamoate carries a boxed warning of PDSS, which results from unexpected solubilization of the molecule. Outside of antipsychotics, a similarly rare toxicity is observed for LAI penicillin benzathine, where slow release is also controlled through use of a poorly soluble salt form. In contrast, a literature review for PALI-C16 found no incidences of sedation postinjection.[45,52] It is easy to rationalize these differences in terms of the lower solubility of the lipophilic prodrug and slow enzymatic reversion of long chain fatty esters back to the parent drug. In the event of accidental solubilization, the conversion of prodrug to parent occurs as a function of the half-life of ester activity, which may be less than 5 min for short chain esters or several hours for some with longer tails.

The lipophilicity/hydrophobicity of prodrugs may be the single largest safety advantage over salts or formulation-based strategies to retard release, trumping both solubility and slow esterase-mediated conversion. This factor drives the tendency to bind nonspecifically to surfaces and partition out of water into whatever organic phase is present. The most direct published demonstration of this phenomenon in the antipsychotic arena compared intravenous administration of FLU-C10 dissolved in ethanol to an aqueous solution of FLU-2HCl, with the results for one of four dogs shown in Figure 4.[29] The

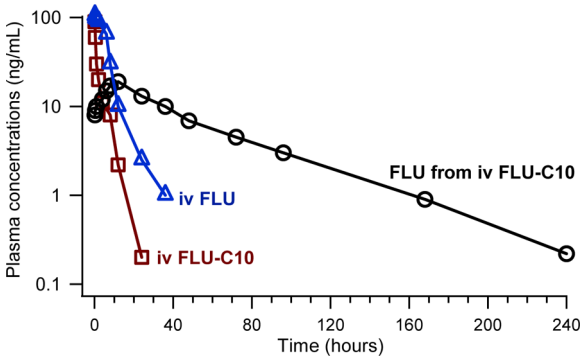

Figure 4. Comparison of plasma levels of FLU and FLU-D (FLU-C10) in dog after intravenous administration of aqueous FLU-2HCl or ethanolic FLU-C10.

plots for all four dogs were shown in the original manuscript, and the results are all consistent: immediately after injection of either compound, the concentration of the injected molecule is near 100 ng/mL; the prodrug leaves the plasma faster than the more water-soluble parent; the maximum concentration of active FLU delivered from the prodrug is 5-fold lower than the amount of prodrug injected; and FLU-C10 has formed a reservoir somewhere outside of the plasma from which it continues to slowly convert to active for more than 7 days. This experiment demonstrates that it is possible for some lipophilic prodrugs to prevent side effects resulting from mis-injection into a vein. Poorly soluble salts cannot compete, as the counterion cannot be expected to remain associated or paired with the dissolved drug in the sea of other ions that is present in the body; once a salt dissolves, it will behave as the parent drug, and this is a fundamental difference from lipophilic prodrugs. Whether or not a prodrug approach could improve the safety of OLZ remains to be seen.

E. CONCLUSIONS

The LAIs that are administered as aqueous suspensions each use a unique combination of drug and delivery technologies, and very little data have been published that would help guide a team to the best strategy for their molecule. PLGA polymeric delivery systems may be the only viable option for small molecules that are water-soluble, especially if small changes in physiological pH can significantly increase the solubility. Poorly soluble salt forms of small molecules may be more prone to "bursts" than other strategies, especially when compared with lipophilic prodrugs. Even when no -OH group is present on the parent molecule, creative strategies have been used to reversibly place fatty acid tails on RISP, APZ, and OLZ. However, it is clear that no tail length is universally preferable for prodrugs that will become aqueous suspensions: PALI entered the market as the C16 prodrug; the C6 and C12 linked esters of APZ have both been tested in phase 1 human clinical trials; and FLU-C16 and -C18 esters were both found to be long-acting in rat models. Further publication of studies comparing the physical properties and behavior of different prodrugs of a given molecule could help to accelerate the transition of oral drugs to safe and reliable LAIs.

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Notes

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