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Clinically established biodegradable long acting injectables: An industry perspective

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ABSTRACT

Long acting injectable formulations have been developed to sustain the action of drugs in the body over desired periods of time. These delivery platforms have been utilized for both systemic and local drug delivery applications. This review gives an overview of long acting injectable systems that are currently in clinical use. These products are categorized in three different groups: biodegradable polymeric systems, including microparticles and implants; micro and nanocrystal suspensions and oil-based formulations. Furthermore, the applications of these drug delivery platforms for the management of various chronic diseases are summarized. Finally, this review addresses industrial challenges regarding the development of long acting injectable formulations.

Contents

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1. Introduction

Parenteral drug delivery systems have been developed for the treatment of numerous diseases via different administration routes including intravenous (IV), subcutaneous (SC), intramuscular (IM), epidural and intra-articular injection, as well as surgical insertion of depots in the organ or tissue of interest [1–3]. For bioavailability of drug molecules, parenteral delivery can provide specific advantages as compared to the oral route of administration; due to the avoidance of the drug absorption step, as well as the gastrointestinal enzyme degradation and liver first pass effect. Despite these advantages of parenteral drug delivery, most drugs have to be frequently administrated in chronic diseases; especially for drug molecules susceptible to rapid in vivo clearance, repeated injections are required to maintain therapeutic levels throughout the treatment duration [4]. Such a high dosing frequency markedly affects patient compliance, which further worsens in chronic conditions like mental and hormone-dependent disorders, where medication is needed for several months to years.

The above limitations have encouraged the development of controlled release strategies that allow extending systemic drug exposure over prolonged periods of time following parenteral administration of a single dose [5,6]. Over the past few years, the target for long acting injectable (LAI) formulations has been expanded from systemic to local drug delivery [7–9]. In this regard, the LAI formulations are directly injected in the proximity of the diseased tissue, aiming for high drug exposure over a desired period in the target tissues and low systemic drug distribution.

Up to now, several LAI technology platforms have found their way into the market. These include polymeric particulate systems (i.e., microparticles and nanoparticles), implants, in situ forming depots, suspensions of drug crystals, oil-based formulations of lipophilic (pro) drugs and liposomes [9–11]. We here give an overview of clinically relevant LAI strategies, by grouping the above-mentioned technology platforms into three categories namely: (i) microencapsulation, (ii) implantation and in situ forming depots (gels/implants) and (iii) molecular (i.e., prodrugs) and particulate (i.e., micro/nanocrystals) drug modification. We next describe formulation characteristics and therapeutic strategies of marketed biodegradable LAI products. Finally, challenges and perspectives regarding the development of LAI drug delivery systems are discussed. Due to their limited extended release capacities, liposomal or polymeric nanoparticles are excluded from this review. Since most of the LAI formulations are protected by patent right and there is limited data available regarding their physicochemical characterizations (e.g., particle size distribution, implant size, detailed information about polymer type etc.), only publicly available data are reported in this review.

2. Overview of strategies for development of long acting injectables

Despite some technological challenges in the industrial development of injectable drug products, which will be highlighted in this review, multiple sustained release platforms have been successfully marketed. This section provides an overview of different strategies that have led to the development of clinically used LAI drug products.

2.1. Microencapsulation

The term “microencapsulation” refers to engineering of particles with sizes between 1 and 1000 μm, where solid or liquid drug substances are entrapped either as a dispersed and/or dissolved in a polymer matrix (microspheres), or as a core surrounded by a polymeric shell (microcapsules) [12]. The polymers used for microencapsulation include both (semi)naturally occurring (e.g., alginate, collagen, chitosan) or synthetic materials (based on e.g., copolymers of lactic and glycolic acid (PLGA) [13]. These biomaterials have been employed to protect the encapsulated drug substance from degradation and minimize its toxicity towards the surrounding tissue, as well as tailoring the release and the therapeutic action of the loaded drug molecules over prolonged periods (from days to months).

According to a PharmaCircle® search, conducted on the 1st of April 2020, the majority of marketed LAI formulations are composed of polymeric materials among which PLGA is the most frequently used one,

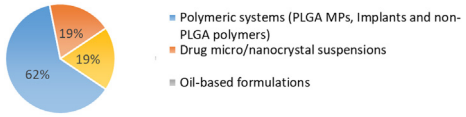

Fig. 1. Marketed drug products and their percentage arising from different parenteral long acting platforms based on the Pharmacircle® database (date of search: April 1st, 2020). The present review deals with only brand-name formulations not generic medicines [14].

accounting for 46% (22 drug products) of all marketed products (Fig. 1) [14]. PLGA is an aliphatic random *co*-polyester of lactic acid and glycolic acid, with different molecular weights, different ratios of glycolic to lactic acid, and different end caps (acid or ester terminated), which translates into different degradation kinetics [15–19]. PLGA has been formulated into microparticles (MPs) for delivery of different types of cargos with tailorable extended drug release profiles [20–22].

The formulation techniques used in microencapsulation processes include coacervation or phase separation, spray drying and solvent evaporation/extraction. [23]. Among these techniques, solvent evaporation/extraction is the most commonly used method for microspheres preparation [16,17]. Depending on the aqueous solubility of the drug candidate, the solvent evaporation/extraction process involves variable emulsification approaches, e.g. single emulsion (oil-in-water (O/W)) and double emulsion methods (water-in-oil-in-water (W/O/W) or solid-in-oil-in-water (S/O/W)) [4,24–26]. Fig. 2 demonstrates the emulsion solvent evaporation technique for PLGA microparticles manufacturing. Depending on the method of manufacturing, both hydrophilic and lipophilic drugs can be loaded into PLGA MPs [26]. In general, O/W is used for loading water insoluble drugs into PLGA MPs. A double emulsion method (W/O/W), which needs to first emulsify drug aqueous solution in the organic PLGA phase, followed by a second emulsification step of the primary emulsion (i.e., W/O emulsion) in a second aqueous phase is used to load water soluble drugs. Several reviews have discussed the strategies and challenges associated with microencapsulation of small drug molecules [12,25–27], as well as peptides and proteins for extended release purposes [5,28–32].

Although successfully employed for LAI product development, microencapsulation techniques are still facing multiple challenges such as controlling particle size and size distribution, tailoring drug release, and ensuring stability of fragile biotherapeutics (e.g., pharmaceutical proteins and peptides, nucleic acid based drugs) [5,33]. MPs are formulated into a size range of 10–250 μm (or ideally 10–125 μm) to allow injection through conventional needles, reducing macrophage phagocytosis and local tissue inflammation [12,34,35]. Although, small MPs (i.e., 2 μm) are shown to be efficient for delivery of antibiotics into alveolar macrophages for the treatment of tuberculosis [36]. Small particles size can be easily injected through a thin needle [37]. Furthermore, since a few big particles can clog the needle a narrow particle size distribution offers the possibility to use thinner needles, thereby reducing pain during administration. Traditional manufacturing techniques normally produce MPs with a relatively broad size distribution, leading to poor injectability. Novel technologies such as membrane emulsification and/or microfluidics have been extensively investigated for production of mono-sized MPs for better injectability through smaller needles [13,38]. It has been further demonstrated that size is an important factor that determines the release kinetics of loaded drugs [39,40]. A limited drug loading capacity of MP formulations (typically ~25% w/w) represents another challenge, especially for actives, which have a relatively low potency and thus require high dosing. This has a direct impact on clinical applicability due to the requirement for the concentration of the MPs suspension (normally ~40% w/v, as higher concentrations result in higher viscosity and thus poor injectability), as well as the injection volume (e.g., limited to approx. 2 mL for IM and 0.1 mL for intravitreal injections) which may affect the nominal dose.

Drug release from PLGA MPs can be tuned from a couple of days to months. Tailoring drug release can be done by manipulating PLGA molecular weight, the ratio of glycolic acid to lactic acid, the end terminus of polymer (e.g., acid or ester terminated) [41], MPs size and surface porosity [42], drug loading (ratio of drug to polymer), and adding other excipients [43,44]. In general, the drug can be loaded into PLGA MPs as molecularly dissolved or solid dispersion. In case of molecularly dissolved systems, the drug is released mainly by diffusion through the polymer matrix but for solid dispersed drugs, release is mainly governed by swelling, degradation and porosity of the polymeric matrix material. Most often, the combination of diffusion and polymer degradation is responsible for release of the drug. In general, PLGA based MPs and implants demonstrate a tri-phasic drug release pattern,

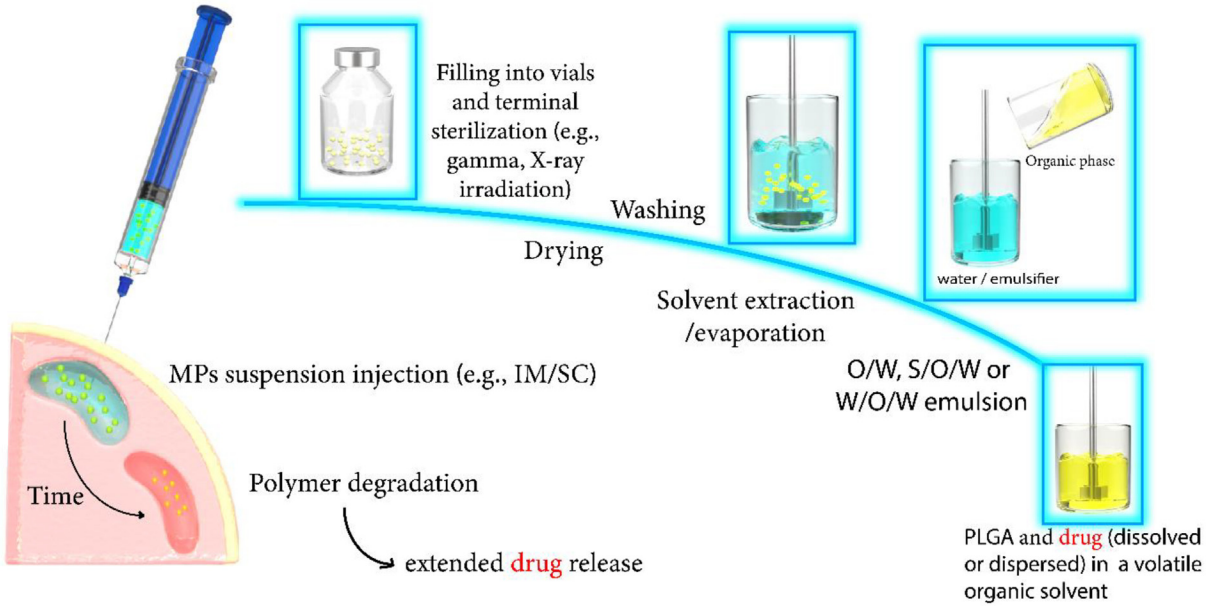

Fig. 2. Schematic image of emulsion solvent evaporation technique for PLGA microparticles manufacturing. Upon administration, PLGA microparticles releases the drug for a prolonged time. The combination of diffusion and polymer degradation is responsible for release of the drug.

characterized by a burst, sustained release, and a second burst release. The mechanisms of drug release from PLGA-based MPs are comprehensively reviewed by Fredenberg et al. [45].

Microencapsulation technologies have been successfully applied to small molecules drugs but formulating macromolecular therapeutics into PLGA MPs remains challenging. Proteins structure is highly dependent on the environment and structural changes can affect their biological activity. Denaturation of proteins can occur due to the method of manufacturing and to incompatibility with PLGA. For example, proteins may undergo denaturation and aggregation at the interface of oil and water during encapsulation into PLGA MPs using double emulsion solvent evaporation method (W/O/W), and/or due to high shear stresses used for emulsification [33,46]. Regarding incompatibility with PLGA, it is worth mentioning that the acidic pH formed inside of MPs during bulk erosion may damage acid sensitive proteins [47,48]. Another drawback of PLGA for protein and peptide delivery is acylation of protein nucleophilic groups (e.g., N-terminal amino group, mercapto- side chain of cysteine and primary amine side chain of lysine) with lactic and glycolic acid units [49–51]. No protein drug based on PLGA MPs is currently marketed. The only protein based PLGA formulation that entered the pharmaceutical market was Nutropin Depot® (Genentech Inc.), but its clinical use was discontinued due to manufacturing difficulties [10].

In spite of the above challenges, microencapsulation remains to be a promising strategy for preparing LAI formulations [52]. There are many small molecules and peptides based PLGA MPs presently used in the clinic [11,53]. These formulations are briefly described in Section 3 of this review.

2.2. Preformed and in situ forming implants

Similar to MPs, implants are polymer-based LAI systems that have successfully entered the pharmaceutical market. There are two main types of implants, i.e., preformed (or classical) implants (e.g., Zoladex®) and in situ forming implants/depots (e.g., Sustol®). The classical implants are cylindrical solid rods with 10–35 mm length and 1–3 mm diameter, prepared by melt extrusion either from biodegradable or non-biodegradable polymers for subcutaneous administration [30,54]. Depending on their size, solid implants are administered either via surgical insertion or SC injection using a large needle (e.g., 16-gauge needle, with outer and inner diameter of 1.65 and 0.065 mm, respectively) [55]. For non-biodegradable implants, surgical operation is typically required to remove the delivery system at the end of the treatment. This highlights the advantage of biodegradable implants, which gradually degrade into metabolizable monomers (e.g., PLGA degrades into lactic and glycolic acid) during the release process. Apart from the need for surgical removal, another problem associated with preformed implants is the painful and sometimes traumatizing influence that patients experience due to the injections. As such, some of the advantages of classical implant technology (e.g., simplicity, low cost, no size/dose restriction) are compromised [55,56].

The limitations of MPs and preformed implants have inspired scientists to develop in situ forming implants/gels, which represent a relatively cheap, rapid and easy-to-use parenteral controlled release technology. In situ forming implants (ISFI) are biodegradable polymer-based liquid or syringeable semisolid formulations that undergo spontaneous solidification/gelation at the site of injection [57]. Depending on the formulation composition, ISFI can form through precipitation (due to phase separation/solvent extraction or sol-to-gel transformation induced by physiological temperature/pH), organo-gelling (due to the thermo-sensitivity of hot melts or self-assembly of lyotropic liquid crystals in aqueous medium) or cross-linking of monomer/polymer chains (in response to photo-irradiation or the presence of ions or enzymes) [58]. Among these ISFI formation mechanisms, in situ precipitation induced by solvent extraction/phase separation (SE/PS) represents the most investigated approach which has brought products to the market [59].

The SE/PS implants are composed of a biodegradable water-insoluble polymer (e.g. PLGA) dissolved in a water miscible organic solvent (e.g., *N*-methyl-*2*-pyrrolidone or dimethyl sulfoxide), and the drug dissolved or dispersed as microcrystals in the polymer solution. Upon SC injection, the organic solvent is extracted from the organic sol, leading to polymer precipitation and formation of a solid depot in which the drug is trapped. The encapsulated drug is then gradually released through diffusion and polymer degradation [60]. As demonstrated in Fig. 3, the use of simple and fast solid-liquid dissolution/dispersion steps for manufacturing as well as conventional needles for injection, with no need for surgery, make ISFI an attractive parenteral LAI technology. It is worth mentioning that the used organic solvents such as *N*-methyl-*2*-pyrrolidone (NMP) are associated with certain levels of local or systemic toxicity depending on the route of administration. According to USP, the maximum daily exposure for NMP in pharmaceutical product is 5.3 mg/day [61]. Such toxicity related issues may limit the development of NMP-based in situ forming gels for other applications. Dimethyl sulfoxide (DMSO) is class 3 organic solvent and its maximum daily dose is 50 mg/day, which makes it attractive for development of in situ forming gels. However, when higher amounts of organic solvents (beyond the daily tolerated limits) are needed in a formulation, further toxicological studies are required to ensure product safety.

2.3. Molecular and particulate drug modification

2.3.1. Molecular drug modification (prodrugs)

The possibility for modification of drug substances at molecular and particulate levels has launched several LAI technologies. One approach used for molecular modifications is covalent attachment of a drug to a fatty acid chain. Prodrug formation using decanoate, enanthate or caproate has already been established for oil-based LAI formulations. In this context, fatty acids form an ester bond with the prodrug. In most cases, esterification of a parent drug with a fatty acid chain not only increases its solubility in the oil formulation but also enhances its partitioning in fatty tissues in the body, which leads to a sustained release kinetics [62]. Therefore, drug release can be controlled by both cleavage of a traceless linker, mostly through hydrolysis of ester bond, and slow drug release from fatty tissues into the circulation. Oil-based parenteral formulations can be used for systemic drug delivery (e.g., IM or SC) or localized drug delivery (e.g. intra-articular delivery). Simple and cost-effective manufacturing process is a unique feature of oil-based depot formulations [63]. Terminal sterilization is often performed using filtration as they can be easily filtered through 0.2 μm sterile filters [64]. Fig. 4 is a schematic representation of oil-based formulations and their simple manufacturing steps.

Oil depot formulations are generally consisted of esterified drug, oil vehicle and benzyl alcohol. The oil vehicle is mainly composed of a vegetable oil like sesame oil, castor oil, arachis oil, or fractionated coconut oil. Viscosity is a key parameter in selection of oil vehicle as high viscose oils are not syringeable and therefor hard to be administered parenterally. On the other hand, low viscosity formulations generally speaking release the drug rapidly [65]. Benzyl alcohol as co-solvent increases not only oil solubility of the prodrug but also reduces oil viscosity, which facilitates prodrug release from depots [66,67].

As shown in Table 5 the octanol-water partitioning coefficient (log P) values of marketed oil-based prodrug formulations are >3.8, suggesting that lipophilicity is a key factor in slowing down drug release from oil depots which can be obtained by increasing the length of fatty acid chains extends [68]. Some of the important parameters for controlling drug release from oil-based depots includes concentration of drug in the oil, the surface area of the oil depot, the partition coefficient between oil depot and tissue fluid etc. After releasing prodrug from the oil depot prodrug with low water solubility shows low tissues absorption and lymphatic transport, whereas more water soluble prodrugs may diffuse directly to central blood circulation where they can be hydrolysed by enzymatic and/or chemical routes into parent drugs [69].

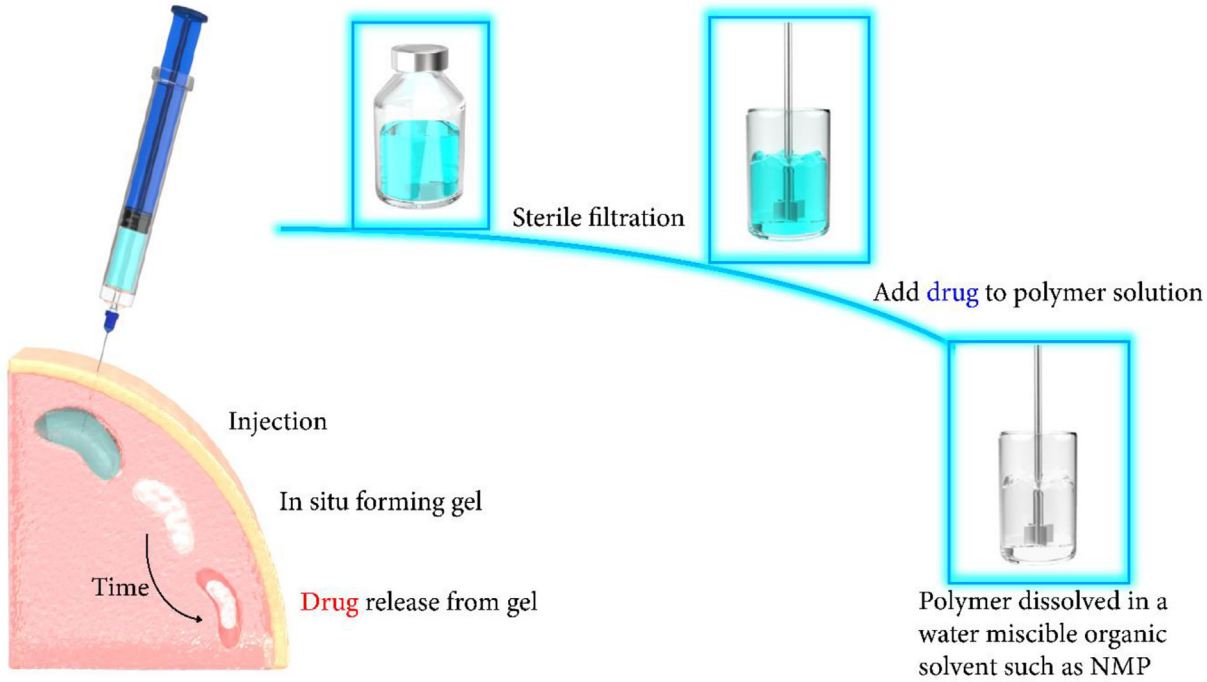

Fig. 3. Schematic image of in situ forming gel manufacturing using PLGA polymer and *N*-methyl-*2*-pyrrolidone (NMP). Upon administration, solvent extraction/phase separation results in in situ gelation of the polymer which releases the drug for a prolonged time.

It is known that conversion of prodrug happens via carboxylesterases, which are mainly present in the blood therefore the prodrug remains mainly intact in the site of injection with less carboxylesterases [70]. Of special note, the rate of bioconversion of prodrug with a long chain fatty acid to the parent drug is modulated by the chemistry of the ester linkage. Slowly hydrolysing esters as compared to more rapidly hydrolysing esters provide time for redistribution of prodrug and minimize burst release which may results in toxic peak concentration [71,72]. Oil-based depot formulations are barely employed in recent clinical trials (only one in phase III, i.e. Fulvestrant + Everolimus + Anastrozole Co-Therapy based on an oil formulation; developed by AstraZeneca and Novartis AG). The limited number of ongoing clinical trials in this area might be due to the difficultly of tuning drug release kinetics. Another promising drug derivatization strategy includes the conjugation of drug molecules to a polymer carrier using a linker that slowly breaks in vivo to release unmodified drug. An illustrative example of this technology is TransCon™ hGH, an investigational long-acting prodrug of human growth hormone (hGH or somatropin) under development by Ascendis Pharma A/S. TransCon hGH is a prodrug composed of somatropin transiently conjugated to a methoxy polyethylene glycol

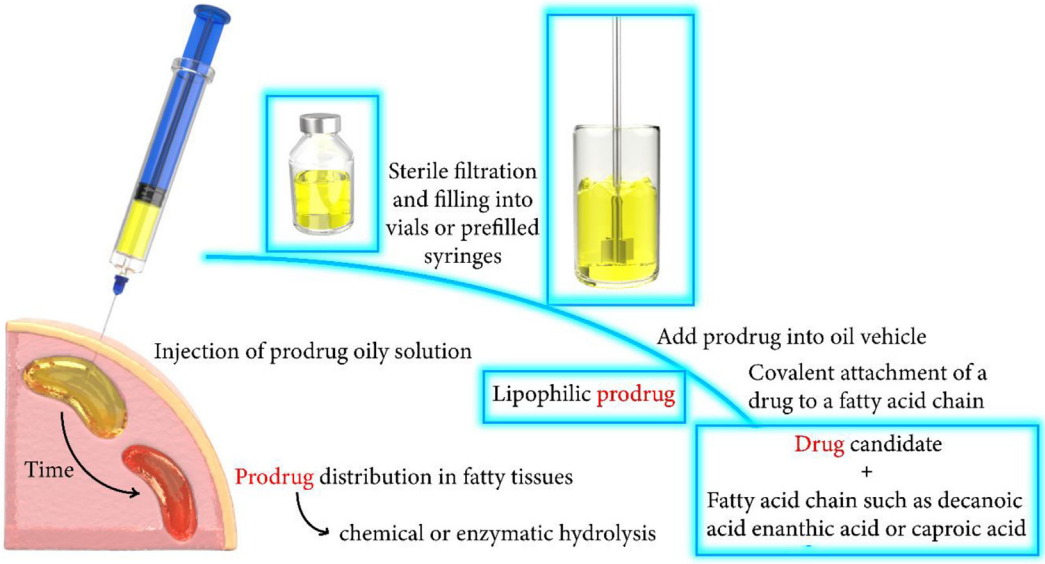

Fig. 4. Schematic image of oil-based formulation and simple manufacturing steps. Upon administration, the prodrugs can be hydrolysis by enzymatic and/or chemical routes into parent drugs in a prolonged time.

(40 kDa) through a proprietary TransCon linker. In this formulation system, the polymer carrier prolongs plasma circulation of hGH by preventing its interactions with hGH receptors in tissues and hampering its renal clearance; while the TransCon linker ensures sustained release of active hGH through slow autohydrolysis occurring under normal physiological conditions [73]. Data from phase 2 clinical trials demonstrated that weekly administrations of TransCon hGH to children with hGH deficiency exhibited hGH and insulin-like growth factor-1 levels similar to those of daily somatropin injections marketed as Genotropin (Pfizer) [74]. Based on clinical safety and efficacy data, the U.S. Food and Drug Administration (FDA) has recently accepted the biologics license application of Ascendis Pharma for TransCon™ hGH against pediatric hGH deficiency; but this therapy has not yet been approved for clinical use [75]. Although prodrug strategies clearly hold some promise for clinical development of long acting injectables, it is important to note that this approach is not applicable to all drug molecules, especially in case of lack of functional groups to be modified. For example, some drugs such as aripiprazole, olanzapine and risperidone do not possess hydroxyl group for esterification.

2.3.2. Particulate drug modification (micro/nano drug crystals)

Physical modification of drug substances into particulate systems such as nano- or microcrystals is a formulation strategy to develop long acting injectables (Fig. 5). This strategy is applicable for drugs with a very low aqueous solubility and their release from crystals is mainly controlled by dissolution kinetics in the local tissue fluid and surface area of drug crystals [76]. The manufacturing of nano and microcrystals can be achieved using three approaches, namely the "bottom-up" technique (e.g., crystallization of a drug from an oversaturated organic solution), the "top-down" approach (e.g., micronization of drug crystals by milling or high-pressure homogenization), and a combination of both techniques. In the bottom-up method, drugs are first dissolved in a good solvent, and the involved critical steps (i.e., nucleation and crystal growth) are influenced by many factors (temperature, stirring and evaporation rate, addition of non-solvents, geometry of the reactor etc.), resulting in poor control of particle size and size distribution. Therefore, these methods are mainly used in the food industry or as a pre-treatment of drugs for later top-down manufacturing. The top-down technology has been successfully implemented for the preparation of nano- or micro-suspensions [77]. For example, wet media milling is a standard and established technology for nanosuspension preparation [76].

Drug crystal-based formulations are aqueous suspensions composed of poorly water-soluble drug/prodrugs in the size range of micro- or nanoparticles, and minimal amounts of one or several stabilizing ingredients (e.g., polysorbates, povidones etc.). These formulations are marketed in the form of either a lyophilized powder (e.g., Zyprexa Relprevv®), which is reconstituted by diluent prior to injection, or in the form of aqueous suspension (e.g. Invega Trinza®). Ready to use aqueous suspensions are preferred, but due to their limited stability, they cannot be applied for all drugs and drug candidates. An unwanted phenomenon that can occur in aqueous crystal suspensions is the so-called Ostwald ripening, in which small drug crystals dissolve and redeposit on the surface of larger drug crystals [78,79]. Since reduction of the number of small crystals and increase of overall particle size reduces the specific surface area of the drug crystal suspension, Ostwald ripening can slow down drug release kinetics. This phenomenon is driven by drug solubility in the formulation, drug crystal polydispersity level and time. Ostwald ripening can be accelerated by temperature fluctuations in the drug product during e.g., autoclaving or storage. High temperature increases the solubility of drug crystals in the suspension especially smaller crystals dissolve and after autoclaving recrystallize on the surface of larger particles. Since temperature cycling during autoclaving is highly standardized, drug crystal growth should be very reproducible using this autoclaving sterilization method. Moreover, care has to be taken to avoid so-called caking of the suspension, which is drug crystal sedimentation and agglomeration at the bottom of vials. This phenomenon can happen in the bulk suspension during manufacturing or in the vial during autoclaving or storage. Caking makes dosing accuracy, resuspendability and injectability challenging. Temperature increase during autoclaving not only temporarily increases drug solubility, but also reduces formulation viscosity. Low viscosity accelerates drug crystal sedimentation in the vial and increases the risk of aggregation of sedimented drug crystals in the cooling phase. Both Ostwald ripening and caking can be minimized by optimization of the formulation composition to reduce drug solubility, e.g., by reducing co-solvent or surfactant levels, addition of viscosity enhancers, narrow particle size distribution and control of storage conditions of the drug product. The optimal balance between those critical

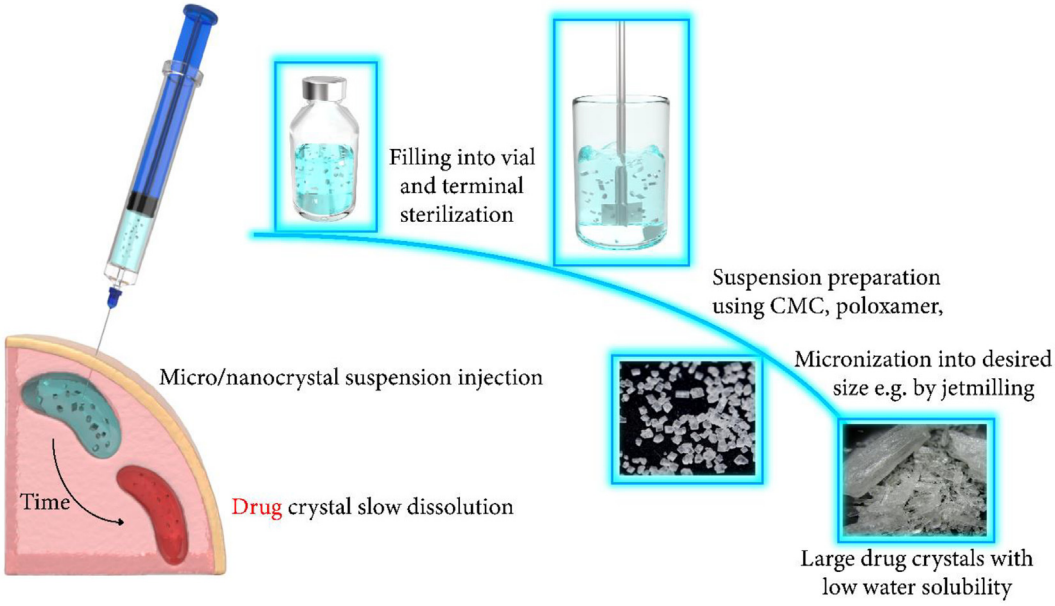

Fig. 5. Schematic image of micro/nano crystal suspension manufacturing. Drug release from crystals is mainly controlled by dissolution kinetics in the local tissue fluid and surface area of drug crystals.

variables is important to enable easy resuspendability and injectability of the drug suspension through reasonably thin needles, e.g. 18–23 gauge [76].

There are factors that slow down release or dissolution kinetics/extend drug release from micronized suspensions, e.g., by increasing lipophilicity of drug (using insoluble salt, chemical modification or co-crystal formation), change of particle size (nano to microparticles) and suspension concentration [76]. Good examples of the application of chemical modification and co-crystal technology for extending drug release based on retarding the kinetics of dissolution are Kenalog® and Bicillin L-A®. Kenalog® is a microcrystal formulation of poorly water-soluble triamcinolone acetonide. It is a chemical derivative of triamcinolone by which two of its hydroxy groups are bound together with one molecular equivalent of acetone as a so-called ketal. This covalent modification renders the molecule more lipophilic and less water-soluble than triamcinolone (0.043 vs 0.847 mg/mL). It has been shown that the micronized suspension of triamcinolone acetonide exhibited extended duration of pharmacological action in the body owing to the drug's low aqueous solubility [80–83]. Bicillin L-A® is an aqueous drug co-crystal suspension of penicillin G with benzathine (Bicillin L-A®) and it is monthly injected via the IM route for the treatment of syphilis and protection from group A streptococcal infections [84,85].

Increasing suspension concentration and drug dose are other ways to extend the duration of drug release. Invega Sustenna® is a nanosuspension of paliperidone palmitate with a skipconcentration of 156 mg/mL that releases the active agent over one month in the body upon IM injection. Invega Trinza® is another drug product based on nanosuspension of paliperidone palmitate with a suspension concentration of 312 mg/mL that releases the drug over 3 months upon IM injection [86]. By increasing suspension concentrations and administration of higher doses, likely the compartment which is surrounding the crystal suspension becomes saturated and drug release from nanoparticles is further extended. It has been shown that when a paliperidone palmitate nanosuspension is administered at doses that were 3.5-fold higher than the corresponding dose for one-month release, the obtained plasma concentrations were similar to the values observed for the one-month release formulation but now lasted up to three months instead of one month. Nanosuspensions of hydrophobic drugs for parenteral delivery offer the advantage of high drug loading (high suspension concentration) which can be injected using small needle size (e.g., 22 or 23G) [87], thus extending drug release due to higher local concentration and minimizing the risk of tissues damage due to smaller needles size.

3. Clinically established long acting parenteral formulations

Based on the different formulation strategies presented in the previous sections, several LAI parenteral formulations have been brought to the clinic, benefiting patients with chronic diseases. We here categorize these products in three groups, namely biodegradable polymeric systems (particularly, MPs and implants, oil-based formulations and drug crystal (nano and micro) suspensions.

3.1. Long acting biodegradable polymeric systems for parenteral use

In the following section, LAI platforms based on biodegradable polymers are categorized into PLGA-based and non-PLGA based systems. As shown in Fig. 1, 46% of the presently marketed LAI products are based on PLGA. Other polymers that are used in FDA approved LAI drug delivery systems include sodium hyaluronate, poly[1,3-bis(carboxyphenoxy) propane-*co*-sebacic-acid] (PCPP-SA), triethylene glycol poly(orthoester) and a complex of anionic sodium carmellose (carboxymethyl cellulose) with cationic abarelix acetate.

3.1.1. PLGA-based long acting biodegradable systems

The marketed products composed of PLGA-based MPs and implants are summarized in Tables 1 and 2 and discussed in detail below.

3.1.1.1. Marketed long acting injectables based on PLGA microparticles

3.1.1.1.1. Arestin®. Arestin® is a ready-to-use single-dose cartridge containing minocycline-loaded PLGA microspheres and available as a dry powder formulation. Arestin® is used as a supplementary component of scaling and root planning procedures for the management of periodontitis. A single subgingival injection of Arestin® MPs into periodontal pocket provides local sustained release of minocycline over 2 weeks [90]. In a study published by Persson et al. [91] the anti-bacterial effects of Arestin® in a patient with peri-implantitis was assessed over 12 months. Arestin® demonstrated significant decrease in bacterial load up to 180 days for most of the investigated pathogens, including *Tannerella forsythia*, *Porphyromonas gingivalis*, and *Treponema denticola*. The most sensitive pathogen to this therapy was *Actinobacillus actinomycetemcomitans* [91]. The antimicrobial efficacy of Arestin® has been also reported elsewhere [88,89].

3.1.1.1.2. Bydureon®. Bydureon® is a PLGA-based MPs formulation containing 5% (w/w) exenatide, a glucagon-like peptide-1 (GLP-1) agonist that is used for type II diabetes. Several studies have demonstrated that Bydureon® has much better hypoglycemic activity and fewer adverse effects than twice-daily SC injection of the free drug 5–10 μg in solution [92,93]. Bydureon® can also be used as combination therapy along with established oral antidiabetic drugs, such as metformin and/or sulfonylurea [94,95]. Nevertheless, a single dose of Bydureon administration exhibits an exenatide release over approximately 10 weeks. An initial release of exenatide can be observed possibly as a result of surface-bound exenatide on MP surface, followed by a gradual release of exenatide from the MP matrix due to the hydration and erosion of PLGA. The gradual release phase shows two subsequent peaks of exenatide in plasma at approximately week 2, and week 6 to 7, respectively [96]. Plasma concentration of exenatide is gradually increased and maintained stable after 6 to 7 weeks at around 300 pg/ml over weekly dosing intervals.

3.1.1.1.3. Lupron Depot®. Lupron Depot® is a sterile PLGA MPs-based formulation that is separately filled with an aqueous vehicle in a dual-chamber syringe. Several variants of Lupron Depot® are clinically available containing different amounts of leuprolide acetate, including 7.5, 22.5, 30 and 45 mg that are administered via IM route in a dosing interval of 1, 3, 4 and 6 months, respectively. The efficacy and safety of Lupron Depot® in hormonal and menstrual suppression in endometriosis patients have been demonstrated [97–101]. In addition, Lupron Depot® was found to be efficacious against cognitive decline in Alzheimer's disease patients under acetylcholinesterase inhibitor therapy [102]. This was explained by Lupron's potential to suppress the peripheral circulating concentrations of gonadotropins and disrupt the expression of the brain's GnRH receptors that are correlated to the areas of Alzheimer's disease neuropathology [103].

3.1.1.1.4. Nutropin Depot®. Nutropin Depot® is the only marketed long acting injectable formulations delivering a protein drug, recombinant human growth hormone (rhGH), Somatotropin of rDNA origin. Nutropin Depot® is administered via SC injection to children with GH deficiency in doses of 1.5 mg/kg monthly or 0.75 mg/kg twice monthly. Kemp et al. [104] examined the pharmacokinetic and pharmacodynamic response parameters after single or multiples doses of Nutropin Depot® in 138 prepubertal children with GH deficiency. Data analysis revealed that at least 50% of GH exposure occurs within the first 48 h after administration and the GH serum levels remained above 1 μg/L to 11–14 days. Nutropin Depot® achieved serum peak levels similar to those observed with daily injections of GH. Another clinical study demonstrated the therapeutic potential of Nutropin Depot® in adults with GH deficiency at much lower single doses (0.25 mg/kg and 0.5 mg/kg) [105]. Despite its proven clinical efficacy, Nutropin Depot® is not commercially available due to manufacturing issues [10], underlining the

Table 1
Marketed PLGA-based microparticle formulations.

Registered name	Drug	Manufacturer	Indication	Route of administration	Dosing interval (week)	Log P	Water solubility (mg/mL)	PLGA type (L/G ratio)	Highest dosage (mg)	Drug loading% (w/w)	Annual sale (Year 2019) M$
Arestin®	Minocycline hydrochloride	OraPharma	Gum infection	subgingival	12	0.5	50.00	PLGA	1.0	Not found	87
Bydureon®	Exenatide	AstraZeneca	Type 2 diabetes mellitus	SC	1	-2.1	1.00	PLGA 75:25	2.0	5.0	549
Lupron Depot®	Leuprolide acetate	Takeda, Abbott	Breast and prostatic cancer	IM	4–26	1.1	0.50	PLA*	45.0	17.0	887
Nutropin Depot®	Somatotropin	Genentech Inc.	GH deficiency	SC	4–5	–	5.00	Not found	22.5	12.0	382 (Year 2005)
Risperdal Consta®	Risperidone	Alkermes & Janssen	Schizophrenia, Psychotic disorders	IM	2	3.0	0.003	PLGA 75:25	52.0	32.9	688
Sandostatin® LAR	Octreotide acetate	Novartis	Acromegaly, Carcinoid Tumors	IM	4	0.4	1.20	PLGA 55/45 star polymer	30.0	4.17	1585
Signifor® LAR	Pasireotide pamoate	Novartis	Acromegaly	IM	4	3.0	0.01	PLGA 55/45 star polymer + PLGA 50:50	60.0	25	72 (Year 2018)
Somatuline® LA	Lanreotide acetate	Ipsen Pharma Biotech	Acromegaly	IM	2	1.1	0.50	PLGA 75: 25	30.0	24.6**	1154
Trelstar® LA	Triptorelin pamoate	Debiopharm, Ipsen, Vifor	Prostatic cancer	IM	4–26	1.7	0.03	Not found	22.5	7.3	456
Vivitro®	Naltrexone	Alkermes & Janssen	Alcohol Opioid dependence	IM	4	1.9	1.63	PLGA 75:25	380.0	33.7	335
Zilretta®	Triamcinolone acetonide	Flexion	Pain killer	intra-articular	12	2.5	0.04	PLGA 75:25	32.0	25.0	73

* Poly(lactic acid) polymer (it is not known whether it is poly(L-Lactic acid) or poly(DL-Lactic acid). Solubility and logP values obtained from drug bank [88].
** From FDA data base [89]; other data are from PharmaCircle® data base [14].

Table 2
Marketed preformed implants and in situ forming implants.

Registered name	Drug	Manufacturer	Indication	Route of administration	Dosing interval (week)	Log P	Water solubility (mg/mL)	Delivery system	Highest Doseage (mg)	Drug loading %(w/w)	Annual sale (Year 2019) M$
Atridox®	Doxycycline hyclate	Atrix Laboratories Inc.	Periodontal disease	subgingival	18	0.6	50.00	Atrigel Delivery System with PLA and NMP	50	10.0	Not found
CiproScrew®	Ciprofloxacin	Bioretec Ltd.	Bone infection in surgery	Intra-bone insertion	42	0.3	1.00	45*45 mm, implantable screws comprised of drug loaded PLA	Not found	Not found	Not found
Leuprone HEXAL®	Leuprolide acetate	Novartis (Sandoz/Hexal)	Breast and prostatic cancer	SC	4 and 13	1.1	0.5	PLGA 50:50 or PLA rodes	5	Not found	Not found
Ozurdex®	Dexamethasone	Allergan	Macular edema, non-infectious uveitis	intravitreal	26	1.9	0.09	PLGA 50:50 rodes	0.7	Not found	298
Suprefact® Depot	Buserelin acetate	Sanofi-Aventis	Prostatic cancer	SC	8 and 13	0.9	0.038	PLGA 75:25 rodes	9.45	20.0	Not found
Propel® and Sinuva®	Mometasone furoate	Intersect	Sinusitis	Intra-ethmoidal	4 and 13	4.1	0.02	PLGA 75:25 rodes or blend of PLGA 50: 50 and PEG rodes	1.35	Not found	109
SinoFuan®	5-fluorouracil	Simcere Pharmaceutical Group	Cancer	intraperitoneal	2	−0.6	1.00	A cylindrical PLGA implants of 0.1–0.5 mm diameters	200	Not found	18 (year 2013)
Zoladex®	Goserelin acetate	AstraZeneca	Breast and prostatic cancer	SC	4 and 13	1.5	0.05	PLGA rods	10.8	29.9	813
Perseris®	Risperidone	Indivior Inc	Schizophrenia	SC	4	3.1	2.33	Atrigel Delivery System with NMP and PLGA 80:20	120	24.2	Not found
Eligard®	Leuprolide acetate	Tolmar Inc.	Prostatic cancer	SC	4, 13, 18 and 26	1.1	0.50	Atrigel Delivery System with NMP, PLGA (50:50), (75:25), (85:15)	45	21.4	127
Scenesse®	Afamelanotide	Clinuvel Pharmaceuticals Ltd.	Erythropoietic protoporphyria	SC	8	1.4	0.023	A rod implant with 1.7 cm length, 1.45 mm diameter	16	51.1	18

Solubility and logP values obtained from drug bank [88]; other data are from PharmaCircle ® data base [14].

need for further efforts in the PLGA-based formulations development addressing ER protein drug delivery.

3.1.1.1.5. Risperdal Consta®. Risperdal Consta® is the first LAI antipsychotic formulation based on PLGA MPs. Risperdal Consta® is administered via IM injection every two weeks for the treatment of schizophrenia and other psychotic disorders, such as schizoaffective disorder or bipolar disorder [106]. A double-blind study demonstrated the possibility of switching schizophrenia patients under oral risperidone to long-acting one (Risperdal Consta®) without compromising the overall treatment efficacy and safety, while improving patient adherence due to reduced dosing frequency [107]. Despite the advantage of improved dosing rates, Risperdal Consta® remains dependent on oral antipsychotic treatment, which is required in the first 3 weeks of treatment to supplement long-acting risperidone. The use of additional supplement is due to the multi-phasic release profile of Risperdal Consta®, exhibiting about 3.5% of initial release followed by a 3-week lag phase of any drug release and finally the actual release for two weeks [108]. This is a typical example of degradation-based drug release from PLGA microparticles known as bulk erosion [109]. This limitation inspired the development of Invega Sustenna®, an aqueous nanocrystal suspension of the active metabolite of risperidone, paliperidone palmitate, with a dose of 150 mg. In addition to efficacy, tolerability and safety profiles comparable to Risperdal Consta®, Invega Sustenna® supplies effective plasma concentrations rapidly and excludes the need for oral antipsychotic supplementation [110]. Further efforts have being being devoted to develop risperidone-loaded MPs with 4-week steady release profiles to prevent extrapyramidal side effects and high-dosing frequency [108,111]. By screening PLGA with different molecular weight and copolymer compositions, Su et al. [108] reported zero-order release of risperidone from PLGA 50:50 for 20 days, which could not be achieved using PLGA 75:25 (Risperdal Consta®). This is likely due to the 3 weeks lag phase observed because of poor water penetration and slower biodegradation of the PLGA (75/25) matrix composed of higher ratio of lactic units. Such results encourage future improvement of this clinically established PLGA formulation. This includes for instance thorough optimization of relevant formulation parameters (e.g., PLGA molecular weight and composition) to improve the release kinetics of risperidone from PLGA MPs.

3.1.1.1.6. Sandostatin® LAR. Sandostatin® LAR is a PLGA-based MPs loaded with a synthetic somatostatin analog, octreotide (as acetate salt). Similar to the endogenous somatostatin, octreotide can normalize the levels of insulin-like growth factor-1 (IGF-1) and growth hormone (GH), thus Sandostatin® LAR is prescribed for the management of symptomatic acromegaly and neuroendocrine tumors [112]. Sandostatin® LAR demonstrated positive effects in both short- and long-term symptomatic treatment of malignant carcinoid syndrome upon monthly IM injections. Its efficacy and safety profiles were similar to those of thrice-daily SC injections of octreotide solution and weekly-biweekly IM injections of lanreotide, a somatostatin analog [113,114]. The IM administration of Sandostatin® LAR 20 mg every 4 weeks was found to be as efficacious and safe as thrice-daily SC injections of octreotide 0.3–0.6 mg (Sandostatin®) to acromegalic patients, explaining the added value of reduced dosing frequency [115–117].

3.1.1.1.7. Signifor® LAR. Signifor® LAR is a PLGA-based MPs containing 25% (*w*/w) pasireotide pamoate as free-base, a second-generation somatostatin analogue. Signifor® LAR has been established for long-term management of symptomatic acromegaly, while pasireotide solution (Signifor®) is a short-acting formulation daily administered via SC route. Signifor® LAR is administered IM. on a monthly basis [118]. Signifor® LAR is specifically indicated for patients with acromegaly that is resistant to the first-line acromegalic therapy, which is composed of first-generation somatostatin analogue, such as Sandostatin® LAR (octreotide-loaded microspheres) [119]. In a randomized clinical study, pharmacokinetics of Signifor® LAR showed high plasma levels on day 1, after IM injection of MPs, followed by a decline in drug release for a week and subsequent increase from week 1 to week 4. Steady-state drug release was obtained from the 3rd month of the treatment (i.e., after three consecutive injections) and lasted for 28 days [120].

3.1.1.1.8. Somatuline® LA. Somatuline® LA is an extended release PLGA-based MP formulation. Similar to octreotide, lanreotide is an octapeptide analogue of somatostatin, thus Somatuline® LA is prescribed for the treatment of acromegaly with an administration frequency of every 2 weeks. Following IM injection, Somatuline® LA exhibits a biphasic release profile, characterized by a rapid initial release within 1–2 h reaching a plasma level of 8.5 $\pm$ 4.7 ng/mL, followed by a slow release from around day 3–5 until day 14–21 featured by a plateau of a plasma concentration of around 1 ng/mL. During the first day after injection, around 7% of the loaded lantrotide is released because of the presence of adsorbed lanreotide on the surface of microspheres, likely due to inefficient washing step during manufacturing. Noteworthy, lanreotide-loaded MPs exhibited favourable PK profiles in acromegaly patients. In addition, a number of clinical trials showed efficacy of Somatuline® LA in normalizing both GH and IGF-1 levels in acromegaly patients. Even though each Somatuline® LA contains 40 mg lanreotide, only 30 mg can be finally delivered to the patients, which is defined as the effective dose, because of the loss during resuspension and administration process [121].

3.1.1.1.9. Trelstar® LA. Trelstar® LA is composed of sterile lyophilized PLGA-microspheres loaded with triptorelin pamoate, which is a synthetic analogue of luteinizing hormone-releasing hormone (LHRH). Trelstar® LA is indicated for the management of prostatic cancer. The single-doses of Trelstar® LA contains 3.75, 11.25 and 22.5 mg of triptoreline intended for IM administration every 1, 3 and 6 months, respectively [122]. A few randomized studies have comparatively investigated the ability of long-acting LHRH agonists (e.g. Trelstar® LA versus Lupron Depot®, leuprolide acetate) to achieve androgen suppression in male patients with prostate cancer. In a comparative clinical trial, Trelstar® LA 3.75 mg/month was found to be better in normalizing castration levels of serum testosterone than Lupron Depot® 7.5 mg [123].

3.1.1.1.10. Vivitrol®. Vivitrol® is a PLGA microsphere formulation loaded with naltrexone, an opioid receptor antagonist. Vivitrol® is administered via the IM route for the management of alcohol and opioid dependence. The efficacy of naltrexone-loaded microspheres has been demonstrated in several clinical trials, with much longer-lasting abstinence to and greater reduction in alcohol and opioid consumption/craving than placebo [124,125]. The successful development of Vivitrol® provides a promising alternative to oral naltrexone formulations, while the latter was limited by poor patient compliance despite its demonstrated ability to reduce alcohol and opioid reinforcement [87,88]. Furthermore, oral administration of naltrexone thrice a week causes high drug exposure to the gastrointestinal tract and high plasma peaks leading to several adverse effects (such as skin rash, body aches or pain), thus discouraging the treatment continuation, which limits the possibility of providing sufficient evidence of clinical efficacy. In addition to the improved adherence, IM administration of naltrexone-loaded microspheres (Vivitrol®) demonstrated better clinical effectiveness and tolerability than oral dosage forms [126–128]. In healthy volunteers upon IM injection of Vivitrol® (380 mg dose), an immediate burst release (1-2 h after dosing) was observed, likely due to the presence of pores in the surface of microparticles and maximum plasma concentration (C_{max}) reached at day 2 post dosing. After two weeks of extended drug release, naltrexone concentrations in plasma declined. However, the mean plasma concentration of the drug remained above 1 ng/mL for more than 35 days [129]. It was also found that a single IM injection of Vivitrol® (380 mg dose) demonstrated 4-flod higher AUC_{28} as compared to 50 mg/day of oral naltrexone administered for 28 days [129].

3.1.1.1.11. Zilretta®. Zilretta® a dry powder composed of PLGA-based microspheres containing triamcinolone acetonide for intra-articular (IA) injection. The FDA has recently approved Zilretta® for the management of pain in osteoarthritis (OA) knee [130]. In a randomized phase III clinical trial, it was shown that Zilretta® extended drug release up to 12

weeks as compared to only 6 weeks extended release of triamcinolone microcrystal suspensions (40 mg) following IA administration. Furthermore, Zilretta® significantly reduced pain, stiffness and physical function as compared to 40 mg triamcinolone acetonide suspension and placebo [131].

3.1.1.2. Marketed preformed and in situ forming implants based on PLGA polymer

3.1.1.2.1. Atridox®. Atridox® is a subgingival in situ forming implant of the antibiotic doxycycline hyclate in Atrigel® delivery technology. Atridox® is a single dose product presented in a two-syringe mixing system. This system includes syringe A that contains Atrigel® matrix 450 mg, which is an in situ gelling depot composed of 36.7% poly(DL-lactide) (PLA) dissolved in 63.3% *N*-methyl-2-pyrrolidone, and syringe B that contains 50 mg doxycycline hyclate (equivalent to 42.5 mg doxycycline). The reconstituted product for subgingival administration is a pale-yellow viscous liquid with 10% doxycycline hyclate indicated for periodontal patients every 4 months. In a clinical study it was demonstrated that local injection of Atridox® was as effective in the treatment of periodontitis [132]. It was concluded that local administration of Atridox®, as a less invasive technique, could be a good alternative to invasive approaches such as scaling and root planning. Another clinical study performed by Zeidner et al. [133], showed that a single SC administration of Atridox® was better prophylactic antibiotic option than oral doxycycline in patients with *Anaplasma phagocytophilum and Borrelia burgdorferi* co-infection. The review by Southard et al. [134] discusses in detail the full potential of Atrigel® technology as well as the clinical findings that led to successful establishment of Atridox® periodontal therapy.

3.1.1.2.2. CiproScrew®. CiproScrew® is a biodegradable implant in the form of screw for fracture-fixation. CiproScrew® is indicated for prevention of ciprofloxacin sensitive infections associated with mechanical fixation of bone fractures, bone grafts and osteochondral fractures as well as osteotomies and arthrodesis. Several studies demonstrated the potential of the screw to supply local bactericidal tissue concentrations for about 42 weeks [135–139]. In a prospective randomized trial, biodegradable poly(lactic acid) screws were as effective as stainless steel screws resulted in an uncomplicated healing of patient's fibular fractures with no evidence of osteolysis. In addition, no need for further screw removal in case of CiproScrew® was required up on drug exhausting due its biodegradability, in contrast to stainless steel screws suggesting CiproScrew® can be an excellent alternative to steel screws for bon fixation [138].

3.1.1.2.3. Leuprone® HEXAL®. Leuprone® HEXAL® is a preformed implant loaded with a gonadotropin-releasing hormone agonist (leuprolide, also known as leuprorelin). Leuprone® HEXAL® is produced in the form of rods. Leuprolide is used as acetate and homogeneously dispersed in PLGA (50/50) or poly(lactic acid) matrix, yielding Leuprone® HEXAL® 1- or 3-months implant, respectively [140]. Leuprone® HEXAL® is injected subcutaneously into the anterior abdominal wall every 1 or 3 months for the treatment of advanced hormone-dependent prostate cancer. Geiges et al. [140] assessed the effects of leuprolide implants for testosterone suppression and normalization of prostate specific antigen levels in a randomized, controlled study. The efficacy and safety profiles of the implants in prostate cancer patients were found to be comparable to those of intramuscularly administered leuprolide MPs. The results provided insights for clinical development of leuprolide implants, which offer the advantage as a ready-to-use formulation (with no need for reconstitution as done for MPs). Moreover, production of PLGA implant is simpler and involves less steps as compared to PLGA MPs.

3.1.1.2.4. Ozurdex®. Ozurdex® is a preformed rod-shaped implant composed of PLGA matrix containing dexamethasone, a synthetic glucocorticoid agent with anti-inflammatory activities. Ozurdex® is used for the treatment of macula oedema, due to diabetes or retinal vein occlusion and non-infectious uveitis [141]. Several studies have reported the clinical efficacy and safety profiles of Ozurdex® [142–146]. Due to the long-lasting release behavior of implant (over 4–6 months), dexamethasone from Ozurdex® controls macula edema effectively with minimized glucocorticoid-related adverse effects e.g., reduced risk for refractory intraocular pressure augmentation or cataract [147]. Ozurdex® exhibits a typical three phase release profile, known for PLGA MPs and implants, which leads to early substantial therapeutic effects within the first 8 weeks of administration, followed by a relatively constant and moderate effect [148]. Despite this multiphasic release, the long-term administration of Ozurdex® remains effective in controlling diabetic macular edema with reduced adverse effects [149]. A case study in patients with retinal vein occlusions demonstrated that Ozurdex® improves resolution of macular edema and enhances visual acuity [150].

3.1.1.2.5. Suprefact® Depot. Suprefact® Depot is a preformed rod-like PLGA implant comprising buserelin, a luteinizing hormone-releasing hormone analogue. This implant is supplied with two different buserelin dosages, 6.3 and 9.45 mg, that are intended for prostate cancer therapy through SC injection every 2 and 3 months, respectively [151]. Pettersson et al. [152] conducted a prospective clinical study to determine the duration of androgen deprivation in prostate cancer patients. The authors observed that a single administration of Suprefact® Depot 9.45 mg decreased the serum testosterone levels below the lower castration limit for about 6 months, which holds the promise for neoadjuvant therapy or long-term management of androgen deprivation.

3.1.1.2.6. Propel® and Sinuva®. The PROPEL® family is a group of sinus stents composed of a PLGA matrix loaded with mometasone furoate, a corticosteroid anti-inflammatory agent. Intersect ENT manufactures PROPEL® implants (PROPEL® for use in the ethmoid sinus, PROPEL Mini® for use in the ethmoid sinus and frontal sinus ostia, PROPEL Contour® for use in the frontal sinus ostia and maxillary sinus ostia) with diverse shapes based on PLGA including a blend of PLGA and polyethylene glycol that are designated for different types of sinuses, but all containing 0.37 mg of mometasone furoate that releases the drug over a 1 month period in the body. SINUVA® (indicated for use in adults with nasal polyps who have had previous ethmoid sinus surgery) is a newer PLGA sinus implant delivering a much higher dose of mometasone furoate (1.35 mg) over a longer drug release duration of 3 months. Both the PROPEL® family and SINUVA® products are administrated using a special delivery system. For example, the PROPEL® or PROPEL® Mini implant is inserted in the ethmoid cavity after endoscopic sinus surgery for preventative control of postoperative obstruction and inflammation. PROPELMini® acts as a sinus spacer and supplies slow and sustained release of mometasone furoate to sinus mucosa for the management of chronic rhinosinusitis. In addition, as shown in Fig. 6, due to its spring-like configuration, the inserted PROPEL® prevents lateralization of the turbinate and the postoperative formation of granulation tissue and scarring [153].

3.1.1.2.7. SinoFuan®. SinoFuan® is a preformed PLGA based implant loaded with 5-fluorouracil, a metabolic anticancer drug, that is intended for intraperitoneal insertion during surgical operation for gastric cancer. In a clinical study, short-term safety of SinoFuan® implants upon resection of primary liver cancer was investigated. These implants demonstrated to be safe with minimum impact on liver biomarkers. The clinical findings have encouraged further investigations to provide new clinical insights into the efficacy of SinoFuan® in hepatic cancer [155]. It has been shown that 5-fluorouracil implants are nontoxic and can extend the survival rate of advanced gastric cancer patients (3-year survival rate of 64.3% vs. 42.4%, $P = 0.018$) [156]. In a case study, a patient with history of peritoneal SinoFuan® implantation, the implant caused local tissue necrosis and fibrotic lumps that overloaded the liver although it demonstrated curative effect on the cancer. Analytical examination of the fibrotic mass showed that it contained fluorouracil. This rare complication of SinoFuan® implants shows the need for better understanding the cause of this problem and improving the application of such implants in different gastric cancer [157].

3.1.1.2.8. Zoladex®. Zoladex® is a preformed cylindrical PLGA-based rod containing an agonist analogue of luteinizing hormone-releasing hormone, indicated for the long-term management of breast and prostate cancer. Zoladex® unit-dose is implanted via SC injection into the anterior abdominal wall every three-months (10.8 mg) or one-month (3.6 mg). The use of goserelin acetate 3.6 mg implant was reported to be comparable to 3-months 10.8 mg dosage form, in terms of both efficacy and safety [158,159]. Zoladex® 3.6 mg has shown some success as a long-acting alternative therapy to surgical castration of patients with prostate cancer [160,161]. In a clinical study by Ahmed et al. [162], monthly insertions of Zoladex® 3.6 mg and constant infusion of goserelin over 60 days demonstrated similar effects on testosterone and luteinizing hormone control. In a randomized multi-center trial conducted in patients with advanced prostate cancer, Zoladex® 3.6 mg exhibited much better tolerability than diethylstilbestrol 3 mg, a daily injectable analogue of luteinizing hormone-releasing hormone. Irrespective of the goserelin acetate dosing, Zoladex® induces an increase in testosterone levels in the first week of implantation, followed by a constant depletion and the castration levels are obtained and maintained from the 4th week to week 18 [163–165]. Despite differences in drug content, the two Zoladex® forms have similar drug release kinetics, and their endocrinological and clinical effects are comparable [166]. Zoladex® 10.8 mg seems to correspond well to 3-consecutive administrations of Zoladex® 3.6 mg, but further in vitro-in vivo correlations studies would provide valuable insights for comparative assessment of these two formulations. An interesting future area for exploitation of Zoladex® could be combination therapies, associating long acting goserelin acetate with hormone replacement therapy (i.e., using estrogen-progestogen conjugate). A prospective placebo-controlled study by Moghissi et al. [167] demonstrated that in endometriosis patients, the combination of Zoladex® 3.6 mg monthly with estrogen-progestogen conjugate 0.3–5 mg daily improves the tolerability of each therapy, without any loss of efficacy. Using this combination regimen, the authors observed a remarkable attenuation of the hypoestrogenic side effects of goserelin and loss of bone mineral density due to the minimized hormone replacement.

3.1.1.2.9. Eligard®. Similar to Atridox®, the design of Eligard® is also based on in situ forming gel (Atrigel® formulation) that is loaded with leuprolide acetate for the treatment of advanced prostatic cancer. Upon use, the Atrigel® delivery system (PLGA dissolved in NMP) is mixed with leuprolide acetate powder, forming suspensions, which subsequently solidify as a depot in vivo that regulates the release of leuprolide. [168]. Eligard® is available in different forms varying in PLGA composition and drug contents [169]. Clinical studies showed that Eligard® could sustain the release of leuprolide over the designed release duration (4–26 weeks depending on the formulation used), with a constant leuprolide serum concentration from 0.1–2 ng/mL for all four dosages [169]. However, 3–5 h after injection, a high burst release was observed, ranging from 25.3 ng/mL for 7.5 mg Eligard® up to 150 ng/mL for 30 mg Eligard®. Such initial release might be due to the slower and incomplete solid depot formation in vivo, causing the "free" leuprolide rapidly washed out form the depot. Another issue for Eligard® is the use of the organic solvent *N*-methyl-2-pyrrolidone (NMP). Even though NMP is used in many FDA approved products, it has a potential for causing local tissue irritation [170]. Thus, current research efforts are focused on development of in situ forming gels from aqueous solution, triggered by body temperature or pH [171].

3.1.1.2.10. Perseris®. Perseris® is another example of Atrigel® delivery system. Perseris® is releasing risperidone for the treatment of schizophrenia in adults. Upon mixing, risperidone forms a suspension in PLGA (L/G 80:20 M ratio) and NMP-based Atrigel delivery system, which then forms a solid depot in vivo. Similar to Eligard®, Perseris® also shows two peaks of risperidone in plasma. The first peak occurs after 4–6 h post administration because of drug leakage during the depot formation process (C_{max} 10.9 ng/mL for 120 mg dose). Around day 10–14 post administration, a second peak was observed with a similar magnitude as the burst release, which is likely due to onset of PLGA matrix degradation and bulk erosion [172].

3.1.1.2.11. Scenesse®. Scenesse® is an afamelanotide (a melanocortin 1 receptor agonist) loaded PLGA rod implant for relieving pain associated with phototoxic reactions from erythropoietic protoporphyria in adult patients. Scenesse® is a single rod implant with a length of 1.7

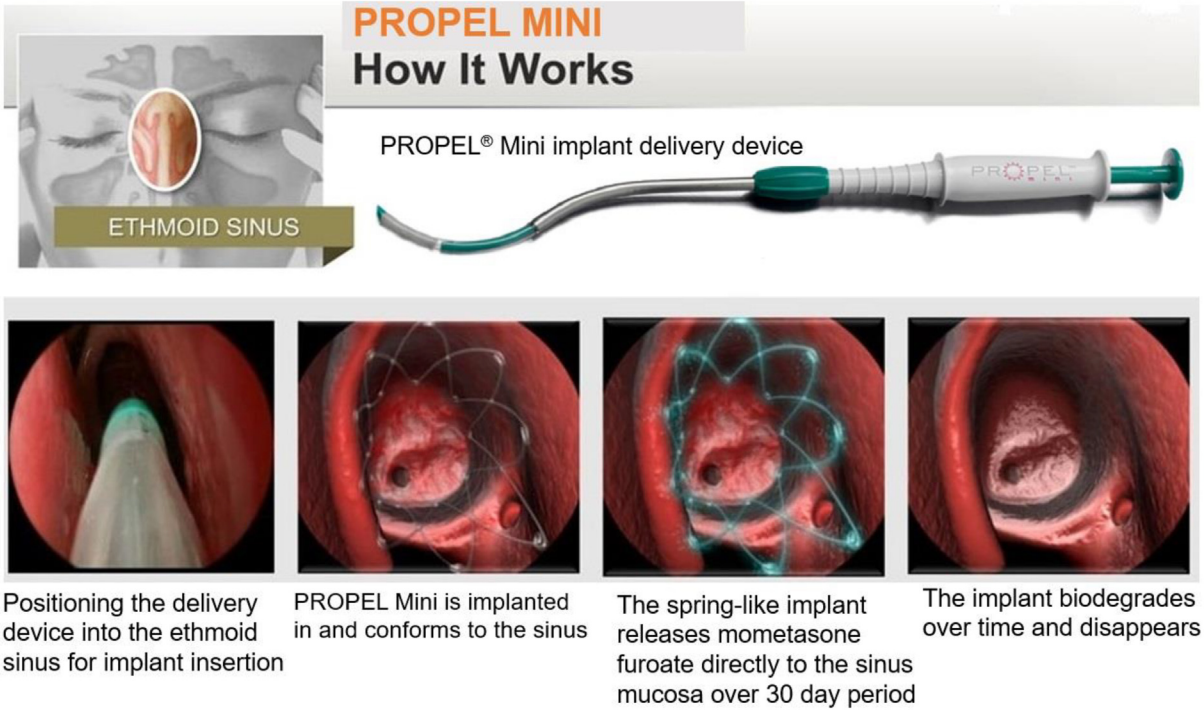

Fig. 6. Image depicting the Propel® Mini implant applicator/delivery device and schematically illustrating the implant when inserted in the inflamed sinus. The spring-like shape not only opens the sinus but also releases the corticosteroid drug over 30 days. Images modified with permission from Intersect ENT [154].

cm and a diameter of 1.45 mm, containing afamelanotide. Upon implantation, Scenesse® showed a median T_{max} of 36 h, and the apparent half-life of afamelanotide was around 15 h. Multiple clinical trials, where more than 800 patients have been treated with Scenesse®, showed that the formulation is well tolerated and reduces the incidence as well as the severity of phototoxic reactions [173].

3.1.2. Marketed non-PLGA long acting parenteral formulations

This section discusses prolonged release parenteral formulations composed of polymers other than PLGA, namely sodium hyaluronate, poly[1,3-bis(carboxyphenoxy)propane-*co*-sebacic-acid (PCPP-SA), triethylene glycol poly(orthoester), etc. These polymers are potential alternatives for PLGA, while sharing similar biocompatibility profiles and providing controlled release over prolonged periods, for loading drug molecules that are incompatible with PLGA. Table 3 summarizes the marketed formulations of this category, and further details are provided in the following paragraphs.

3.1.2.1. Somatropin biopartners®. Somatropin Biopartners® (Decalge®) is a sustained-release formulation composed of MPs of sodium hyaluronate (microgels) loaded with Somatropin, a recombinant human growth hormone (rhGH). Somatropin Biopartners® is produced using spray-drying. This method was found to be suitable for microgel preparation, and the bioactivity of the encapsulated rhGH was preserved conserved upon manufacturing. The formulation containing rhGH and sodium hyaluronate in mass ratio of 1:1 exhibited constant increase in serum concentration in cynomolgus monkeys for 6 days [174]. The indications for Somatropin Biopartners® include growth hormone deficiency and turner syndrome, which are both treated by weekly injections of the microgels via SC route. A case study demonstrated that Somatropin Biopartners® 6 IU (2 mg), that was administered weekly for 26 weeks, improved body composition and quality of life without any significant adverse effects in adult patients with somatopause [175]. In another clinical study, the effect of extended release growth hormone therapy on survivor patients with severe skin burn wound was investigated [176]. Somatropin Biopartners® 6 IU was found to be effective and safe for 3 months treatment of sarcopenia (loss of muscle mass due to severe burning), which previously required daily injection of rhGH 1 IU. In this randomized study, Somatropin Biopartners® exhibited significant increase in oxygen consumption, insulin-like growth factor I and adiponectin levels, with no remarkable effects on body weight, blood pressure, body fat content and bone mineral composition [176].

3.1.2.2. Gliadel® wafer. Gliadel® Wafer is biodegradable implant with a diameter and thickness of 1.45 cm and 1 mm, respectively. Each wafer is composed of polyanhydride copolymer 192.3 mg (polifeprosan 20), and 7.7 mg carmustine, an antineoplastic drug. Polifeprosan 20 is a biodegradable polymer composed of poly [bis (*p*-carboxyphenoxy) propane:sebacic acid] in a molar ratio of 20:80 [177]. Regarding formulation of Gliadel®, it is worth mentioning that the drug was first incorporated into polymeric MPs by spray-drying method, and then the preformed MPs were compression-moulded to yield implantable wafers, as shown in Fig. 7, to fill the resection cavity after brain tumour surgery [178]. Gliadel® Wafer's biodegradability in human brain was determined in a study that demonstrated degradation of about 70% of the polymeric network within three weeks post implantation; but Wafer remnants were found to be present up to 232 days during re-operation and autopsy. The composition of these remnants mainly included water and monomeric components as well as traces of carmustine [179]. Following surgical brain tumour resection, the implantation of up to 8 wafers alongside the wall of the resection cavity

Table 3
Marketed non-PLGA long acting parenteral formulations.

Registered name	Drug	Manufacturer	Indication	Route of administration	Dosing interval (week)	Log P	Water solubility (mg/mL)	Type of carrier system	Highest dosage (mg)	Drug loading %(w/w)	Annual sale (Year 2019) M$
Somatropin Biopartners®	Somatropin	Biopartners and LG Life Sciences, Ltd	GH Deficiency, Turner Syndrome	SC	1	NA	5.00	Hyaluronate	24.0	Not found	Not found
Gliadel® Wafer	Carmustine	Eisai	Glioblastoma multiforme	SC	–	1.5	4.00	Wafer made of Polifeprosan 20, poly [bis (pcarboxyphenoxy)] propane and sebacic acid in a 20:80 M ratio, diameter 1.45 cm, thickness 1 mm	7.7	3.85	40 (Year 2007)
Sustol®	Granisetron	Heron therapeutics	Vomiting (chemotherapy)	SC	1	2.6	0.43	Biochronomer® technology: tri(ethylene glycol) poly (orthoester) (TEG-POE), 392 mg, and polyethylene glycol monomethyl ether, 98 mg)	10.0	2	14
Trivaris®	Triamcinolone acetonide	Allergan	Intraocular inflammation	intrvitreal	3 and 6	2.5	0.04	2.3% (w/w) sodium hyaluronate; 0.63% sodium chloride; 0.3% sodium phosphate, dibasic; 0.04% sodium phosphate, monobasic; and water for injection	8.0	Not found	Not found
Buvidal®	Buprenorphine hydrochloride	Camurus AB	Opioid dependence	SC	1 and 4	4.9	0.02	FluidCrystal Depot	32.0	Not found	Not found
Plenaxis®	Abarelix	Speciality European Pharma	Prostate cancer	IM	4	2.8	0.01	Abarelix/CMC complex	100.0	84	Not found
Somatuline Depot®	Lanreotide acetate	Ipsen Pharma Biotech	Acromegaly	SC	4	1.1	0.50	Peptide self-assembly	120.0	100	1154
Firmagon®, Gonax®	Degarelix acetate	Astellas	Prostate cancer	SC	4 and 14	3.1	0.02	Peptide self-assembly	240.0	55.2	Not found

Solubility and logP values obtained from drug bank [88]; other data are from PharmaCircle® data base [14].

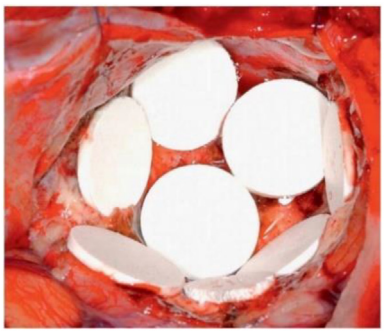

Fig. 7. Gliadel Wafers implanted into a tumour resection cavity upon brain tumour surgery [178]. Reproduced with Permission from Elsevier.

allows to localize chemotherapy in the peritumoral surgical bed [180]. Gliadel® Wafer was tested in a randomized placebo-controlled, double-blind phase III trial using 240 patients intraoperatively diagnosed with initial malignant glioma [181]. Data indicated that Gliadel® Wafer implantation on primary surgical resection is well tolerated, as no systemic toxicities or adverse effects were observed, and does not necessitate another surgery since the resultant local chemotherapy provides sufficient clinical benefits (with death risk reduction of 29% for treated group). In another phase III clinical trial, Gliadel® Wafer implanted at the resection cavity achieved 100-fold higher local concentrations than systemic administration of carmustine formulation, thus providing enhanced site-specific efficacy as well as reduced systemic toxicity, based on the undetectable drug levels in plasma [182]. In addition, the authors observed a significantly longer median survival for the treatment group (11 patients treated with Gliadel® Wafers) compared to the placebo group (13 patients treated with placebo Wafers), 14.7 versus 9.5 months, respectively. For more information about release and degradation of Gliadel® Wafers see our previous review study [7].

3.1.2.3. Sustol®. Sustol® is a compact kit consisting of a single-dose syringe that contains a sterile in situ gelling viscous liquid. The main composition of Sustol® includes an antiemetic agent, granisetron, and two biodegradable polymers triethylene glycol poly(orthoester) polymer and polyethylene glycol monomethyl ether (mPEG), respectively. Poly(orthoester) polymeric matrix undergoes surface biodegradation. Surface erosion leads to controlled drug release and maintaining neutral pH in the core of the matrix, which can be an advantage for loading pH sensitive drugs. Polyethylene glycol is added to the triethylene glycol poly(orthoester) polymer likely to dissolve the drug, lower the viscosity of the polymer for ease of injection and facilitate drug release from the matrix. It has been shown that addition of 2 kDa mPEG 1% (w/w) to poly(orthoester) polymer significantly increases the release kinetics of model drug from the matrix [183].

Sustol® is administered on a weekly basis, via SC injection into the upper arm or abdomen that releases granisetron over more than 5 days. [184]. Sustol® is used for prevention of acute and delayed nausea and vomiting due to highly or moderately emetogenic anticancer chemotherapy or chemotherapeutic combination of anthracycline and cyclophosphamide [185]. The Extended release formulation Sustol® after SC administration exhibits much greater plasma half-life (26–28 h) than IV and oral granisetron (i.e., 9 and 6 h, respectively) [186].

3.1.2.4. Trivaris®. Trivaris® is a preservative-free gel of triamcinolone acetonide, a synthetic water-insoluble glucocorticoid corticosteroid for intrvitreal injection [187,188]. A multicenter randomized clinical trial demonstrated the efficacy of intravitreal triamcinolone injection in treating vision loss associated with macular edema due to central retinal vein occlusion [189,190]. In terms of safety, Trivaris® is preferred by many specialists over other preservative-containing intravitreal formulations of triamcinolone (e.g. Kenalog® that contains benzylic alcohol, see Section 3.3), which expose to high risk for retinotoxicity [188,191]. Drug release from this formulation is governed by dissolution kinetics and particle size of the drug rather than hyaluronic acid polymer. Sodium hyaluronate is added to this composition most likely as viscosity enhancer to enable better injectability. As compared to Kenalog® higher drug concentration (40 mg/mL vs 80 mg/mL) is used in Trivaris® and therefore a viscosity enhancer such as hyaluronic acid was used to minimize the sedimentation and enhances the injectability. Particle size was found to be the key determining drug release duration of two marketed long acting formulation of triamcinolone acetonide [192]. Particle size (X90) was 47 μm for Kenalog and 22 μm for Trivaris and therefore Kenalog showed longer drug exposure in vitreous of rabbits.

3.1.2.5. Buvidal®. Buvidal® is a pre-filled solution for extended release of buprenorphine, an opioid drug indicated for opioid dependency. Buvidal® is based on FluidCrystal Depot technology, which is a solution containing soybean phosphatidylcholine, glycerol dioleate and ethanol (weekly dose) or NMP (monthly dose). Upon injection, ethanol is exchanged by water and the lipids transform into a liquid crystalline gel structure encapsulating buprenorphine. Drug release is driven by gel matrix degradation, catalyzed by locally present lipase. After administration of Buvidal®, a median T_{max} of 24 h and 6–10 h was obtained with a complete absolute bioavailability for the weekly and monthly dosage group, respectively. For the respective dose interval 8–32 mg and the dose interval 64–128 mg, buprenorphine exposure is proportionally increased with the given dose [193]. In a double-blind, double-dummy randomized clinical trial, weekly and monthly SC buprenorphine depots (Buvidal®) were found to be noninferior to daily sublingual administrations of buprenorphine/naloxone combination in 428 subjects with opioid use disorder treated over 24 weeks [194,195]. The authors observed that 35.1% of the participants in the Buvidal® group tested negative in the opioid urine testing, while only 28.4% in the daily sublingual buprenorphine group showed negative urine screens.

3.1.2.6. Plenaxis®. Plenaxis® is based on the LEAP (Ligand Evolution to Active Pharmaceuticals) technology, which combines the anionic polymer of sodium carmellose and the cationic abarelix acetate, a synthetic peptide. Due to the electrostatic interactions of the two oppositely charged molecules, they form a complex leading to precipitation. The precipitated complex is then isolated, dried and milled to produce products with the desired particle size. The active molecule, abarelix, is a gonadotropin releasing hormone receptor antagonists, thus Plenaxis® is indicated for prostatic cancer. Each Plenaxis® complex contains 100 mg abarelix, and upon use, the complex is reconstituted with 2.2 mL 0.9% sodium chloride solution into suspensions that are monthly injected via the IM route. Following administration, abarelix is slowly released reaching a mean peak concentration of 43.4 ng/mL approximately after 3 days post administration [196].

3.1.2.7. Somatuline® Depot. Somatuline® Depot or Somatuline® Autogel is another version of lanreotide long acting formulation indicated for the treatment of acromegaly with a dosing interval of 1 month. Unlike Somatuline® LA that is based on PLGA MPs delivery system, Somatuline® Depot is a carrier free system containing only water for injection and acetic acid for pH adjustment based on peptide self-assembly technology. The success of Somatuline® Depot is based on a liquid crystal technology, and lanreotide is believed to undergo self-assembly, forming dimers firstly and finally nanotubes. The nanotubes are densely packed, contributing to a smaller injection volume (max. 0.5 mL). Upon injection and contact with physiological fluids, a local depot is formed sustaining the release of lanreotide via dissociation of peptide monomers and dimers from nanofibers. In clinical studies, during the first day post dosing, C_{max} was obtained in the range of 4.3–8.4 ng/mL for

the 60, 90 and 120 mg dose with a mean absolute bioavailability of 73.4, 69.0, and 78.4%, respectively [197]. Lanreotide showed sustained release with a half-life of 23 to 30 days and average serum concentrations >0.9 ng/mL throughout 28 days for all dose groups. This product showed linear pharmacokinetics in repeated administration once every 28 days. Cmin, Cmax and AUC elevated in a dose-dependent linear trend followed by reduction in GH levels in acromegalic patients. It is an appealing technology since neither polymers nor other excipients are needed, however, the applied self-assembly process is only suitable for certain peptides [198,199].

Self- assembly in peptides is driven by several forces including van der Waals forces, electrostatic interactions, hydrophobic interactions, hydrogen bonding and π–π stacking (aromatic) interactions [200]. In lanreotide the main driving force for self-assembly is hydrogen bonding and π–π stacking interactions between its residues [201]. Up to now, lanreotide is a unique example of a peptide with pharmacologic activity which has self-assembling property while other self-assembling peptides with biological activity have been developed based on conjugation of a assembling moiety, such as hydrocarbon chains, to exploit hydrophobic interactions for assembling induction [202].

3.1.2.8. Firmagon® and Gonax® 3 month Depot (Japan). Firmagon® and Gonax® 3 Month Depots are based on peptide self-assembly technology which, provide sustained release of degarelix acetate, a gonadotropin releasing hormone (GnRH) receptor antagonist, for 1 and 3 months, respectively [203]. Degarelix acetate has a high-water solubility (100 mg/mL). However, when the concentrations are in the range of 0.1–10 mg/mL, the solution tends to form gels after certain time and dependent on the concentration and temperature. The peptide self-assembly serves as a depot for sustained release without the need of any polymers or additional treatment of the drug substance. The only excipient for Firmagon® is mannitol, possibly as a bulking agent or stabilizer during lyophilization. The PK behavior of degarelix extended release is strongly impacted by drug concentration in the injection solution, since gel formation is concentration dependent. Firmagon® is provided in 240 mg (given as two injections of 120 mg each reconstituted in 3 mL water for injection) as the starting dose, and then 80 mg (reconstituted in 4 mL water for injection) is administrated as the maintenance dosage every 28 days. Before administration, the drug powder is reconstituted with water for injection, followed by SC injection. Clinical studies of Firmagon® in patients with prostate cancer, by using leuprolide 7.5 mg (Lupron Depot®) as the control group, showed the efficacy of Firmagon® in suppressing testosterone secretion and maintaining such suppression to castration levels (testosterone ≤50 ng/dL) during 12 months of treatment [203].

3.2. Marketed oil-based long acting parenteral formulations

As shown in Table 4, several oil-based parenteral formulations have reached pharmaceutical market that demonstrates potential of the technology to achieve clinical success. The following paragraphs provide key details about the marketed long acting parenteral oil-based formulations.

3.2.1. Androcur Depot®

Androcur Depot® is an oil-based solution in 3 mL ampoules, containing mainly castor oil and cyproterone acetate, which is a derivative of progesterone with anti-androgen effects. Androcur Depot® is developed for parenteral management of prostatic cancer. The same dosing (300 mg IM) was as efficient as 50 mg tablets of cyproterone acetate administered orally twice a day in the treatment of hot flush symptom, a hostile symptom associated with antiandrogen therapy in prostatic cancer patients [204]. Similar studies reported that weekly IM injections of Androcur Depot® yielded the same plasma levels of cyproterone acetate as 50 mg tablets orally administered 4 to 8 times a day (200–400 mg/day) [205,206]. In other words, one injection of Androcur Depot® (300 mg) is only 21% of the minimal oral dose (200 mg × 7 days) required for weekly management of prostatic cancer.

3.2.2. Clopixol Depot®

Clopixol Depot® is an oil-based formulation of zuclopenthixol decanoate, a neuroleptic agent, composed of Viscoleo® a medium chain triglycerides/miglyols. Clopixol Depot® is indicated for maintenance treatment of schizophrenia [207]. It is administered intramuscularly at the dose of 200–400 mg every 2–4 weeks, depending on disease evolution and patient tolerance. As a long-acting injectable formulation, Clopixol Depot® administered every two weeks (72 mg/2 weeks) exhibited sustained zuclopenthixol serum levels that were in the same range as those observed with oral administrations of pure zuclopenthixol 4–30 mg on daily basis [208]. Javed et al. [209] reported a significant reduction in self-harming behavior of a 32-years old woman following fortnight IM injection of Clopixol Depot® 400 mg.

3.2.3. Delatestryl®

Delatestryl® is an injectable oil-based solution of testosterone enanthate, a testosterone prodrug dissolved in sesame oil. Delatestryl® is intended for the treatment of hormone deficiency (male hypogonadism) [210], but some clinicians prefer using weekly SC injections of 50 mg [211]. A 24-week multicenter, randomized, parallel-group study by Dobs et al. [212] compared biweekly IM injection of Delatestryl® 200 mg with nightly topical application of a testosterone-based transdermal gel 2.5 mg (Androderm®). It was found that the two treatments were efficacies in replacing testosterone in hypogonadal men [212]. However, 60% of patients reported skin irritation with topical Androderm® whereas IM injection of LAI formulation exhibited 33% local reaction. But, unwanted increase in haematocrit was higher for the IM group as compared to topically administered group (43 versus 15%) [212].

3.2.4. Fluanxol Depot®

Fluanxol Depot® is composed of decanoic ester of flupenthixol, a neuroleptic thioxanthene, dissolved in Viscoleo® for the treatment of schizophrenia. A comparative study revealed no difference between serum levels of flupenthixol following IM injections of 20 and 100 mg/mL [213]. The lack of correlation between depot concentration and therapeutic response cannot be explained by simple diffusion of lipophilic prodrug from oily depot to surrounding tissues. However, it is likely due to metabolic breakdown of the formulation that takes place in the local tissue or distribution of prodrug to blood circulation via lymphatic system and converting to active drug by chemical or enzymatic rout. This similarity in depot properties of the two formulations with different drug contents was supported by Kirk et al. [214], who also observed similar serum concentrations with IM injections of 15–300 mg to different individuals' groups (every 2, 3 and 4 weeks) for 4 months. It seemed that the administered dose was enough to reach the maximal plasma level of 6 ng/mL on day 4–7 upon injection. However, a significant difference was observed when comparing repeated daily oral administrations with weekly IM injections of flupenthixol decanoate. Oral administrations exhibited slow absorption, with quicker peak plasma concentrations (3–6 h) and shorter half-lives (19–39 h) than those of the IM injections, respectively 3–5 day and 3–8 days [215,216]. The intervention report by Mahapatra et al. [217] demonstrated no difference in clinical efficacy of flupenthixol decanoate IM depot in comparison with oral antipsychotics in schizophrenia patients. The study revealed similar outcome in terms of survival, global impression, relapse rate and leaving the study early.

3.2.5. Haldol Depot®

Haldol Depot® is an oil-based solution of haloperidol decanoate in sesame oil. Haldol Depot® is used for the management of psychotic disorders (e.g. Tourette's syndrome, Schizophrenia). The maximum plasma concentrations of haloperidol are obtained on around day 6 and its half-life is approximately 3 weeks [210]. Using a three-year

Table 4
Marketed oil-based long acting parenteral formulations.

Registered name	Drug	Manufacturer	Indication	Route of administration	Dosing interval (week)	logP	Water solubility (mg/mL)	Highest Dosage	Annual sale (Year 2019) M$
Androcur Depot®	Cyproterone acetate	Bayer	Cancer, Prostate, Other	IM	2	3.8	0.0010	100 mg/mL in 3 mL	Not found
Clopixol Depot®	Zuclopenthixol decanoate	H Lundbeck A/S	Schizophrenia, Maintenance	IM	4	7.4	0.0026	200 mg/mL in 10 mL	Not found
Delatestryl®	Testosterone enanthate	Valeant	Breast cancer and hypogonadism	IM	4	5.1	0.0004	200 mg/mL in 5 mL	2 (Year 2008)
Lyogen Depot®	Fluphenazine decanoate	H Lundbeck A/S	Psychotic Disorders, Other	IM	6	7.2	0.0002	25 mg/mL in 10 mL	Not found
Haldol Depot®	Haloperidol decanoate	Johnson & Johnson	Tourette's syndrome, Schizophrenia,	IM	3	7.2	0.0100	100 mg/mL in 1 mL	Not found
Fluanxol Depot®	Flupenthixol decanoate	H Lundbeck A/S	Schizophrenia, Maintenance	IM	4	7.2	0.0002	200 mg/mL in 1–5 mL	Not found
Makena®	17 Alpha-hydroxyprogesterone caproate	Lumara Health	Preterm Birth	IM	1	5.8	0.0008	250 mg/mL in 1–5 mL	122
Faslodex®	Fulvestrant	AstraZeneca Plc	Breast cencer	IM	4	6.5	0.0067	50 mg/mL in 5 ml	892
Naldebain ER®	Dinalbuphine sebacate	Lumosa Therapeutics Co., Ltd.	Pain management	IM	1	5.3	0.0044	75 mg/mL in 2 mL	Not found

Solubility and logP values obtained from drug bank [88]; other data are from PharmaCircle® data base [14].

multisite study conducted at various systems of schizophrenia care in the United States, Shi et al. [218] demonstrated a clear difference between patients treated with haloperidol oral and those treated with haloperidol depot, in terms of patient's characteristics and drug use patterns. The parenteral formulation showed higher medication possession ratios, while oral administration necessitated an augmentation and prolongation of the antipsychotic regimen. These efficacy- and compliance-related observations were further confirmed by Zhu et al. [219]. These authors demonstrated that schizophrenia patients can tolerate Haldol Depot® for much longer periods than oral administration of haloperidol (which can be subject to discontinuation somewhere soon).

3.2.6. Lyogen Depot®

Lyogen Depot® is the ester of decanoic acid with fluphenazine (a piperazine phenothiazine), dissolved in sesame oil. Used for the treatment of chronic psychotic illness (schizophrenia). Following Lyogen Depot® administration, the peak plasma concentrations of fluphenazine are observed within 8–24 h, while the apparent half-life is about 14 days. The correlation between dose and plasma concentration was found to be higher for the depot formulation than after oral administration, which also exposes the drug to potential enzymatic deactivation in the gut and first-pass metabolism in the liver [220]. However, the rapid increase in plasma concentrations on day 1 of the first IM injection was associated with unwanted adverse effects (including extrapyramidal symptoms), which were observed only temporarily due to the subsequent decrease and maintenance in plasma concentrations [221].

3.2.7. Makena®

Makena® is a solution of 17 α-hydroxyprogesterone caproate (a synthetic progestin) in castor oil. It is administered for prevention of singleton spontaneous preterm birth in women. After IM injection, the plasma concentration of the drug reaches 27.8 ng/mL after 4.6 days, with an elimination half-life of 7.8 days [67]. A randomized and placebo-controlled trial investigated the efficacy of Makena®. The weekly IM administration of Makena® 250 mg for 16–20 weeks, in 463 women with high risk of spontaneous preterm deliveries, demonstrated the clinical long acting efficacy of the formulation and led to FDA-approval of Makena® [66].

3.2.8. Faslodex®

Faslodex® is fulvestrant injection in ethanol 96%, benzyl alcohol, benzyl benzoate and castor oil. Fulvestrant is an estrogen receptor antagonist, which can downregulate the estrogen receptor. Fulvestrant binds to the estrogen receptors in a competitive manner with a similar level of affinity to estradiol. Faslodex® is indicated for the treatment of breast cancer in postmenopausal women. Compared to IV or IM injection of fulvestrant, which is rapidly cleared at a rate of 10.5 mL plasma/min/kg (similar to hepatic blood flow), Faslodex® can maintain the plasma level of fulvestrant in a range of maximal 3-fold difference between peak and trough concentation 28 $\pm$ 3 days post dosing. In a phase III open-label, randomized, multicentre trial conducted over about 14.4 months, it was observed that monthly IM administrations of Faslodex® 250 mg/mL were as effective as daily oral administrations of anastrozole 1 mg in 451 postmenopausal women with hormone receptor-positive advanced breast cancer [222]. In fact, data revealed similar clinical benefits from the two formulations; with median times to progression of 5.5 and 5.1 months, and objective response rates of 20.7% and 15.7%, monthly fulvestrant and daily anastrozole, respectively.

3.2.9. Naldebain®

Naldebain® is a long acting formulation of nalbuphine, a semi-synthetic opioid, for pain management. Naldebain® is a diester of sebacic acid and nalbuphine that yields the prodrug dinalbuphine sebacate, which is slowly released into the blood stream and chemically and/or enzymatically hydrolyzed to the parent drug, which exerts its analgesic effect [223]. In an open-label phase I study, Naldebain® was IM injected to healthy volunteers by using 20 mg nalbuphine HCl as the reference (20 mg, IM, Bain® by Genovate Biotechnology Co., Ltd., Taiwan). The bioavailability of nalbuphine from Naldebain® relative to that from nalbuphine HCl was 85.4%. The mean absorption time of nalbuphine from Naldebain® was 145.2 h with a release duration of 6 days [224]. In the 6 center clinical studies, 221 patients received treatment by Naldebain® or placebo, and extended analgesic effects were shown by Naldebain®, with pain intensity significantly reduced through 48 h and 7 days after hemorrhoidectomy [225].

3.3. Marketed long acting drug products based on drug crystal suspensions

Poorly water-soluble drug particles (drug crystals) may arise from co-crystallization and/or particulate modification of drug substance. Owing to high drug concentrations commonly used (200–400 mg/g), the use of drug crystal technology enhances bioavailability and drug exposure irrespective of the administration route [76,226]. Despite the challenges associated with tissue exposure to pure drug particles

(which may cause local tissue damage in the case of irritative drugs such as non-steroidal anti-inflammatory drugs) [77], there have been several regulatory approvals of drug crystal suspensions for long-term parenteral applications. Marketed parenteral micro and nanocrystal suspensions are summarized in Table 5. Detailed descriptions of these products are provided in the following paragraphs.

3.3.1. Agofollin Depot®

Agofollin Depot® is a microcrystalline aqueous suspension of estradiol benzoate, an oestrogenic hormone synthesized by esterification of estradiol with benzoic acid. This ester derivative shows poor water solubility (2–4 mg/mL) and, as a prodrug, requires ester bond hydrolysis for pharmacological action, which explains its long-acting profile. Agofollin Depot® is supplied in ampoules containing 5 mg/mL for hormone therapy (i.e., hypoestrogenism) by SC injection on a weekly basis. Due to its depot effect, SC administration of estradiol benzoate 1 mg/week for 4 weeks was effective in inducing significant changes in the bone blood flow and mineral content of the tibia in an in vivo study on rats [227]. Similar results were obtained after SC administration of Agofollin Depot® at the dose of 5 mg/kg body weight once a week [228,229]. Agofollin Depot® was also IM administered at different doses. For example, IM injection of 10 mg/kg body weight in mice twice a week was used for regulation of both serum leptin levels [230] and anterior pituitary prolactin levels which was also achieved by IM injection of 1 mg twice a week in rats [231].

3.3.2. Aristada® and Aristada Initio®

Aristada® and Aristada Initio® are injectable suspensions for IM use, both delivering aripiprazole lauroxil, an atypical antipsychotic, for the management of schizophrenia in adults. Aristada Initio® (675 mg dose) is used as initial regimen in Aristada® based therapy in combination with oral aripiprazole (30 mg dose), in conjunction with the first Aristada® injection [232,233]. Aripiprazole lauroxil is a prodrug of aripiprazole, which has a lower aqueous solubility than aripiprazole (0.000237 and 0.00777 mg/mL, respectively) and allows the preparation of a crystal suspension. After administration, the aripiprazole lauroxil crystal suspension forms a local depot, resulting in sustained release of aripiprazole lauroxil over 4–8 weeks. The prodrug aripiprazole lauroxil is possibly first converted into *N*-hydromethyl apripiprazole by enzyme-catalyzed hydrolysis and subsequently it is chemically hydrolysed into aripiprazole. Aristada® and Aristada Initio® are not exchangeable because they have different PK profiles in vivo. This difference in PK kinetics is likely caused by the smaller particle size of Aristada Initio® suspension, which allows for quicker dissolution and faster achievement of desirable aripiprazole levels [232–234]. The clinical efficacy and safety of aripiprazole lauroxil depots has been demonstrated in randomized, double-blind, placebo-controlled trials in schizophrenia or schizoaffective disorder patients [234,235]. For instance, the clinical study by Meltzer et al. reported significant improvements in the positive and negative syndrome scale from day 8 to 85 following gluteal monthly administration of 441–882 mg of aripiprazole lauroxil to 623 patients with acute exacerbation of schizophrenia [234].

3.3.3. Betason L.A®

Betason L.A® is a long-acting injectable suspension of betamethasone, an anti-inflammatory corticosteroid agent. Betason L.A® is supplied as a dual acting formulation in 1 mL ampoules containing betamethasone acetate 3 mg and betamethasone (as disodium phosphate) 3 mg. Owing to the anti-inflammatory and immunosuppressive activities of betamethasone, Betason L.A® is used for multiple indications, such as inflammatory or allergic reactions, rheumatic disorders and for neoplastic diseases as a palliative treatment. Depending on the indications, the administration of Betason L.A® is done through intramuscular, intra-articular, intrabursal or intradermal injections. A pharmacokinetic study by Salem et al. [62] elucidated the controlled release capabilities of this dual-acting suspension upon IM injection into healthy human volunteers. The observed pharmacokinetic profiles demonstrated the prodrug nature of hydrophobic betamethasone (acetate ester), which is responsible for extended release characteristics of the formulation while the soluble betamethasone (phosphate ester) releases fast to achieve prompt onset of activity. A double-blind trial of intra-articular injections of betamethasone phosphate/betamethasone

Table 5
Marketed long-acting parenteral suspensions.

Registered name	Drug	Manufacturer	Indication	Route of administration	Dosing interval (week)	logP	Water solubility (mg/mL)	Highest Doseage (mg/mL)	Annual sale (year 2019) M$
Agofollin Depot®	Estradiol benzoate	Biotika Bohemia	Hypoestrogenism	SC	1	4.5	2–4	5 mg/mL in 2 mL	
Aristada® and Aristada Initio™	Aripiprazole lauroxil	Alkermes	Schizophrenia	IM	4–8	7.9	0.0002	275.83 mg/mL in 2.4 mL	189
Betason L.A®	Betamethasone	Caspian Tamin Pharmaceutical Co.	Inflammatory & allergic states	IM, intra-articular, intrabursal or intradermal	2	1.8	0.066	6 mg/ml in 1 mL	Not found
Bicillin® L-A	Penicillin G benzathine	Pfizer	Syphilis, Prophylaxis	IM	4	1.9	0.285	2,400,000 IU in 4 mL	59 (Year 2007)
Depo-Medrol/Lidocaine®	Methylprednisolone acetate/lidocaine hydrochloride	Pfizer	Epicondylitis, Others	intra−/peri-articular and intra-bursal	1	2.6	0.019	10 mg/mL lidocaine hydrochloride/40 mg/mL methylprednisolone acetate in 1–5 mL	469
Depo-subQ Provera 104® and Depo-Provera	Medroxyprogesterone acetate	Pfizer	Contraception & Endometriosis	IM	14	4.1	0.001	160 mg/mL in 0.65 mL	127 (Year 2016)
Invega Sustenna® and Invega Trinza®	Paliperidone palmitate	Janssen Pharmaceuticals	Schizophrenia	IM	4 and 14	8.1	0.007	312 mg/mL in 0.875–2.625 mL	3330
Kenalog®	Triamcinolone acetonide	Bristol-Myers Squibb	Arthritis, inflammatory diseases	IM, intravitreal	1	2.5	0.04	80 mg/mL in 0.0625–2.5 mL	Not found
Zyprexa® Relprevv®	Olanzapine pamoate	Eli Lilly and_Co	Schizophrenia	IM	4	4.6	0.004	405 mg in 1–2.7 mL	419

Solubility and logP values obtained from drug bank [88]; other data are from PharmaCircle® data base [14].

acetate suspension demonstrated an average duration of about 14 days for symptoms of pain relief in patients suffering from rheumatoid inflammations [236].

3.3.4. Bicillin® L-A

Bicillin® L-A is an aqueous suspension of penicillin G benzathine (600,000 units per 1 mL). Penicillin G benzathine is a practically insoluble product, formed by co-crystallization of 2 molecules of penicillin G with one molecule of benzathine. Bicillin® L-A exhibits long-lasting antibacterial effects due to slow dissolution of penicillin molecules from the almost insoluble co-crystals. Bicillin® L-A 1.44 g (2.4 million units) is administered monthly by IM injection for the management of primary or late syphilis (as a single immediate does or in three doses, respectively). Bicillin® L-A is also used for the treatment and prophylaxis of yaws and group A streptococcal pharyngitis associated with rheumatic fever and rheumatic heart disease. The doses administered for these indications are 450 mg (0.6 million units) and 900 mg (1.2 million units) for children and adults, respectively [85].

3.3.5. Depo-Medrol/Lidocaine®

Depo-Medrol/Lidocaine® is an injectable suspension containing methylprednisolone acetate and lidocaine hydrochloride. Depo-Medrol/Lidocaine® is a LAI formulation intended for use in inflammatory or rheumatic conditions requiring local glucocorticoid effects. Both doses (0.1–2 mL) and parenteral routes of administration vary depending on the localization of inflammation or rheumatism. When needed, Depo-Medrol/Lidocaine® is injected weekly via intra−/peri-articular and intra-bursal routes or into the tendon sheath accordingly. Although Depo-Medrol/Lidocaine® is a reputed long-acting formulation for localized anti-inflammatory or anti-rheumatic management, there have been several cases of anaphylaxis following its intra-articular injection [237,238]. The allergic reaction after injection can be caused by sensitivity to the drug itself or excipients such carboxymethylcellulose or less frequently polyethylene glycol [237], therefore further investigations are needed to understand the cause of allergic reaction to ensure safe use of Depo-Medrol/Lidocaine®.

3.3.6. Depo-subQ Provera 104®

Depo-subQ Provera 104® is a contraceptive formulation containing medroxyprogesterone acetate 104 mg/0.65 mL presented in a sterile prefilled and mono-dose injection system, called Uniject®. Depo-subQ Provera 104® was developed from its parent formulation, namely Depo-Provera®, which was a 150 mg/mL solution of medroxyprogesterone acetate used for IM contraception at the same dosing frequency (every three months). Apart from convenience and easy administration, the use of SC injection (Depo-subQ Provera 104®) offers several advantages including administration of only medroxyprogesterone acetate 104 mg (instead 150 mg by IM) and reduced peak plasma concentrations. In comparative studies between Depo-Provera® and Depo-subQ Provera 104®, the later demonstrated better pharmacokinetic characteristics, including much stable sustained plasma levels of the drug, as well as higher adherence and acceptability by the patients [239–245].

3.3.7. Invega Trinza® and Invega Sustenna®

Invega Trinza® is a sterile nanosuspension of paliperidone palmitate. The first registered paliperidone palmitate was Invega Sustenna®, a dose of 150 mg/human that shows one month release as compared to Invega Trinza® with a dose of 525 mg/human that is administered every three months [86]. The dose range for one-month injections is 50, 75, 100, or 150 mg/human whereas the dose range for three-month injections is 175, 263, 350, or 525 mg/human. Nanocrystal suspensions enables easy injection of high concentrated suspensions e.g., in case of Invega Trinza® 525 mg drug is injected as single dose. Noteworthy, paliperidone palmitate is a prodrug synthesized by esterification of paliperidone with palmitic acid and particulate modification (nanosizing of the insoluble ester particles using nanocrystal technology, wet media milling). Due to the limited solubility of paliperidone palmitate nanocrystals and the necessity for ester bond hydrolysis (to free the water soluble paliperidone), both the Invega Trinza® and Invega Sustenna® depots exhibit sustained release following IM injection [87]. The time interval for Invega Trinza® administration is 14 weeks for long-term management of symptomatic schizophrenia, which is recommended only after at least 4-months treatment with Invega Sustenna® on a monthly basis [86]. Following IM administration, the plasma concentration of the active metabolite (paliperidone, which is 9-hydroxy-risperidone) is detectable after 1 day, and its half-life is 25–49 days [246], which results in a long-lasting pharmacological action. This extended release profile led to better tolerability, safety, convenience and compliance of antipsychotic therapy, in comparison with oral administration [247].

3.3.8. Kenalog®

Kenalog® is an aqueous suspension of triamcinolone acetonide, a poorly water-soluble derivative of triamcinolone, an anti-inflammatory drug. When compared to injectable triamcinolone solution in a clinical study, triamcinolone acetonide LAI was associated with less blood glucose elevation in patients with type-2 diabetes mellitus that were treated for knee osteoarthritis as corticosteroids are known to increase blood glucose. Long acting triamcinolone acetonide resulted in lower peak plasma levels and lower systemic exposure compared to standard triamcinolone [248]. Similar systemic exposure of both triamcinolone types was observed for patients with hip osteoarthritis [249]. Kenalog® is not only used for the management of osteoarthritis; it is also administered via intravitreal injection for treating vitreoretinal diseases such as refractory uveitis, diabetic retinopathy, retinal vein occlusion, macular edema and degeneration. Despite the clinical successes reported, there have been several safety issues related to intravitreal administration of Kenalog® when compared with preservative-free formulations of triamcinolone acetonide (e.g. Trivaris®) [191]. The administration of Kenalog® was accompanied with retinal toxicity after 14 days, while triamcinolone acetonide suspended in non-preserved saline solution showed no toxicity after 3 months. Based on this observation, Lang et al. [250] suggested that the Kenalog® related retinotoxicity could be due to one of its excipients, probably benzyl alcohol. This was supported by Fong et al. [251], who observed much higher endophthalmitis incidence with Kenalog® (benzyl alcohol 1.5%) than Kenacort-A (benzyl alcohol 1.0%). Nevertheless, it must be mentioned that other factors such as particle size and shape, suspension concentration, volume of injection may impact local tolerability of the formulation. Therefore, further investigations led to revision of the composition of Kenalog® and development of preservative-free formulations, such as Trivaris®.

3.3.9. Zyprexa® Relprevv®

Zyprexa® Relprevv® is composed of microcrystalline powder of olanzapine pamoate monohydrate for reconstitution. Upon reconstitution with its diluent, Zyprexa® Relprevv® produces a suspension that remains homogeneously dispersed for 24 h. The suspended particles exhibit poor water solubility due to the hydrophobic nature of the prodrug/derivative (olanzapine pamoate), the microcrystalline salt of olanzapine with pamoic acid. Following IM injection, the driving forces for the release of the pharmacologically active drug (olanzapine) from the depot include microcrystals dissolution of the salt into native olanzapine and pamoic acid [246]. Since these processes occur slowly, a single dose of Zyprexa® Relprevv® achieves sustained release of olanzapine over 4 weeks and maintains plasma concentrations within the same therapeutic window as daily oral administrations [252]. Zyprexa® Relprevv® is used for the treatment of schizophrenia at the dose of 150–300 mg every 2–4 weeks or 300–405 mg every 4 weeks [253].

4. Discussion and perspectives

The significance of LAI as a means to prolong the action of drugs in the body is well-documented [7,8,254,255]. These delivery systems have a big impact on pharmaceutical market with sale of approximately 16,940 M$ in 2019 [14]. To date, the Food and Drug Administration (FDA) has approved about 48 brand-name medicines based on biodegradable LAI delivery systems including PLGA MPs, implants, non-PLGA extended release depots, crystal suspensions and oil-based formulations of lipophilic prodrugs [256]. Table 6 summarizes the strengths and weaknesses of different delivery systems that are presented and discussed in this review.

In the past few decades, many LAI technologies have found their path into the clinic. Nevertheless, the development of long-acting injectable products remains challenging and usually takes long time, that is why they are usually introduced as life-cycle management projects of existing immediate release therapies. Therefore, the following paragraphs highlight some of challenges in the development of LAI systems in conjunction with the drug attributes (e.g., potency, therapeutic index and stability), manufacturing and sterilization protocols, syringeability/injectability, in vitro/in vivo release and in vivo local tolerability.

4.1. Drug substance attributes for LAI development

For LAI formulation, a drug candidate needs to be highly potent with slow plasma clearance to enable lower frequency of dosing. In early phase of drug discovery, proper tool molecules (drug like molecules) that are potent in vitro and can be produced in sufficient quantities are usually selected for in vivo experiments. They are utilized to understand the extent and duration of in vivo target engagement required for efficacy, this is first step to design a potent drug molecule [257]. For preparation of LAI, not only a drug candidate needs to be potent but also needs to be loaded into a carrier system (e.g., PLGA MPs and implants) with high loading capacity to supply the dose required for an extended period (i.e., weeks to months), since the volume of injection is often limited depending on the site of injection.

Small drug molecules offer great opportunities to manipulate and tailor their physicochemical properties. It is possible to design molecules that are suited for already established LAI technologies (e.g. encapsulation into PLGA MPs, oil/lipid-based formulations, or drug substance micro- or nano-suspensions), in parallel to lead optimization in the research phase. As an example, low aqueous solubility can be engineered in small molecules design by providing high crystal lattice energy and/or poor hydration in aqueous environment. The former category usually encompasses rigid and flat molecular structures that pack densely in the crystals and provide strong intermolecular bonds via van der Waals interaction, π — π stacking, and hydrogen bonding, while the latter class of poorly hydrated compounds commonly features high lipophilicity [258–260]. A recent molecular study has established the correlation between the number of aromatic rings in a drug molecule and its physicochemical properties [261]; it was demonstrated that even within a defined lipophilicity range, increased number of aromatic rings leads to decreased aqueous solubility. A medicinal chemist can therefore build on distinct molecular features that drive the physicochemical profile towards a desirable space. Early investigations on solid-state properties, such as crystallinity, melting characteristics, polymorphism landscape, and physicochemical stability during milling processes, are instrumental to compound triaging. For example, thermodynamic solubility should be determined from a defined high-melting crystalline form in a biorelevant medium to select suitable candidates for the generation of injectable micro- or nano-suspension depots. A drug that is released from a depot carrier primarily via passive diffusion can be optimized towards low partitioning from the depot phase to the (aqueous) tissue compartments, or by implementing high diffusion barriers (e.g. via large molecular size). Finally, certain manufacturing processes, e.g. oil-in-water emulsification for the preparation of PLGA microparticles, may require sufficient drug solubility in specific suitable organic excipients.

The conventional early drug discovery toolbox must be therefore expanded by a solid set of physicochemical assays, including differential scan calorimetry, X-ray powder diffraction, granulometry, and thermodynamic solubility in customized media. Concerning the labor-intensive process of physicochemical characterization, it is paramount important to start with the need to generate reproducible crystallization protocols in the chemistry lab and culminate in the delivery of a stable and well-defined injectable suspension to the in vivo pharmacology group. It is imperative that selected candidates show exquisite potency in relevant biological assays. This prerequisite will minimize the burden of injectable dose and volume, which can both contribute to the safety and tolerability of the respective application. Fig. 8 illustrates how different pharmaceutical research disciplines can act together in an exemplary flowchart to ensure an optimal combination of drug molecule and LAI formulation that can be applied in vivo.

Table 6
Strengths and weaknesses of established LAI delivery systems.

Formulation	Strength	Weakness
PLGA-based MPs	• Drug release can be modulated (e.g., from weeks to months) • In principle it is possible to load both hydrophilic and hydrophobic drugs • Smooth and soft surface → low risk of mechanical tissue irritation	• Gamma sterilization or aseptic production is required • Not simple and rather expensive • High drug loading is challenging, ˃ 50% of formulation is polymer • Difficult to scale up
Preformed implants	• Drug release can be modulated to some extent • In principle it is possible to load both hydrophilic and hydrophobic drugs	• Gamma sterilization or aseptic production is required • Not simple and rather expensive • Invasive (in some cases surgical procedures are required) • High drug loading is challenging ˃ 50% of formulation is polymer
In situ forming implants	• Drug release can be modulated to some extent • Simple and cost-effective preparation methods • Filtration sterilization • Easy scale up	• Limitation for using organic solvents • Limited options for tailoring drug release • High drug loading is challenging ˃ 50% of formulation is polymer
Non-PLGA based systems	• Polymers such as poly (orthoester) polymers that degrade via surface erosion → acid degradation in not accumulating in the delivery systems → compatible with acid sensitive drugs	• Gamma sterilization or aseptic production is required • Not simple and rather expensive • Only few marketed products → limited knowledge available about versatility of this polymers
Crystal suspensions	• Simple and cost-effective preparation methods • Highest drug loaded carrier system → allowing high drug dosing per volume	• Rough particle surface → high risk of mechanical tissue irritation • Micronization is required • Gamma, heat sterilization or aseptic manufacturing is required • Limited options for tailoring drug release e.g., by particle size tuning
Oil-based formulations	• Simple and cost-effective preparation methods • Filtration sterilization • Easy scale up	• Not possible for many drug molecules to from prodrug (only hydrophobic drug with functional groups) • Limited options for tailoring drug release

Further, an evaluation of successfully marketed injectable depot formulations shows that most of the loaded drugs are highly lipophilic. Although poorly reputed for oral route of administration, high lipophilicity appears to be beneficial for LAI systems. As shown in Tables 1–5 and summarized in Fig. 9, most of the marketed LAI drugs are poorly water-soluble. Out of 48-marketed drug products presented in this review, only four formulations contain drugs that are water-soluble. Therefore, we foresee drug lipophilicity not as a limitation but rather as an opportunity for the development of LAI formulations.

For LAI formulation, a drug candidate needs to have broad therapeutic index to achieve efficacious concentrations without causing toxicity due to burst release or being non-efficacious due to slow release phase. Zero order drug release kinetics is the most desired release mechanism, but it is not easily achievable by current marketed delivery systems such as biodegradable MPs/implants or drug crystals suspensions. In zero order pattern, the drug is released at a constant rate for an extended period and the release kinetics is independent of its initial concentration. First order drug release is based on simple diffusion, dependent on the initial drug concentration according to the Fick's second law. If the therapeutic window is narrow, zero order release is a key to ensuring the drug concentration remains within the therapeutic window for an extended time. However, for drug molecules that have broad therapeutic window first order drug release remains a good alternative.

Physicochemical stability of drug candidate for the development of LAI formulation is very important, as most often manufacturing of such formulations involves harsh conditions such as high temperature, dissolution in aqueous and/or organic solvents, chemical drug interactions with the carrier components such as polymers (e.g., acylation). The FDA has approved a limited number of formulations based on biomaterials (such as PLGA and PEG) available for development of LAI systems, which makes it difficult to find suitable carrier for delivering delicate drug candidates such as macromolecular therapeutics. The drug and LAI formulation needs to be stable upon terminal sterilization (e.g., gamma, x-ray, e-beam, heat etc.), as discussed in the following paragraph.

4.2. Manufacturing processes for LAI development

Complex manufacturing processes are part of the factors that may hinder the development of LAI formulation. For example, the development of PLGA MPs involves extensive process development

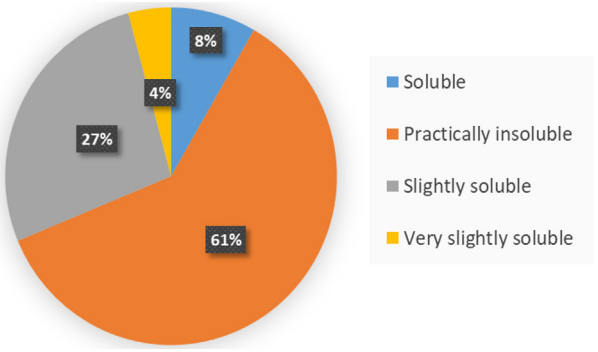

Fig. 9. Solubility of drug molecules that have been used in clinically established LAI formulations. Only 8% of drug molecules in marketed LAI formulations are water-soluble based on USP solubility definition (i.e., 61% practically insoluble: <0.1 mg/mL, 27% slightly soluble: 1–10 mg/mL, 8% soluble: 33–100 mg/mL and 4% very slightly soluble: 0.1–1 mg/mL).

and scale-up from lab, pilot plant to manufacturing plant. For successful scale-up, close collaboration and smooth handover between formulation scientists and pharmaceutical engineers is required. Moreover, early investment in scalable equipment (from lab scale through full production scale), implementation of process analytical technology (PAT) tools for monitoring manufacturing of drug product and early identification of critical process parameters make a vital combination for successful scale up manufacturing. According to pharmacopeia parenteral drug delivery systems must be produced with high quality, purity, and sterility, including being essentially free from foreign visible particles. Generally, drug product manufacturing to this standard is very challenging and about 20% of drug product batch recalls is due to foreign visible particles contamination [262]. In general, standard parenteral solutions are sterile filtrated and have low risk of foreign particle contamination. However, parenteral suspensions, MPs and implants cannot be sterile filtered. Therefore, strategies to control the level of foreign particles for drug substance and in drug product manufacturing processes must be implemented. Considering the above-mentioned parameters, when compared to standard parenteral formulations, the development of LAI formulations is more complex, time consuming and expensive.

Preparation of parenteral suspension or implants under aseptic conditions has high production costs, especially for early stage development of drug products. Therefore, terminal sterilization is preferred to ensure sterility of the final drug product [263–266]. The commonly

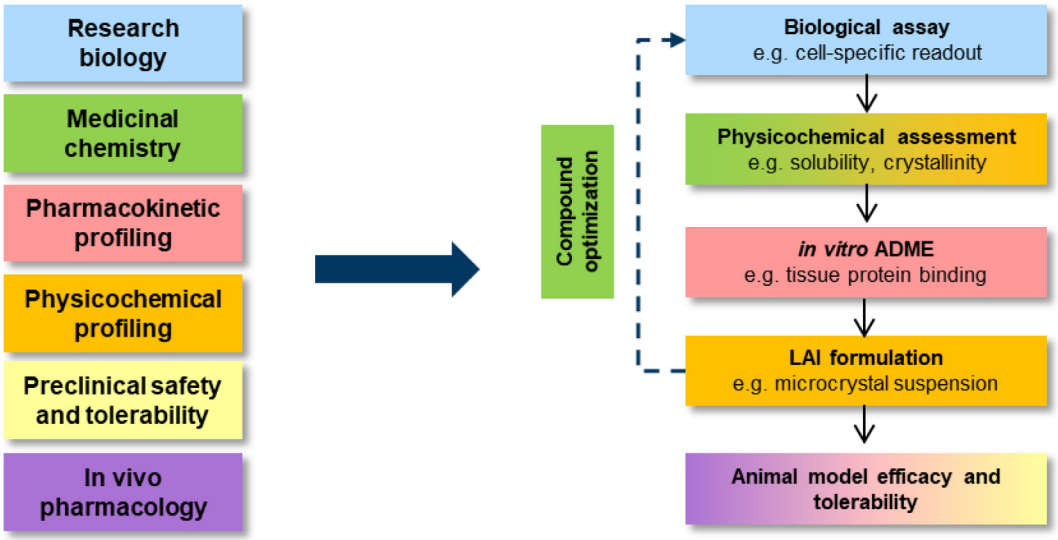

Fig. 8. The interplay of pharmaceutical research disciplines in the early discovery of candidates for LAI formulation development.

employed terminal sterilization methods are by steam, dry heat, ethylene oxide gas, x-ray, electron beam and γ- irradiation [267–269]. Among these methods, dry heat and steam sterilization are carried out at high temperature (e.g., 121 °C) and therefore they are not suitable for PLGA microparticles or implants as the glass transition of PLGA polymers is often <50 °C, but they may be used for drug crystal suspension. Ethylene oxide may release toxic residues; therefore, it is not an option for terminal sterilization of drug products [266,270–272]. Thus, γ-irradiation and x-ray irradiation are preferred methods for terminal sterilization of PLGA MPs and implants due to their high efficiency and low thermal effects. The γ-irradiation can efficiently treat a wide range of drug products composed of diverse materials with different densities. X-ray irradiation is as efficient as γ-irradiation in addition to reducing processing times and potentially lower damage to the products. Electron beam on the other hand has low penetrating effect and it is not a preferred option for the treatment of parenteral drug product, but single used medical devices [273]. Although γ-irradiation is widely used for terminal sterilization of parenteral products, including PLGA microparticles and implants, it accelerates the cleavage of polymer ester bonds and generates free radical and crosslinking [274,275]. Polymer chain cleavage due to sterilization can accelerate drug burst release. However, the impact of standard irradiation dose (i.e., 25 kGy) on molecular weight reduction and consequently drug release is usually negligible. Nonetheless, some drug molecules are not stable against irradiation; therefore, it is important to evaluate the impact of irradiation type/dose on the formulation in early stage of development.

4.3. Syringeability and injectability of LAI formulations

Efficient injection of parenteral formulations through conventional needles is crucial in clinical translation of LAI. The ability of an injectable formulation to transfer from a vial through a needle into a syringe is called syringeability, whereas the performance of a formulation while being injected into the body is called injectability [276–278]. Particle size, shape, density, viscosity and suspension concentration are important factors regarding the syringeability and therefore injectability of parenteral formulations [279–281]. Large particles or aggregates in the formulation often cause needle clogging. The needle clogging can also occur due to bridging effect of the microspheres suspension with high polydispersity while passing through the needle. Novel technologies such as membrane emulsification and/or microfluidics enable production of mono-sized microspheres that are easily injectable through smaller needle size as compared to polydisperse particles. Smaller needle size reduces the local tissue damage and associated pain, enhancing patient compliance [282]. Recently, Robert Langer and his colleagues [283] demonstrated that the geometry of the syringe and needle plays an important role in injectability of the microparticle formulation. Using a computational fluid dynamics (CFD) and experimental results, an injectable device was designed to maximize the injectability in both in vitro and in vivo models. The custom-made syringe and needle enabled a six-fold increase in injectability of PLGA MPs as compared to commercial syringes with the same needle gauge. This study demonstrated a framework for optimum injection of MPs and microcrystals-based drug delivery systems.

4.4. In vitro and in vivo release from LAI formulations

In vitro characterization of drug release is one of the most important tests during early and late phase LAI development. A bio-indicative in vitro release set up can guide the development team in terms of formulation selection and process optimization; batch-to-batch quality control evaluation can serve as surrogate for bioequivalence trials at later stage if in vitro-in vivo correlation (IVIVC) is established. As the LAI field is still at the emerging stage, there is no official guideline or requirement about in vitro release set up for specific type of delivery system. Recently, USP has published a draft informational chapter on "*In vitro* release test methods for parenteral drug preparations", discussing methods currently used for in vitro testing of injectable delivery systems [284]. Different experimental conditions (e.g., type of instrument, release medium composition and temperature) exhibit significant impact on the release profile. Therefore, key product attributes [285], release mechanism (often multi-phased process e.g., burst, lag phase and steady release) [45] and environment that influence drug release in vivo must be understood for successful in vitro method development [286,287]. Wide variety of techniques are utilized for release measurements, with continuous flow (USP IV) and sample-and-separate approach being the most common ones. Sample-and-separate methodology is convenient as it can be scaled-down to small volumes at early stage of development and is applicable for particulate-based delivery systems [288,289]. USP IV is a compendial apparatus offering defined hydrodynamics, prevention of particle agglomeration by application of glass beads and can be adapted for dialysis cell, which makes it suitable for evaluation of oil-based and nano-sized delivery systems [290–292]. USP II apparatus with modifications designed especially for designated delivery system are also reported [293,294]. Release medium selection is another important parameter. Variants of simulated biological fluids, with addition of proteins or enzymes representing different tissues, are reported in the literature [295,296]. For analytical simplicity and reproducibility, simple neutral buffers (pH 7.4) are the most used. As majority of LAI drugs have rather low aqueous solubility, manipulation with pH, osmolality, temperature and addition of surfactants are frequently required to achieve drug dissolution in reasonable time-frame [297–299]. When accelerating drug release in vitro, it is essential not to alter release mechanism, so that obtained profiles are still representation of real-time in vivo release. As variations of medium components often cause changes in release mechanism (e.g., polymer degradation in PLGA-based delivery systems), additions of surfactants are preferred options for in vitro solubility increase. The ultimate goal of the in vitro release method is to confirm the biorelevance and later establishment of IVIVC. IVIVC is mathematical correlation between in vitro property of the drug (e.g., in vitro release profile) and in vivo response (e.g., C_{max} or AUC). In addition to complex in vitro release mechanism of delivery systems, in vivo environment in terms of (patho)physiology, metabolism and host response at specific administration site, pose another challenge in successful IVIVC establishment [300]. Hand in hand with physiologically based pharmacokinetic (PBPK) modeling, IVIVC is still emerging with successful correlations established based on animal data. The importance of understanding in vivo environment and host response after intra muscular injection of crystalline suspension was investigated by Darville et al. [301,302]. They discovered key role of macrophages surrounding suspension depot and acting as additional phase/compartment of overall drug release/absorption. These types of findings can help design meaningful in vitro release setup that can serve as basis for IVIVC establishment. For PLGA-based systems, animal-based IVIVCs are published for risperidone and leuprolide acetate microparticles [303] based on USP IV and sample-and-separate approach, respectively. For the oil-based depot formulations, no information about IVIVC attempts are publicly available. The reported established IVIVCs are of great importance for formulation and physiology understanding. However, translation between species remains a big gap. The published cases can serve as guidance during formulation development, nevertheless, for establishment of IVIVC as substitution of in vivo studies (bioequivalence, post approval changes), more understanding and human data must be provided and elaborated. Although much research is being conducted, the long acting parenteral area is still at the emerging stage, and available knowledge and understanding are far from oral products, as most frequently used products. Further improvements in terms of in silico and in vitro evaluation of LAI is needed to govern better understanding of delivery system and faster LAI development.

4.5. In vivo behavior and tolerance of LAI formulations

For successful LAI development, it is important to understand the in vivo behavior of delivery system upon administration [304–306]. The administration of LAI products leads to a cascade of events involving the innate and adaptive immune responses with the ultimate goal to repair tissue injury (e.g., from injection or surgical implantation of the degradable biomaterial) and to remove the foreign material by foreign body response (FBR). For biodegradable material, Anderson and Shives [307] have described the process in three phases, from an acute initial response (phase 1) to more chronic responses of particle uptake and breakdown (phase 2 &3). FBR is a complex dynamic process, which continues to be of interest in order to refine, optimize and control biocompatibility, degradation and rejection of implants and biomaterials. In fact, immediately after tissue injury, proteins release from blood and extracellular matrix (ECM) triggers a signaling cascade (including the coagulation system, cytokines and danger signals), leading to acute inflammation with neutrophils (polymorphonuclear leukocytes, PMNs) as one dominant cell type involved. PMNs secrete additional enzymes, ROS and cytokines to recruit more immune cells, including lymphocytes, plasma cells, monocytes and macrophages. Over time, when initial tissue damage is repaired, the process becomes more chronic, with macrophages as dominant cell type. In a dynamic and complex interplay, macrophage signaling will further recruit additional immune cells and more macrophages to boost phagocytosis for removal of the foreign material. Depending on the "digestibility" of the material and the nature of the elicited chronic inflammation, macrophage fusion to foreign body giant cells (FBGCs), activation of extracellular matrix and fibroblasts, granuloma and fibrous capsule formation may occur at the site of depot or implant. In some cases, the extent of the inflammatory or foreign body response may even lead to premature breakdown of the implant [308]. The benign outcome and time course of the FBR will mainly depend on degradability of the biomaterial and successful phagocytotic activity of macrophages and FBGCs. Poorly digestible (or even indigestible) materials may lead to increased formation of FBGCs with reduced capacity for phagocytosis, while secretion of enzymes (like acid hydrolase), reactive oxygen species (ROS) and protons is increased [309,310]. This phenomenon, referred to as "frustrated phagocytosis", may ultimately enable degradation and resorption of materials susceptible to these secretory products, and the FBR can resolve after full resorption [309,311]. Particles having sizes <5 μm are taken up easily by phagocytosis [312]; and therefore frequently linked to macrophage response, suggesting biodegradable materials of >10 μm size to be able to escape the phagocytosis and control inflammation [13]. However, this may only apply to spherical particles; since particle geometry and curvature, and tangent angle during macrophage surface receptor contact play an even more important role [313,314]. Additional properties (such as shape, scaffold [34] deformability, surface charge, polarity, hydrophilicity, opsonisation and the type of interaction with different macrophage surface receptors [315]) influence the elicited cytokine secretion to a more pro- or anti-inflammatory response with different macrophage phenotypes [34]. Increased attention to mechanistic understanding of phagocytosis and immunologic events of FBR has provided technological advances in biomedical applications [316] that will be crucial for future development of slow release injectable implants, devices, and cell-based therapies. The summary of long acting parenteral drug development steps is depicted in Fig. 10.

To wrap up this review, LAI formulations are more complex than standard injectable solutions and therefore often have longer development timelines. Nevertheless, they can be competitive due to noticeable clinical benefits and sustained sale over longer time since they are not easy to copy. Most importantly LAI formulations are crucial for the patient compliance in chronic diseases. As outlined above, the research team needs to work early on with the development team to design a drug molecule that is both therapeutically efficient and has suitable physicochemical characteristics to be formulated as LAI. In the past, pharmaceutical companies used to introduce LAI projects as life-cycle management projects of already existing immediate release therapies. But nowadays, the focus on the development of LAI has changed to early-on involvement of the research and development teams working closely to design an ideal drug molecule with suitable delivery system for LAI applications, a promising approach that can significantly shorten development timelines.

5. Conclusion

Long acting injectable formulations are developed to sustain the action of drugs in the body. Evaluation of marketed injectable depot shows that most of the formulated drugs are potent, physically and chemically stable with low water solubility and broad therapeutic window. To shorten the duration of drug product development and increase the chance of success in discovery projects, it is important to anticipate challenges such manufacturing issues (e.g., scale up production, sterilization, syringeability and injectability), IVIVC establishment, local tolerability and in vivo fate of the formulations. Furthermore, early on collaboration between research and development teams is required to design ideal drug molecules with suitable delivery systems.

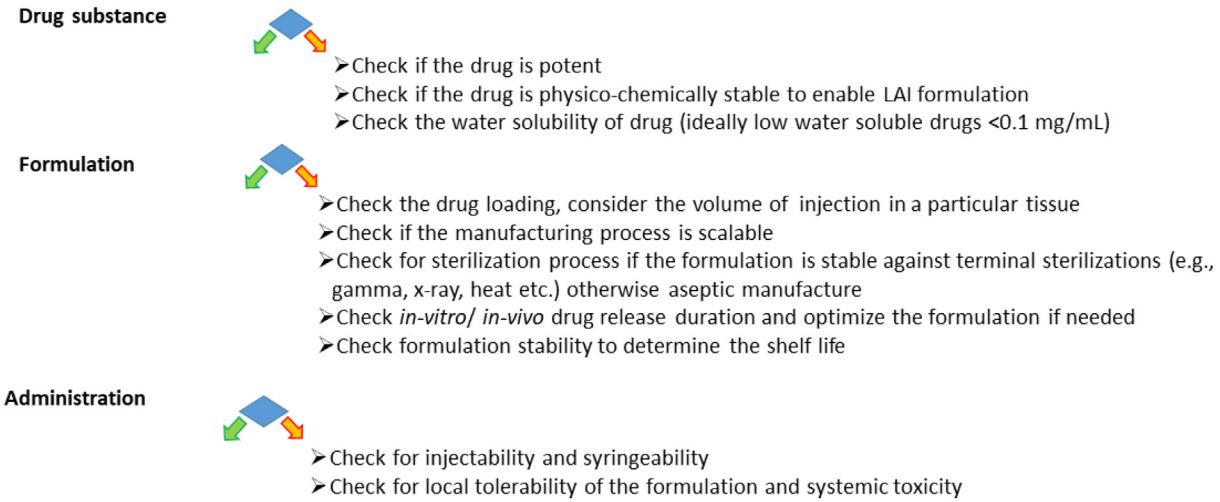

Fig. 10. The summary of important steps for LAI formulations development.

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