ASCENDIA PHARMA

Long-Acting Injectable Nanoparticle Formulations

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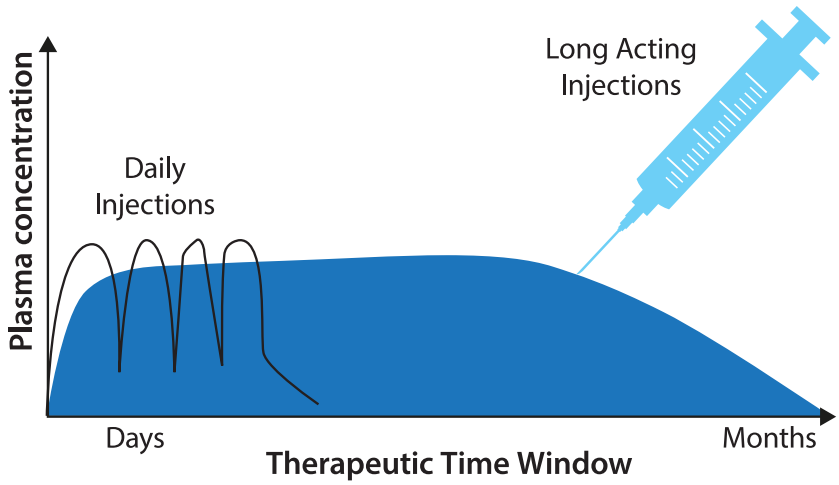
Introduction

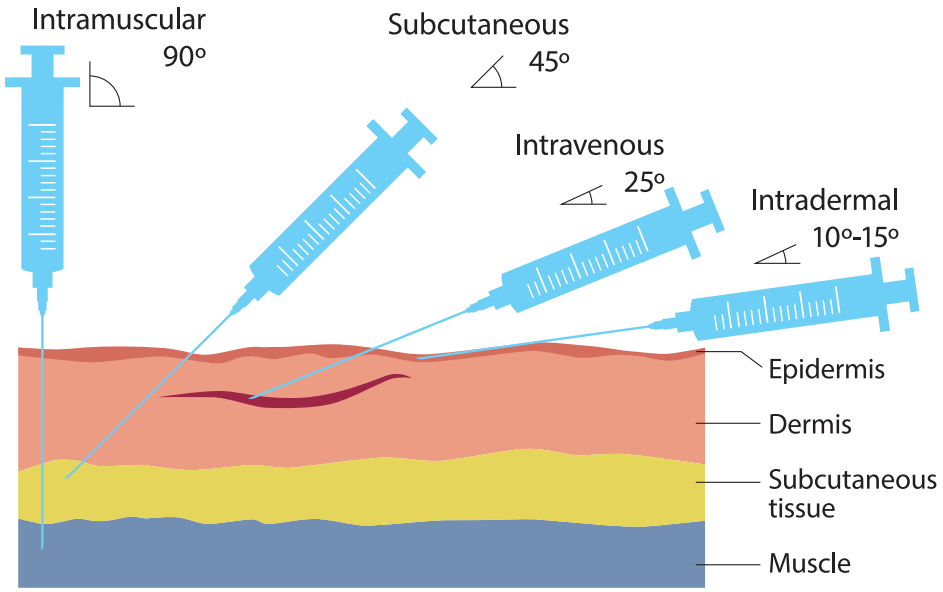
Long acting injectable (LAI) formulations have been the subject of continued interest in the recent past due, in part, to their longer systemic circulation requiring less frequent dosing of drugs.[1] Less frequent administration, as illustrated in Figure 1, make LAIs more attractive from patient compliance perspectives. While delivering the extended release, LAIs can reduce toxicity and enhance the efficacy and safety of drugs. Other benefits also include the accessibility of medicines at nominal cost for underserved patient populations for treatment of life-threatening diseases like HIV, as compared to long-term implants.[2]



Nanoparticles (NPs) continue to play an important role in the formulation and delivery of LAIs. As the interest in NPs continues to grow due to over 80% of new chemical entities and over 50% of marketed drugs being poorly soluble (in 250 ml volume and at pH 1-7.5), the industry is looking into alternative technologies for bringing insoluble Class II and Class IV molecules to market.[3]

LAI drugs are often formulated in appropriate carriers for their performance and longer shelf life. Those carriers in the formulations are for the most part lipids, polymers and surfactants that make them attractive as delivery vehicles because of their commercial availability and suitability with the route of administration, such as intramuscular, intravenous and/or subcutaneous.[4] Figure 2 illustrates the mode of injection of drugs.

For example, intramuscular (IM) requires a deep injection at a 90° angle in the muscles, thereby allowing drugs to be available in circulation for an extended period. On the other hand, in intravenous (IV) injection, the drug is administered at 25° angle directly in the bloodstream, avoiding the body defense systems; and in subcutaneous administration the drug is administered at 45° angle under the skin for systemic absorption, while in intradermal, it requires a 10°-25° angle administration for accessibility of drugs under the skin.[5]



As illustrated in Figure 2, the major modes of injection include intravenous, intramuscular, subcutaneous, and intradermal, among others. Injectable route of administration remains an indispensable method of treatments for practically all the modalities. In comparison with the oral route of administration, the parenteral route is most stringent and widely accepted for many unmet needs. It requires careful selection of ingredients free of bioburdens and endotoxins with greater compatibility for rapid onset, thus avoiding first-pass metabolism and bypassing the harsh gastrointestinal environment, and most of all improving patient safety. All these challenges also bring opportunities to drug developers and contract manufacturers as long as the product's critical attributes are satisfied to meet the FDA’s safety standards and guidelines.

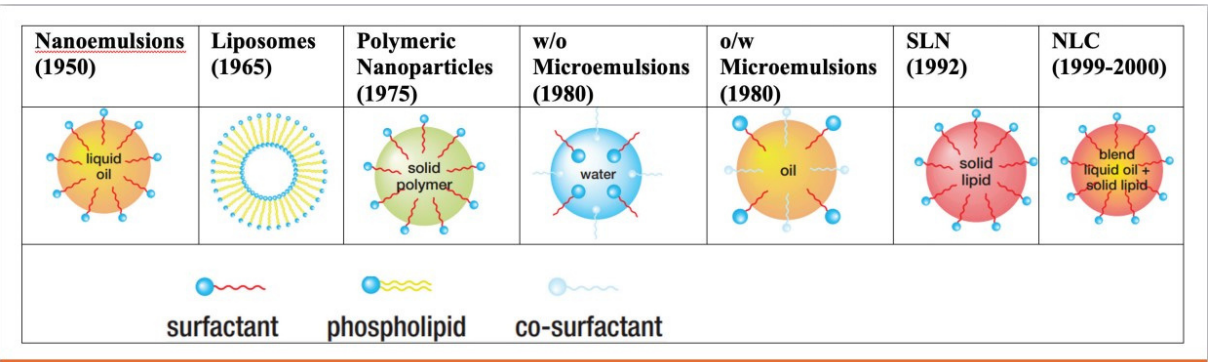


Figure 3. Progression of NPs over five decades

Landscape of Nanoparticles and Injectable Drugs

Considering the efforts made over the years, specifically in parenteral NPs, the number of approved drugs is limited, and that is, due, in part, to challenges with poorly soluble molecules and challenges with tissue targeting.[6] Perhaps it is no surprise and no different from the limited number of approved drugs, such as amorphous polymeric solid dispersions in oral dosages or lipid-based SEDDSs solution/ dispersions in oral liquids, but the effort continues. As innovative NP technologies continue to unfold for yielding better and smarter formulations, the industry is open to adapt for bringing the new molecules to market.[7] The lack of appropriate regulatory guidelines on NPs for addressing the often complex dosage requiring novel excipients or technologies, for example, could be an impediment in the approval of new drug products.[8] Other challenges stemming, for instance, from lack of guidance on method, validation, manufacturing, particle size reduction, high-pressure homogenization, sonication, extrusion, milling, use of organic solvents and impurities, stabilization and lyophilization among others, may lead to further delays.

An understanding of physical characteristics of NPs is important to address the risks in a drug product. NPs are characterized as nanoemulsions, liposomes, polymeric nanoemulsions, micro-emulsions and saturated lipid nanoparticles and nanostructured lipid carriers. Lipids and/or polymeric aggregates have abilities to incorporate drugs in the interior lipophilic core allowing the exposure of hydrophilic moieties to outside aqueous media. The encapsulation of drugs depends on hydrophilic lipophilic balance (HLB) values of lipids/solubilizers.

Longer retention of drug within the inner assemblies due to stronger interactions with lipophilic carriers, recrystallization and precipitation, and premature leakage of drugs in storage over longer shelf lives, could pose challenges in design of robust NPs, especially, with fragile molecules like proteins and peptides in lipid-based emulsions, microemulsions and nanoemulsions, liposomes, and to a lesser extent SLN and NLC. In such cases, the polymeric nanoparticles are widely considered, which are relatively more stable than surfactant/lipid-based NPs, and, therefore, they are better suited for sustained release applications.[9,10] Factors affecting the development of long-acting injectable formulations also include, but are not limited to, reaction at the injection site or dilutions leading to drug recrystallization or minimizing the interactions of drugs with matrix leading to precipitation. All these challenges can be offset by designing and characterizing the right NPs by overcoming their solubility challenges. Figure 3 illustrates the evolution of NPs over the years, leading to more widely and predictable use of SLN and NLC for encapsulation, longer stability, and efficient delivery of drugs.[11]

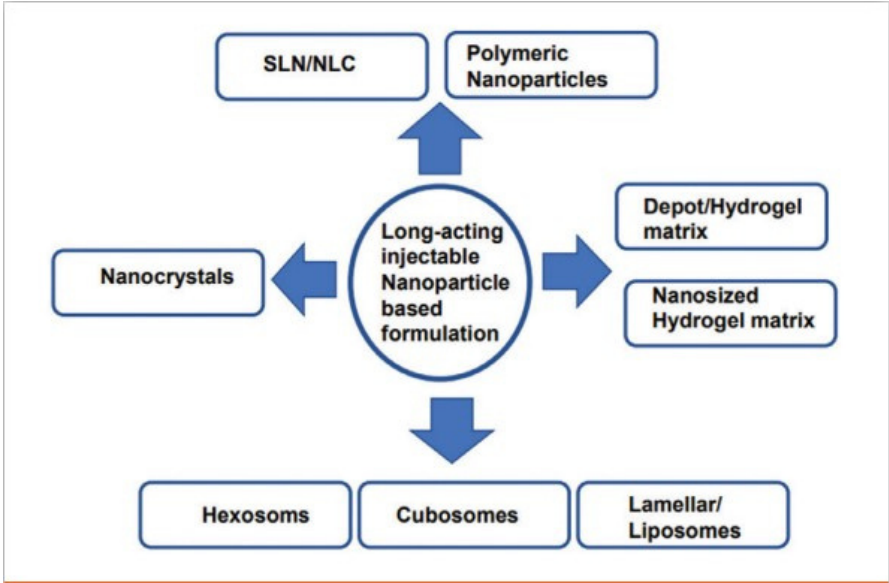


Figure 4. Nanotechnology platforms for design of long-acting injectable NPs

Figure 4 illustrates the nanoplatform technologies for LAI formulations.[12] These formulation technologies have been used as the drug delivery carriers for parenteral, intramuscular, and subcutaneous formulations for different modalities. Those include nanocrystals, polymeric nanoparticles, depots, hydrogels, SLN/NLC, liposomes, and liquid crystalline lamellar assemblies.

Relevance for Smaller Particle size

Particle size reduction is one of the important attributes leading to higher dissolution rates caused by higher surface area as it can be predicted by Noyes-Whitney equation 1. dm/dt is the dissolution rate, D is the diffusion coefficient, A is the surface area, h is the diffusion layer thickness, Cs is saturation concentration, Ci is concentration in solvent, and t is time.

$$\frac{dm}{dt} = \mathrm{A}.[D/h].(Cs - Ci)$$

Thus, smaller particle size means larger surface area, faster rate of dissolution and faster the rate of absorption of drugs.

From a manufacturing perspective, particle size reduction is vital, which plays an important role in designing better and smarter LAI injectable formulations. The size reduction by mechanical devices can be achieved by a number of techniques.

For example, producing the LAI nanosized suspension involves a top-down approach wherein the API and the ingredients are mechanically mixed and[13]homogenized or milled together, avoiding the use of organic solvents altogether. This method also requires use of stabilizers and/or solubilizers to keep the particles small without flocculating or aggregating, and to maintain the longer shelf life. The top-down approach is probably the most widely used for manufacturing liquid suspensions for parenterals because it can produce the desired particles size from larger ones. It involves techniques such as wet and jet milling where the grinding of the larger particles takes place through mechanical motion of the ball milling beads, and by high pressure homogenization process, in which the particle size reduction takes place through a jet stream homogenizer. There are other challenges associated with developing and characterizing LAI nanosized particles, which are not limited to, for example, lack of cGMP manufacturing and characterization protocols, drug loading and targeting, and release characteristics as it is all dependent upon the particle size distribution of nanoparticles.[14]

From mechanism perspectives, the particle size reduction plays an important role in cell recognition for their therapeutic efficacies. NPs contribute to immunotherapy by tagging the protein moieties that triggers the activation of receptor signals on the T-cells.[15]Medium-sized NPs of about 300 nm have shown to trigger stronger immunogenic response as compared to smaller particles with 50 nm in size.[16]

It is also known that NPs with specific size promote their recognition and able to tag on by various circulating antibodies in the blood stream and/or able to activate the complement proteins upon interaction with blood opsonins. These pathways lead to phagocytosis by macrophages.[17] In another scenario, NPs can be surface modified to substantially minimize the interactions with complements to trigger the immune response, thereby, they can be used in long-acting injectables by enabling longer systemic circulation.[18]

These attributes are essential, for example, in the development of immunotherapeutics and vaccines with NPs engineered by enabling significant interactions, and/or posing a lesser degree of interactions for development of long acting formulations. These are important questions and embarked on with the notion of engineering these surface-modified NPs to be amenable to meet the product's critical attributes.

Long-Acting Injectable Marketed Drugs

Table 1 shows the list of FDA drugs approved in lipid- and polymeric-based NPs.

Table 1.

Product	Nanocarrier	API	Route	Indication
Abelcet®/ AmBiosome®/ Amphtec®	Ribbon-like structures/ Liposome/disc like structure	Amphotericin B	IV	Fungal infection
Abraxane®	Albumin-paclitaxel conjugate	Paclitaxel	IV	Oncology
DaunoXome®	Liposome	Daunorubicin citrate	IV	Oncology
DepoCyt®	Liposome	Cytarabine	Intrathecal	Oncology
Diprivan®	Nanoemulsion	Propofol	IV	Anesthesia
Eligard®	Polymeric nanoparticle	Leuprolide acetate	SC	Oncology
Fungizone®	Micelle	Amphotericin B	IV	Fungal infection
Invega Sustenna®	Nanocrystal	Paliperidone palmitate	IM	Schizophrenia
Myocet®	Liposome	Doxorubicin	IV	Oncology
Opaxio®	Polymeric nanoparticle	Paclitaxel	IV	Oncology
Visudyne®	Liposome	Verteporfin	IV	Osteoarthritis

Over the years several LAI drugs have been approved. Those drugs are marketed in crystal nanosuspensions, liposomes, polymeric nanoparticles, and also in oil suspensions, and/or hydrogels. In liposomes, for example, the drug is encapsulated within the bilayers, allowing the drug to release through a membrane. In LAI prodrug formulations, the fatty acid-derived drug is released slowly by cleavage of the lipophilic chains, or by slowly dissolving and releasing in systemic circulation.[19]

Olanzapine pamoate, for example, a prodrug of olanzapine, slowly releases the parent molecule upon intramuscular (IM) injection. Invega Sustenna®, Invega Trinza®, and Invega Hafyera® marketed as prodrugs for treatment of schizophrenia and dosed as LAI suspensions monthly, every three months, or every six months, respectively, also release slowly by cleavage of parent molecules over extended periods. Commercially available first generation and second generation of LAI anti-psychotic drugs are shown in Table 2 (first generation) and Table 3 (second generation).[20]

Table 2. First-generation antipsychotics available as long-acting injectable drugs

Drug	Starting dose (mg)	Maintenance dose (mg)
Haloperidol decanoate	50	50–200 every 3–4 weeks
Fluphenazine decanoate	12.5	12.5 - 50 every 2–3 weeks
Flupenthixol decanoate	20	50–300 every 2–4 weeks
Zuclopenthixol decanoate	100	200–500 every 1–4 weeks

Table 3. Second-generation antipsychotics available as long-acting injectable drugs

Drug	Manufacturer	Formulations
Aripiprazole monohydrate Aripiprazole lauroxil Olanzapine pamoate	Otsuka/ Lundbeck Alkermes Lilly	300,400 mg vials, prefill syringe 441, 662, 882 mg prefill syringe 210, 300, 405 mg vials
Paliperidone palmitate	Janssen	39,78,117,156 or 234 mg
Paliperidone palmitate	Janssen	273, 410, 546, 819 mg prefill syringe
Risperidone microspheres	Janssen	12.5, 25, 37.5 or 50 mg vials

Table 4.				
Drug	**Active**	**Indication**	**Duration**	**Dose**
Lupron Depot®	Leuprolide acetate	Prostate cancer	1-6 months	7.5–45 mg
Bydureon® Type 2	Exenatide	Diabetes Type 2	1-week	2 mg
Trelstar®	Triprorelin pamoate	Prostate cancer	1-3 moths	3.75-22.5 mg
Sandostatin® LAR	Octreotide acetate	Acromegaly/Neuroendocrine Tumor (NET)	1 month	20-30 mg
Signifor® LAR	Pasireotide pamoate	Acromegaly/Cushing disease	1 month	10-60 mg
Zoladex®	Goserelin acetate	Prostate and breast cancer	1-3 months	3.6 mg, 10.8 mg

Table 4 shows the PLGA based LAI microspheres/implants marketed drugs.

Several marketed LAI products have been developed utilizing oil-based systems,[8] aqueous suspensions, polymeric microspheres, and hydrogels among others.[21] Long-acting injectable lipid-based formulations are the first wave of products entering the market utilizing an oil-based solution in which drug is dissolved in the oil with or without a cosolvent. As the number of poorly soluble molecules continues to rise, the LAI approach has been more relevant for maintaining the drug in systemic circulation with longer efficacies and with less frequent dosing for treatment of life-threatening ailments.

In other words, the sustained release achieved by subcutaneous, intramuscular or intravenous solution oil/emulsions and suspensions, probably bears the hallmarks of long-acting injectable formulations. The molecular weight and size of the particulates play a key role in long-acting release. For instance, the macromolecules with MW 16 kD or less, and particle size 100 nm or less, can be cleared from the tissues by lymphatic systems, whereas, the larger particulates may retain longer and act as the long-acting formulations due to their smaller surface area to volume. Thus, an understanding of encapsulating a drug in larger nanoparticles for extended release is important for designing the long-acting injectable systems.

The oil-based long-acting and lipid-based long injectable systems, however, face some challenges. For example, the oil-based LAI can lead to long-lasting pain and irritation at injection site. Therefore, to overcome[22] these issues, the lipophilic lipid-based or polymeric-based nanoparticles for lipophilic drugs have been used as alternatives to oil-based systems.

Higher drug loading and stability of molecules encapsulated in NPs have been obvious reasons for concerns and opportunities. Therefore, finding an appropriate carrier with the ingredients compatible with the drug in the LAI matrix has been subject of continued interest and is used as a tool to assess the stability and release mechanism. NPs, due to their outer rigid protective nature, may lower the barrier for API's penetration in the systemic circulation through blood or lymphatic systems. Local long-acting and systemically injected long-acting formulations play a key role in extended release of drugs from engineered nanoparticles by prolonging the release of payload from the nanocarriers. In sustained release, however, the nanoparticles get accumulated in the targeted tissues allowing the drug release via passive mechanism.

Long-Acting Injectable Suspensions

LAI lipid-based formulations can either be oil-based solutions, suspensions or more complex lipid-based nano carriers such as liposomes, emulsions/microemulsions, or lipid-based depots such as oleogels or liquid crystals. There is a continued interest in LAI suspensions or liquid crystals for controlled release applications. As it sounds, these suspensions provide a slower or sustained release and have advantages over oral formulations because of their less frequent administration and better controlled mechanism with reduced side effects in an aqueous suspension.

An aqueous LAI suspension might be thermodynamically unstable due to heterogeneous insoluble particles, but can be stabilized with lipid-based solutions like polyoxyl 35 castor oil, polysorbate 80 or polymeric-based ingredients like povidone (PVP) or poloxamer, and/ or can be stabilized by lyophilization with cryoprotectants for longer shelf life and for facile reconstitution in buffer.

APIs prone to hydrolysis, such as prodrugs, or derived from lipophilic moieties tethered with ester linkages, can trigger the slower release over extended periods when formulated or reconstituted in aqueous suspensions from lyophilized powders. The physical instability of suspensions, triggered by flocculation, phase separation and/or by Oswald ripening, could be challenging due to lack of clear understanding of the mechanisms. In cases like these, certain ingredients can be used to minimize the morphological changes and maintain the particle size with optimal drug loading. The maximum achievable concentrations of the drugs in the suspension could range 200-300 mg/ml, and with higher drug loading, it could run into instability leading to precipitation and crystal growth. In such cases, use of stabilizers, anti-oxidants, particle size reduction, viscosity inducing agents, buffer strengths among other factors, should be considered.[23]

Table 5. In vitro release characteristics of LAI formulations			
Method	**Formulation**	**Description**	**Result**
Non-membrane	1. Fatty acid gelators soybean oil (Paliperidone and coumarin-6) 2. Aq. solution of Poloxamer 407 (Oxytocin) 3. Aromatic amino acids, sunflower oil and Rivastigmine	Phosphate buffer, pH 7.2, sample transform into gel in a tube and kept at 37° C water bath	In vitro- release over 14 days, poor IVIVC correlation due to shorter release in vivo
Dialysis	1. Liquid crystal e.g. Leuprolide acetate 2. Microcrystal suspensions in peanut oil e.g. Drospirenone 3. Aqueous solution of Poloxamer 407 gel with Oxytocin	Dialysis tube submersed in physiological buffer pH 7.4 at 37°C in a USP bath Type 2, and agitated, dialysate is analyzed	In vitro: faster release, poor discriminatory ability, concentration dependent release, could be poor IVIVC correlation
USP Type 1 (basket)	1. Aqueous solution of Poloxamer 407 with Oxytocin 2. Glutamate based gelators and soybean or medium chain triglycerides (MCT)	Basket is used to contain the LAI samples with or without mould	In vitro: useful method if used to investigate release by degradation but not widely used
USP Type 2 (paddle)	Aqueous solution of Poloxamer 407 with Oxytocin	Hydrogel contained within mould and placed at the bottom of vessel	In vitro: no significant differences shown between release profiles No vivo correlation
USP Type 3 (Venkel)	Aqueous solutions of Poloxamer 407 with Oxytocin	Bottom screen size 177 microns to retain semisolid formulation	In vitro method works well, good compared to others IVIVC correlation no comparison

Long-Acting Injectable Lipid-Based Formulations

Lipid-based LAIs are oils, aqueous suspensions and olegels. There are several oil-based LAIs approved in the market drugs, for examples, with castor oil (Fulvestrat - Faslodex®), cotton seed oil (Testosterone cypionate - Depo-Testosterone®), sesame oil (Haloperidol decanoate-Haldol®), and cotton seed oil (Zuclopenthixol decanate - Clopixol®), are all administered intramuscularly (IM). LAI activities of these drugs stem from lipophilic fatty acid tethered prodrugs that allow the release of a parent molecule by hydrolysis or by cleavage of the ester linkages. While the longer fatty acid slows down the release of drug due to higher partition barrier from oil phase to aqueous phase in oil or suspension-based LAIs, it also runs the risk for reducing the potency of parent molecules, that could lead to failure in toxicological studies. [24] Lipophilicity and higher log P tend to slower release following IM injection, allowing the API uptake predominantly by lymphatic systems.[25] In cases where API is hydrophilic, for example, olanzapine, molecular modification with fatty acid, can further reduce the solubility to offset the rapid release of drug, making it ideal for sustained release and uptake by lymphatic systems.[26]

Other factors such as viscosity of injectable oils may have a significant impact on the release of drugs. Sesame oil and organogels with higher viscosity and an excellent tolerability by IM can lead to slower release and partitioning by diffusion mechanism from oil/gel into body fluid. Suspensions in oil of drug crystals is an alternative to oil-based LAIs. It is different from the suspensions in aqueous for injection. Oil-based suspensions have limited scope because of injection difficulties and pain at the injection site, therefore, the aqueous solutions-based LAI suspensions are preferred and are better alternatives than oil-based suspensions. Lipid-based liquid crystal forming systems are another alternative to LAI formulations. The liquid crystalline ability of lipids can provide a controlled release mechanism by entrapping the drugs into the inner core of the fatty acid lipids. Hence, the sustained release is the result of slower diffusion of drug through mesophase membrane. There are three options mesophase - lamellar, hexagonal and cubic - with hexagonal and cubic being most widely studied.

In Vitro Drug Release Characterization

There is no reliable pharmacopeial guidance on *in vitro* drug release assessment of IM drug formulations. There are some methods used *in vitro* for the assessment of drug release but none is without any challenges. Larsen and Larsen, 2009, used several methods for oil-based parenteral solutions, the in vitro methods have been modified. Table 5 shows the *in vitro* methods for assessment of drug release from lipid-based LAI oleogel/liquid formulations. [27]

Sterilization Methods

The sterility of the LAI suspensions is also of relevance in maintaining the stability of nanosized particles. Thus, not all the methods used for sterilization are suited for these formulations. For instance, autoclaving or terminal heat sterilization are less likely used as they can destabilize the physical stability and compromise the product's critical quality attributes, especially those derived from LNPs. Gamma radiation sterilization might be a better option for suspensions or by aseptic filling conditions in closed containers or syringes to avoid cross-contamination.[28]

As shown in Table 6, a number of sterilization methods have been used for NPs that might be extended for other formulations.[29] The excipients in the formulation should also be sterilized by several methods. When considering the scale-up and sterilization of these LAI nanosized suspensions, the process is cumbersome and may lead to batch variabilities if the processes are not optimized, leading to poor product quality attributes and compromised performance of drug products.

Table 6. Methods of sterilization, conditions and challenges

Sterilization method	Condition	Pros	Cons
Dry heat	80°C for 30 min or 170°C for 1 hour or 160°C for 2 hours	Kills pyrogens	API/excipient heat sensitivity matters
Autoclave/ moist heat	121°C for 15 min	Requires certain heat/moist temperature	API/excipient heat/moisture dependent instability
Sterile filtration	0.2 µ filter	Filter integrity checked/ maintained	Applicable to temperature/heat sensitive lipids/nanoparticles and similar assemblies
Gamma/E Beam irradiation	25 kG effective	Containers and packaging materials stable	Not recommended for heat sensitive APIs/excipients

It is obvious that the choice for method of sterilization is based on the formulations and nature of the ingredients used in the NPs and LAIs.

Sterile Aseptic Filing and Lyophilization Injectable Formulation Capabilities

Ascendia is a specialty CDMO having the sterile capabilities for NPs and LAIs. Its proprietary solubilization enabling technologies aimed at improving the solubility and bioavailability of molecules - NanoSol®, EmulSol®, and LipidSol® - can handle the molecules (small, large or biologics) and enable the efficient delivery of these molecules. In NPs, drug is encapsulated and stabilized into interior lipophilic cores of oils/ aqueous suspension or in liposomes.

Carvedilol, a marketed drug in tablets, has been formulated @6.8% in lipid-based liposomes comprised of about 52% DMPC, 21% Cholesterol and 22% DSPE with particle size distribution of 75-150 nm and polydispersity of 0.12-19 and encapsulation efficiency of 80-90%. For comparison, carvedilol both in aqueous solution and in liposomes encapsulated @7.6% and comprised of 65% egg phospholipids and 27% cholesterol (freshly prepared and lyophilized and reconstituted) were also used to evaluate in vitro drug release and examine the pharmacokinetic profiles in rats. The carvedilol was single dosed at 2.5 mg/kg. In vitro release and pharmacokinetic (PK) data of drug from 3 animal groups (Group 1 with DMPC, Group 2 from egg PC and aq. solution Group # 3) were also evaluated and the results are shown in Figure 5.

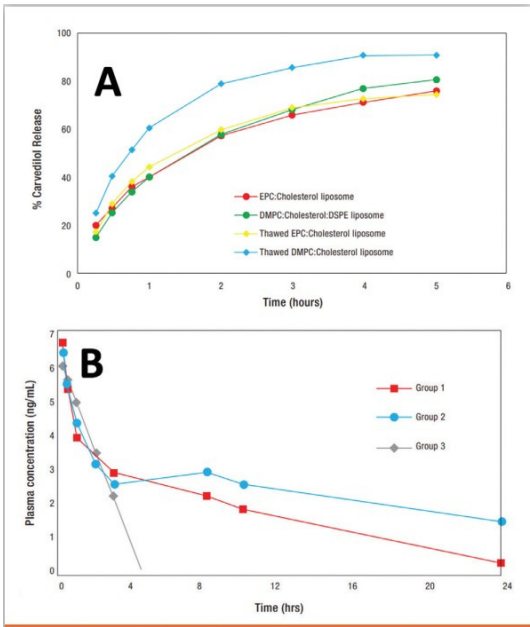


Figure 5. In vitro dissolution of carvedilol in liposome formulations (A) and PK profile of drug encapsulated in DMPC/Chol/DSPE (liposomes 1) and egg PC/Chol (liposomes 2) and aq. solution

In vitro dissolution data shows that the drug is released over several hours from the liposomes prepared with egg PC/cholesterol or DMPC/ cholesterol/DSPC. The PK data suggests that liposome entrapped carvedilol shows an extended release over 24 hours as compared to non-liposomal formulation.

There are other examples of LAIs utilizing the PLGA for sustained release of several drugs. Ascendia's enabling solubilization technologies can overcome the challenges by designing the smarter formulations for extended-release over several weeks or months (data not shown).

Table 7. Ascendia's capabilities in sterile and non-sterile cGMP manufacturing

Capability	Sterile Dosage Form			Non-Sterile Dosage Form	
	Pilot sterile	S-1 sterile	S2-large sterile	Early Phase 1/II	2-Commercial
Capacity	5 suites with freeze dryer (Pre-fill syringe/Vial)	4 suites (Pre-fill syringe/Vial)	5 suites (Vial)	5 suites	8 suites
ISO Classification	100/10,000	10/10,000	100/10,000	100,000	100,000
Output	5,000 units per batch	24,000 units per batch	150,000 units per batch	100,000 units per batch	> 100, 000 units per batch
Processing area	100 sq. ft	1,500 sq. ft.	10,000 sq. ft.	4,000 sq. ft.	15,000 sq. ft.

Designing the LAIs for sustained release over an extended period requires a careful selection of appropriate lipids, solvents and/or polymers. Wilkinson et al. (2022) describes a range of ingredients suited for such application with cautions because of toxicity/safety concerns, compatibilities and stability issues.[30] For example, super refined oils can minimize the oxidation and hydrolysis of drugs in LAI formulations.[31] Thus, longer stability in fatty acids and oil phase of drugs sometimes could be problematic if it is designed over several weeks or months for delivery. Ascendia's capabilities in long-term stability ICH chambers offer clients confidence in the development of LAIs formulations for different modalities. Table 7 shows the company's sterile for parenteral and non-sterile for oral capabilities.

Conclusion

As new molecules continue to come out from discovery, the lack of resources persists within the industry to tackle the different modalities, especially those requiring special techniques and handling capabilities. CDMOs like Ascendia will play an important role in formulation development and manufacturing of drug products for bringing them faster to clinics and market.

The formulation and analytical expertise and cGMP manufacturing sterile, aseptic pre-fill syringes and lyophilization capabilities would be most acceptable criteria in minds of partners when developing the LAI drugs to reduce time and save cost. Ascendia's internal capabilities in LAIs having with technical expertise in R&D and cGMP manufacturing will invite the companies to build stronger partnership for launching the new life-saving medicines.

References

1. L. Rahnfeld and P. Luciani, Injectable Lipid-Based Depot Formulations: Where Do We Stand?, Pharmaceutics, 2020, 12, 0567; 1b. A. N. Kurnool and P. Tavari, Long acting injectables, J. Pharm. Sci., 2019, 11, 2857-2861.
2. T. Kirby, T., 2022. Long-acting injectable for HIV approved for use in the UK. Lancet Infect. Dis. 22, 26.
3. S. Kalepu, and V. Nekkanti, Insoluble drug delivery strategies: Review of recent advances and business prospects. Acta Pharm. Sin. B 2015, 5, 442–453.
4. Y. Shi, A. Lu, X. Wang, Z. Belhadj, J. Wang, and Q. Zhang, A review of existing strategies for designing long-acting parenteral formulations: Focus on underlying mechanisms and future perspectives, Acta Pharma. Sinica B., 2021, 11, 2396-2415.
5. https://en.wikipedia.org/wiki/Subcutaneous_administration
6. V. Kasina, R. J. Mownn, R. Bahal and G. C., Sartor, Nanoparticle delivery systems for substance use disorder, Neuropsychopharmacology, 2022, 47, 1431-1439.
7. A. C. Anselmo and S. Mitragotri, Nanoparticles in the clinic, AChI Bioeng. Trans. Med., 2016, 1, 10-29. (doi: 10.1002/btm2.10003)
8. F. Selmin, U. M. Musazzi, G. Magri, P. Rocco, F. Cilurzo and P. Minghetti, Drug Discovery Today, 2020, 25, 321-329.
9. A. Gonella, S. Grizot, F. Liu, A. L. Noriega and J. Richard, Long-acting injectable formulation challenges and opportunities for the delivery of fragile molecules, Expert Opinion on Drug Delivery, 2022, 19, 927-944.
10. C. Li and S. Wallace, Polymer-drug conjugates: Recent development in clinical oncology. Adv. Drug Deliv. Rev. 2008, 60, 886–898.
11. J. Huang and S. Ali, Lipid nanoparticles: Enablers for efficient delivery of drug molecules, J. Anal. Pharm. Res., 2022, 11, 126-129.
12. M. A. Boushehri, D. Dietrich and A. Lamprecht, Nanotechnology as a platform for the development of injectable parenteral formulations: A comprehensive review of the know-hows and state of the art, Pharmaceutics, 2020, 12, 510
13. J. Huang, Formulation Forum- rational design & development of long-acting injectable dosage forms, Drug Development & Delivery, March 2020. Y. W. Chien, Long-acting parenteral formulations, J. Parenteral Sci. Tech., 1981, 108.
14. D. Guo, Injectable nanomedicines- New developments in long-acting injectable nano-formulations, Drug Dev. Deliv., May 2018.
15. J. C. Sunshine and J. J. Green, Nanoengineering approaches to the design of artificial antigen-presenting cells, Nanomedicine 2013, 8, 1173–1189.
16. J. W. Hickey, F. P. Vicente, G. P. Howard, H-Q. Mao, and J. P. Schneck, Biologically inspired design of nanoparticle artifi cial antigen-presenting cells for immunomodulation. Nano Lett. 2017, 17, 7045–7054.
17. M. A. Dobrovolskaia and S. E. McNeil, Immunological properties of engineered nanomaterials. Nat. Nanotech., 2007, 2, 469–478.

18. A. C. Anselmo, B. Prabhakarpandian, K. Pant and S. Mitragotri, Transl. Mater. Res., 2017, 4, 0414001 (doi:10.1088/2053-1613/aa5468)
19. S. Deodhar, B. Sillman, A. N. Bade, S. N. Avedissian, A. T. Podan3, J. M. McMillan, N. Gautam, B. Hanson, B. L. D. Shetty, A. Szlachetka, M. Johnston, M. Thurman, D. J. Munt, A. K. Dash, M. Markovic, A. Dahan, Y. Alnouti, A. Yazdi, B. D. Kevadiya, S. N. Byrareddy, S. M. Cohen, B. Edagwa, and H. E. Gendelman, Transformation of dolutegravir into an ultra-long acting parenteral prodrug formulation, Nature Communication, 2022, 13, 3226.
20. (i) M. Zolezzi, R. Abouelhassan, Y. Eltorki, P. M. Haddad and M. Noorizadeh, Long-acting injectable anti-psychotics: A systemic review of their non-systemic adverse eff ect profi le, Neuropsychiatric Disease & Treatment, 2021, 17, 1917-1926. (ii) https://psychopharmacologyinstitute.com/publication/long-acting-injectable-antipsychotics-a[1]practical-guide-for-prescribers-2201)
21. K. Chaudhary, M. M. Patel, and P. J Mehta, Long-Acting Injectables: Current Perspectives and Future Promise, Crit Rev Ther. Drug Carrier Syst., 2019, 36, 137-181.
22. A. Li, F. Yang, J. Xin, and X. Bai, An efficient and long-acting local anesthetic: Ropivacaine[1]loaded lipid-polymer hybrid nanoparticles for the control of pain. Int. J. Nanomed. 2019, 14, 913–920.
23. R. Holm, Long-acting injectable suspensions, Am. Pharm. Rev., 2022, June 1.
24. J. F. Remenar, making the leap from daily oral to long-acting injectables: lessons from the antipsychotics, Mol. Pharm., 2014, 11, 1739-1749.
25. R. W. Kalicharan, P. Schot, H. Vromans, Fundamental understanding of drug absorption from parenteral oil depot, Eur. J. Pharm. Sci., 2016, 83, 19-27.
26. L. C. Blumberg, T. A. Zeidan, A. Maddaford, N. C. Warren and P. Hutchison, Novel N-5-(acyloxyalkoxy) carbonyl prodrugs of olanzapine with physicochemical properties for extended-release. RSC Adv. 2013, 3, 16270–16278.
27. S. Weng-Larsen, and C. Larsen, Critical factors influencing the in vivo performance of long-acting lipophilic solutions–impact on in vitro release method design. AAPS J. 2009, 11, 762–770.
28. M. R. Toh, and G. N. C. Chiu, Liposomes as sterile preparations and limitations of sterilization techniques in liposomal manufacturing. Asian J. Pharm. Sci. 2013, 8, 88–95.
29. M. G. Kang, Sterile preparation formulation, Chapter 4, 51-66.
30. J. Wilkinson, D. Ajulo, V. Tamburrini, G. Le Gall, K. Kimpe, R. Holm, P. Belton, and S. Qi, Lipid based intramuscular long-acting injectables: Current state of the art, Eur. J. Pharm. Sci., 2022, 178, 106253 1-20. https://doi.org/10.1016/j.ejps.2022.106253.
31. A. Motulsky, M. Lafleur, A-C. Couffin-Hoarau, D. Hoarau, F. Boury, J-P. Benoit, J-C. Leroux, Characterization, and biocompatibility of organogels based on L-alanine for parenteral drug delivery implants. Biomaterials, 2005, 26, 6242–6253.

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