Injectable formulations of poly(lactic acid) and its copolymers in clinical use☆

Anjali Jain a, Konda Reddy Kunduru b, Arijit Basu b, Boaz Mizrahi c, Abraham J. Domb b,⁎, Wahid Khan a,⁎⁎

a Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad 500037, India
b School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem 91120, Israel
c Faculty of Biotechnology and Food Engineering, Technion, Haifa 32000, Israel

Abstract
Poly(lactic acid) and its copolymers have revolutionized the field of drug delivery due to their excellent biocompatibility and tunable physico-chemical properties. These copolymers have served the healthcare sector by contributing many products to combat various diseases and for biomedical applications. This article provides a comprehensive overview of clinically used products of poly(lactic acid) and its copolymers. Multi-dimension information covering product approval, formulation aspects and clinical status is described to provide a panoramic overview of each product. Moreover, leading patented technologies and various clinical trials on these products for different applications are included. This review focuses on marketed injectable formulations of PLA and its copolymers.

Keywords:
Poly(lactic acid)
PLA copolymers
Injectable depot
Microspheres
PLA clinical products

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☆ This review is part of the Advanced Drug Delivery Reviews theme issue on "PLA biodegradable polymers".
⁎ Correspondence to: A.J. Domb, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, and Jerusalem College of Engineering (JCE), Jerusalem 91120, Israel.
⁎⁎ Corresponding author.
E-mail addresses: avid@ekmd.huji.ac.il (A.J. Domb), wahid@niperhyd.ac.in (W. Khan).

http://dx.doi.org/10.1016/j.addr.2016.07.002
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1. Introduction

Emergence of controlled release drug delivery concept has revolutionized the pharmaceutical field. They offer consistent therapeutic drug concentration, abolishing the need of frequent dosing and associated toxicity issues. The concept made its way from bench to clinics after emanation of polymers, possessing inherent properties of release retardation with the added advantage of biodegradability and biocompatibility. Poly(lactic acid) (PLA) and its copolymers were widely explored in this arena due to their excellent biocompatibility, biodegradability, low immunogenicity and desired mechanical properties [1–3]. Among its copolymers, poly(lactic-co-glycolic acid) (PLGA) is acknowledged as the most attractive polymer due to its excellent biocompatibility as well as flexibility to modulate drug delivery features by varying compositions, molecular weights (MWs) and chemical structures [4,5]. Fig. 1A depicts the various delivery systems designed using PLA and its copolymers and their clinically approved products.

Initial development of PLA/PLGA delivery system started with small molecules when pharmaceutical companies began to investigate for the delivery aspects of luteinizing hormone-releasing hormone (LHRH) analogs. The first successful step in this direction was the introduction...
of Decapeptyl® to the European market in 1986 by Debiopharm group, for the treatment of prostate cancer. It was the first injectable, degradable microparticle depot system to obtain regulatory approval, and is still in the market. Later, Takeda-Abbott Products, a joint venture formed between Abbott Laboratories and Takeda Pharmaceuticals also developed a PLGA microsphere product for the delivery of a LHRH analog (leuprolide, Lupon Depot®) that was approved by the USFDA in 1989. Zoladex® was another product of LHRH analog (goserelin), approved in 1996. Later in 2000, Treistar® was approved by the USFDA for palliative treatment of advanced prostate cancer. In parallel, Supercur® and Suprapt®/Profact® and Endanotent® depot were approved in various countries. Elgard®, a PLA-LHRH solution in N-methyl pyrrolidone that forms in situ “implants” after subcutaneous (s.c.) or intramuscular (i.m.) injections of the formulations, was approved in 2002 for the treatment of prostate cancer [6,7]. Fig. 1B indicates the market approval timeline for various products of PLA and its copolymers.

Although, cancer was the most widely explored area in terms of clinically approved products of PLA and copolymer, PLA based products were also developed for other diseases (Fig. 1C). For psychotic disorders, the USFDA approved Resperidal®/Consta® in 2003. Vivitrol® was approved for the treatment of alcohol dependence and opioid dependence in 2006 and 2010 respectively. Periodontal disease treatment has benefited by PLA copolymers with the USFDA approval of Atridox® in 1998 and Arestin® in 2001. Atrisorb®, a biodegradable PLA based barrier membrane for guided tissue generation of periodontal tissue is also available in the market. PLA polymer marked its entry in the cosmetics field with the USFDA approval of Sculptura®, an esthetic formulation for the treatment of facial lipotrophy in 2004. Similarly, Sandostatin® LAR (USFDA approval in 1998), Somatuline® (USFDA approval in 2007) for the treatment of acromegaly and Nutropin® Depot (USFDA approval in 1999) for the treatment of growth hormone deficiency are some products for management of growth hormone related disease.

Another PLA copolymer of clinical importance is poly(ethylene glycol)-block-poly(ε,ε-lactide) (PLA–PEG), used widely in diblock and triblock forms. In diblock PLA–PEG formulations, PEG chains orient themselves toward the external aqueous phase to form micelles. These dangling chains act as a barrier for foreign molecules by virtue of hydration induced steric repulsion. These micelles significantly improve the solubility and stability of encapsulated hydrophobic molecules [8,9]. Genexol®-PM is a cremophor free, polymeric micelle based formulation of paclitaxel with amphiphilic diblock copolymer monomethoxy poly(ethylene glycol)-block-poly(ε,ε-lactide) for the treatment of advanced cancers [10]. Triblock polymers of PLA–PEG combination have been reported to exhibit temperature-induced spontaneous physical gelation. These polymers remain in sol form at room temperature due to dominance of hydrogen bond between hydrophilic PEG chains and water molecules in aqueous medium. At higher temperature, hydrophobic interactions among PLGA segments become stronger, resulting in gelation [11–13]. This temperature induced sol-gel transition was recognized under the name of ReGe® technology (described in detail in Section 3.2) and was utilized to design OncoGe™, a cremophor free, paclitaxel formulation of PLGA–PEG–PLGA copolymer for local tumor management. This review gives a concise picture of various PLA and its copolymer based products available in the market. Patented technologies behind these products and various clinical trials involving these products in combination with other agents/therapies are also covered.

2. Clinically available products

Comprehensive information related to clinically available products of PLA and its copolymer is provided in this section. Most of these products are available as implants and microspheres. A brief summary of these products and pharmacokinetic features are given in Tables 1 and 2 respectively.

2.1. Poly(lactic acid) (PLA)

2.1.1. Lupron Depot®

Lupron Depot®, a formulation containing leuprolide acetate/leuprolelin encapsulated PLGA microspheres, is among the initial products of polymer based controlled release system for peptide delivery. Takeda-Abbott Products, a joint venture formed between Abbott Laboratories and Takeda Pharmaceuticals in 1977, originally developed Lupron Depot®. Leuprolelin was approved in 1985 as s.c. injection. Later, the USFDA approved Lupron Depot® (7.5 mg/vial) in 1989 for the treatment of advanced prostate cancer. Subsequently, it was available in 22.5 mg/vial and 30 mg/vial for every 3 and 4 months

| Table 1 | Clinically used products of PLA and its copolymers. |
| --- | --- | --- | --- | --- |
| SN | Clinical products (approval year) | Active agent | Delivery system | Indication | Company |
| 3. | Atrisorb® | Doxycline | PLA resorbable membrane | Advanced prostate cancer | Takeda Pharmaceuticals, Abbvie Endocrine Inc. |
| 5. | Genexol®-PM Cyrimingo™ | Paclitaxel | PEG-PLA polymeric micelle | Cancer | BTC Plc. |
| 6. | OncoGe® (failed in phase II) | Paclitaxel | PLGA-PEG-PLGA sol-gel system | Local tumor management | Aifique Pharmaceuticals |
| 11. | Decapeptyl® | Tripotrenol | PLGA (injectable suspension) | Prostate cancer | Sanofi-Aventis |
| 15. | Enanotent® depot | Leuprolide acetate | PLGA based depot | Periopamental disease | Ora Pharma |
| 19. | Suprecur® | Buserelin acetate | PLGA microspheres | Growth hormone deficiency | Alkermes and Genentech |
Lupron Depot®

- Lupron Depot® is a leuprolin containing microsphere formulation, available in different dose strengths. Subcutaneous administration of 3.75, 7.5, 11.25, 15 and 30 mg depots resulted in mean peak plasma leuprolin concentrations (C_{max}) of 13.1, 20.8 to 21.8, 47.4, 54.5 and 53 μg/L, respectively within 1 to 3 h compared to s.c. injection of 1 mg dose non-depot formulation, resulting in 32 to 35 μg/L at 36 to 60 min.
- Sustained drug release from the PLGA microspheres maintained plasma concentrations between 0.4 and 1.4 μg/L over 28 days after single 3.75, 7.5 or 15 mg depot injection.
- Mean volume of distribution of leuprolin is 37.1 after a single subcutaneous injection of 1 mg, and 36, 33 and 27 L after depot administration of 3.75, 7.5 and 15 mg, respectively. An implant to deliver leuprolin for 12 months resulted in a steady mean leuprolin concentration of 0.93 μg/mL until week 52, suggesting zero-order drug release from the implant.

Risperdal® Consta®

- Risperdal® Consta® is a long acting depot formulation containing risperidone for the treatment of psychotic disorders.
- The pharmacokinetics of risperidone is linear in the dose range of 25–50 mg injected every 2 weeks. After a single intramuscular injection with Risperdal® Consta®, the release profile consists of a small initial release of risperidone (~1% of the dose), followed by a lag time of 3 weeks. The release of risperidone starts from week 3 onwards, maintained at steady state from 4 to 6 weeks, and subsides by week 7.
- After repeated i.m. injections of 25 or 50 mg Risperdal® Consta® every two weeks, median trough and peak plasma concentration of the active antipsychotic fraction fluctuated between 9.9–19.2 μg/mL and 17.9–45.5 μg/mL respectively. No accumulation of risperidone was observed during long-term use (12 months) in patients who were injected with 25–50 mg every two weeks.
- The volume of distribution is 1–2 L/kg. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone and its active metabolite are 90% and 77% respectively.

Vivitrol®

- Vivitrol® is an extended release naltrexone (XR-NTX) formulation to achieve continuous naltrexone (NTX) exposure for 1 month.
- The overall pharmacokinetic profile of naltrexone following administration of a Zoladex® 10.8 mg depot to patients with prostate cancer was determined. The initial release of naltrexone from the depot was relatively rapid resulting in a peak concentration at 2 h after dosing. C_{max} 8.85 ± 2.23 ng/mL, t_{max} 1.80 ± 0.34 h and elimination half-life 4.16 ± 1.12 h were observed, from day 4 until the end of the 12-week dosing interval, the sustained release of naltrexone from the depot produced reasonably stable systemic exposure.
- Administration of four Zoladex® 10.8 mg depots to patients with prostate cancer resulted in testosterone levels that were suppressed to and maintained within the range normally observed in surgically castrated men (0–1.73 nmol/L or 0–50 ng/dL), over the dosing interval in approximately 91% (145/160) of patients studied.

Trelstar®

- Trelstar®, a triptorelin pamoate containing depot formulation provides plasma concentrations of triptorelin over a period of 1 month following i.m. injection. The pharmacokinetic parameters following a single i.m. injection of 3.75 mg of Trelstar® depot to 20 healthy male volunteers indicated C_{max} 28.43 ± 7.31 ng/mL, t_{1/2} 1 h and AUC 223.15 ± 46.96 h ng/mL. The plasma concentration declined to 0.084 ng/mL at 4 weeks.

Sandostatin® LAR depot

- Sandostatin LAR is a long acting octreotide containing formulation for the treatment of acromegaly. Pharmacokinetic features, after a single i.m. injection of 380 mg of XR-NTX resulted in mean NTX concentration of -1 ng/mL over 28 days, t_{max} 2–3 days, t_{1/2} 5–7 days and AUC_{∞} 144 ± 30 ng d/mL.
- Zoladex® (goserelin acetate implant) is designed for s.c. administration with continuous release of goserelin over a 12-week period.
- The overall pharmacokinetic profile of goserelin following administration of a Zoladex® 10.8 mg depot to patients with prostate cancer was determined. The initial release of goserelin from the depot was relatively rapid resulting in a peak concentration at 2 h after dosing. C_{max} 8.85 ± 2.23 ng/mL, t_{max} 1.80 ± 0.34 h and elimination half-life 4.16 ± 1.12 h were observed, from day 4 until the end of the 12-week dosing interval, the sustained release of goserelin from the depot produced reasonably stable systemic exposure.

Somatuline® Depot

- Somatuline® Depot consists of lanreotide acetate microspheres and supplied in pre-filled syringe with dose ranges of 60, 90 and 120 mg for deep s.c. injection.
- In healthy subjects, a single deep s.c. administration of Somatuline® Depot resulted in mean absolute bioavailability of 73.4, 69.0 and 78.4%, for the 60, 90 and 120 mg doses, respectively. Sustained release of lanreotide was observed with a half-life of 23 to 30 days and mean serum concentration of 1-ng/mL was maintained throughout 28 days for 90 mg and 120 mg doses while <0.9 ng/mL for 60 mg dose.
- Repeat-dose administration of Somatuline® Depot every 28 days resulted in steady-state trough serum lanreotide concentrations of 1.8 ± 0.3, 2.5 ± 0.9 and 3.8 ± 1.0 ng/mL at 60, 90 and 120 mg doses respectively. Limited initial burst effect and a low peak to trough fluctuation (81% to 108%) of the serum concentration were observed at the plateau.

Nutropin® Depot

- Nutropin® Depot is a long-acting formulation of micronized particles of recombinant human growth hormone for the treatment of growth hormone deficiency (GHD) in pediatric patients. Single dose of Nutropin® Depot (0.5 mg/kg IBW) was administered to 25 adults and serum GH concentration vs. time profile indicated mean peak serum GH concentration (C_{max}) 20.13 ± 12.92 μg/L, t_{max} 12.86 ± 2.79 h while AUC_{0–∞} = 88.28 ± 31.30 μg·h/L.
- Bydureon®

- Bydureon® is a once-weekly extended release formulation of exenatide used as an adjunctive therapy to improve glycemic control in type II diabetes mellitus.
- Following weekly administration of 2 mg prolonged-release exenatide, mean exenatide concentration exceeded the minimal efficacious concentration (~50 pg/mL) in 2 weeks and increased gradually over 6 to 7 weeks to reach steady state (~300 pg/mL) concentration. Steady-state exenatide concentration was maintained during the one-week interval, between the doses with minimal peak to trough fluctuation from this average therapeutic concentration.
- Pharmacokinetic characteristics of exenatide are independent of the dose. The mean apparent volume of distribution following a single dose of exenatide is 28 L while the mean apparent clearance of exenatide is 9 L/h. Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation.

respectively. It has also been approved for management of endometriosis and for the treatment of central precocious puberty in children [7, 14]. Lupron Depot® is marketed under various brand names such as Viadur® (Bayer AG), Eligard® (Sanofi-Aventis), Leuprolert® (TAP Pharmaceuticals and Varan Daroo Pajooh), Lupron Depot® (Abbott Laboratories), and Prostap® SR (Takeda UK).

Leuprolin, a 1-month depot injection was developed using PLGA with MW of ~14,000 kDa and a lactic acid/glycolic acid ratio of 75/25. Initial screening of suitable copolymer for leuprolin formulation was performed by an s.c. implant of square plate of PLA with average MW of 6000–50,000 kDa and copolymer PLGA with average MW 6000–13,500 kDa and lactide to glycolide molar ratio 90/10 to 55/45. A biphasic pattern of polymer loss was observed with an initial lag time followed by exponential degradation of polymer. The lag time and half-life of degradation period increased with an increase in MW or with a decrease in glycolide content. The in vivo release profile of leuprolin from PLGA with MW ~14,000 kDa and copolymer ratio 75/25 was ideal for a 1-month formulation [15]. This formulation reduced the total dose of leuprolin to one-eighth of the daily injectable dose required to achieve castrate testosterone levels. The
3-month depot injection differs from the 1-month depot injection by replacement of PLGA copolymer with PLA as the vehicle and this product does not contain gelatin [16,17].

Leuprorelin one-month depot formulation (3.75 mg) resulted in peak serum levels within 1 h, followed by a rapid fall over the next 24 h. A dose-dependent plateau was maintained over at least five weeks, representing a constant release of leuprorelin from the copolymer [18]. Repeated monthly injections over a treatment period of 45 months resulted in constant therapeutic level of leuprorelin and there was no evidence of accumulation following the depot injection [19]. The main advantage of Lupron Depot® is significant reduction in number of injections required for the treatment, increasing both patient compliance and convenience. Moreover, PLGA polymer provided tunable degradation kinetics, with controlled release and well established safety and biocompatibility [19,20]. Being one of the initially developed sustained release peptide formulations, Lupron Depot® encouraged pharmaceutical market to bring many more such products that offer patient compliance and better efficacy.

2.1.2. Atridox®

Atridox®, a product of Atrix Laboratories, Fort Collins, Colorado, USA, was approved by the USFDA in 1998 for the treatment of periodontal disease. Periodontal infections are common in all age groups, affecting the supporting structures around the teeth. The severity may range from simple gum inflammation to major damage of soft tissue and bone that supports the teeth. Atridox® is a 10% formulation of doxycycline hyclate in a bioresorbable gel system containing PLA and N-methyl-2-pyrrolidone (NMP) mixture. This product is supplied in two syringe mixing system. Syringe A contains 450 mg of the AtriGel® mixture (described in detail in Section 3.3), which is a bioabsorbable, flowable polymeric formulation containing 36.7% (w/w) PLA dissolved in 63.3% NMP (w/w). Syringe B contains 50 mg of doxycycline hyclate equivalent to 42.5 mg doxycycline. The flowable polymer gel fills and confines to pocket morphology, then it solidifies to a wax-like consistency upon contact with gingival crevicular fluid. The gel resulted in sustained release of doxycycline over 7 days and reduced anaerobic pathogen counts to 60% within 6 months post-treatment [21–25].

In patients with chronic periodontitis, significant reduction in pocket depth (1.3 mm) and improved clinical attachment level (0.8 mm) was observed with doxycycline gel, which was comparable to scaling and root planing (SRP) alone at 9 months following treatment [26]. Further, smoking condition did not diminish the clinical improvements observed with doxycycline gel [27]. Atridox® is also used as an adjunct to SRP clinical practice [28].

2.1.3. Atrisorb®

Atrisorb® is a doxycycline containing synthetic absorbable barrier for guided tissue generation in periodontitis. Periodontitis is a medical term used to describe the destruction of periodontal tissues followed by tooth loss and associated problem [29]. Different materials are used in the regeneration of periodont for the guided bone regeneration (GBR)/guided tissue regeneration (GTR). In the early stages, periodontal regeneration was facilitated by expanded polytetrafluoroethylene and dense-polytetrafluoroethylene membranes, but they were non-absorbable [30–32]. Atrisorb® is a synthetic absorbable GTR barrier with 4% doxycycline containing PLA polymer in NMP. It was designed to minimize the bacterial colonization of the membrane and marketed by Atrix Laboratories Inc. Fort Collins, Colorado, USA, in 1999. The potential of this barrier membrane was evaluated by measuring the probing depth, clinical attachment level and gingival recession and it offered favorable regeneration of damaged periodontal tissue [33–35].

2.1.4. Sculptra®

Sculptra®, also known as Sculptra® esthetic, is a microsphere formulation of PLA categorized under cosmetics and approved in 2004 by the USFDA for the treatment of facial lipoatrophy. Initially, different techniques were adopted for the treatment of age/disease induced facial deficit and collagen fillers and hyaluronic acid fillers were some commonly used materials for this purpose. Later, Dermik Laboratories Bridgewater NJ, a division of Sanofi-Aventis US introduced Sculptra® for the treatment of lipoatrophy in patients with HIV [36–39]. The formulation of Sculptra® contains PLA microparticles, nonpyrogenic mannitol, and sodium carboxymethylcellulose. This formulation is available as a lyophilate and can be injected by mixing with sterile water. The exact function mechanism of Sculptra® is unknown. However, preclinical studies have revealed that PLA is responsible for fibroplasia, which results in the formation of collagen [40,41]. Clinical studies on injectable PLA for the treatment of lipoatrophy in HIV patients resulted in significant improvement in dermal thickness and quality of patient’s life [42–45]. Treatment with Sculptra® may take as long as 2 years, whereas traditional fillers give immediate response with less durability. The longer treatment times of Sculptra® allow the patients to have a natural look after treatment [46]. During administration, preferably the cross-fanning pattern with a 25 or 26-gauge 1/2-inch needle is used for the injection of PLA into deep dermis or s.c. tissue in a series of injections with a time gap of at least 4 weeks [36,47]. A study involving the use of PLA vs. polyacrylamide hydrogel for the treatment of lipoatrophy showed similar efficiencies of both formulations but late occurrence of inflammatory nodules was reported with polyacrylamide hydrogels in some patients [48].

2.2. Poly(lactic-co-glycolic acid) (PLGA)

2.2.1. Clinical products for CNS disorders

2.2.1.1. Risperdal® Consta®. Long term maintenance therapy is essential during treatment of psychotic disorder to prevent the relapse of disease but this goal was not achieved until the entry of long-acting depot formulation Risperdal® Consta® [49]. Janssen Research Foundation developed the formulation, containing oral atypical antipsychotic drug risperidone, for the first time using the Medisorb™ (described in detail in Section 3.1) technology where the drug was encapsulated inside PLGA microspheres. Upon i.m. injection, these microspheres begin to absorb water resulting in swelling of the microspheres followed by release of the drug in a sustained manner. PLGA copolymer of MW ~ 90 kDa was used in Risperdal® Consta® microspheres. The drug loading and particle size range reported for these microspheres were ~ 38% w/w and 25–150 μm, respectively. Glass transition temperature (Tg) of Risperdal® Consta® microspheres was 48.84 ± 0.34 °C [50].

The in vitro release of Risperdal® Consta® microspheres performed under real time conditions (37 °C) showed an initial burst release (24 h release) of 1.6% followed by a lag phase of about 24 days. The lag phase was followed by a drug release phase from day 24 to 40. To compensate initial lag time, oral antipsychotic supplementations are given during the first 3 weeks. Accelerated in vitro release testing was performed by elevating the temperature from 37 to 45 °C. It resulted in burst release (24 h release) of approximately 2% and reduction in lag phase from 24 days at 37 °C to 4 days at 45 °C followed by a rapid drug release phase for up to approximately 7 days [51]. The total release duration was further, reduced to approximately 3 and 2 days at 50 °C and 54.5 °C, respectively. Accelerated in vitro release profiles obtained at temperatures (50 °C and 54.5 °C) showed linear in vitro–in vivo relationship with in vivo profile after time scaling [52].

Risperdal® Consta® is available in strengths of 25 mg, 37.5 mg and 50 mg. The pharmacokinetics of risperidone is linear in the dose range of 25–50 mg, injected every 2 weeks. Repeated i.m. injections with 25 or 50 mg every two weeks resulted in median trough and peak plasma concentrations of risperidone plus 9-hydroxy risperidone (active metabolite) between 9.9–19.2 ng/mL and 17.9–45.5 ng/mL respectively [53]. Risperdal was first approved by the USFDA to treat schizophrenia in 1993 and became available in Europe from August 2002 onwards.
2.2.1.2. Vivitrol®. Vivitrol® is among the top five key products of Alkermes Pharmaceuticals Inc., which was approved in 2006 by the USFDA for the treatment of alcohol dependence and later in 2010 to treat opioid dependence. In the early 1970s, naltrexone first came into picture as a leading candidate and by 1981, phase II studies of oral naltrexone had been performed which resulted in compliance problem thus limiting its clinical utility [55,56]. Early preparation involved naltrexone molded beads of lactic/glycolic copolymer (1.5 mm) that achieved some of its targets. However, it could not circumvent the problem of residual solvents associated with the manufacturing process, and thus failed to get the USFDA approval. In 1994, the USFDA approved oral naltrexone for the treatment of alcohol dependence. The target of extended release preparation of naltrexone came into reality with the emergence of Medisorb™ technology by Alkermes Inc., which involves encapsulation of naltrexone within matrix of PLGA with 75:25 lactide to glycolide content. These microspheres of about 0.1 mm in size began to absorb water almost immediately after injection followed by swelling. The release of the drug from PLGA microspheres was influenced by water uptake, diffusion of the drug from the microsphere surface and gradual biodegradation of the polymer into lactic acid and glycolic acid, which were metabolized and eliminated [57,58].

Extended release naltrexone (XR-NTX) microspheres are available as sterile, off-white to light tan powder with dose strength of 380 mg of naltrexone per vial. Each gram of microspheres contains 337 mg of naltrexone. The diluent, which contains carboxymethylcellulose sodium salt, polysorbate 20, sodium chloride, and water for injection, is supplied to suspend the microspheres prior to injection. Pharmacokinetic studies of XR-NTX in animals [59,60] and humans [61–63] indicated a stable, pharmacologically relevant plasma level of naltrexone for at least 28 days. Pharmacokinetic data for single-dose XR-NTX (380 mg monthly) were found to be superior than oral naltrexone (50 mg daily). Single i.m. injection of 380 mg of XR-NTX resulted in mean NTX concentration of >1 ng/mL over 28 days, \( t_{\text{max}} >2–3 \) days, \( t_{\frac{1}{2}} >5–7 \) days and AUC\(_{\text{0-\infty}} = 144 \pm 30 \text{ ng d/mL} [62,64]. Several pharmacological characteristics appear to be unique to XR-NTX. The most important feature was dose reduction of XR-NTX compared to oral naltrexone that could be achieved due to avoidance of first pass effect associated with oral naltrexone. Further, it markedly increased the proportion of naltrexone in blood relative to the principal metabolite 6-naltrexol. Also, XR-NTX resulted in four times higher plasma AUC compared to daily oral naltrexone upon i.m. injection [65].

2.2.2. Clinical products for gonadotropin-releasing hormone regulation

Gonadotropin-releasing hormone (GnRH), also known as follicle stimulating hormone-releasing hormone (FSH-RH) and luteinizing hormone-releasing hormone (LH-RH), is a tropic peptide hormone that stimulates the release of FSH and LH from the anterior pituitary. Synthetic GnRH receptor agonists (leuprolide, buserelin, and goserelin) have been used for the treatment of prostate cancer. These agonists eventually cause the inhibition of LH production, thereby suppressing testosterone and dihydrotestosterone which are primarily responsible for the growth of prostate cancer cells [66].

2.2.2.1. Zoladex®. Zoladex®, a biodegradable injectable implant of goserelin (LHRH analog) with PLGA, was developed by AstraZeneca and was approved by the USFDA in 1996. The specific indications of Zoladex® are treatment of advanced breast cancer in pre and perimenopausal women and treatment of endometriosis and advanced prostate cancer.

Depot was developed with 50:50 M ratio PLGA in the form of a rod of about 1 mm in diameter and 3–6 mm in length. The drug is dispersed in the polymer matrix using hot-melt extrusion method. Initial depot for animal studies contained 0.5 to 1 mg of goserelin while depot developed for human clinical studies contained 3.6 mg of goserelin given once in 28 days [67,68]. Later, 3.6 mg implant was replaced by 10.8 mg implant (3 months release) that produced pharmacodynamically similar effect as the former. Initial development of sustained release formulation of goserelin faced many challenges such as large MW of polypeptide that hindered its free diffusion from polymeric matrix. Adjuvant-induced immunological response at implant site and biological labile nature of polypeptide further complicated the situation. Application of biodegradable PLGA polymer for encapsulation of polypeptide circumvented immunological reactions and provided a sustained release profile by hydrolytic degradation of polymer. Micro scale porosity generated after hydrolytic degradation further enhanced water uptake and facilitated enhanced diffusion of polypeptide from polymer matrix [69].

Initial phase I clinical trial of Zoladex® conducted on fifty-three premenopausal patients with advanced breast cancer has shown a response rate of 31% [70]. In this study, 684 premenopausal patients with node-positive breast cancer were treated with goserelin versus cyclophosphamide, methotrexate, and fluorouracil (CMF) combination with a follow-up period of 6 years. In ER-positive patients (approximately 74%), goserelin was equivalent to CMF for disease-free survival while in ER-negative patients, it was inferior to CMF (95% confidence interval). Incidences of amenorrhea were more in goserelin treated patients than CMF patients, which reversed after the termination of therapy. Moreover, chemotherapy-related side effects such as nausea/vomiting, alopecia, and infection were higher with CMF than with goserelin during CMF treatment. Side effects related to estrogen suppression were initially higher with goserelin, but reduced below the CMF group after termination of goserelin treatment [71].

Goserelin was compared with the combination therapy of CMF to improve quality of life (QoL) in premenopausal and perimenopausal patients with node-positive, early breast cancer. It offered an improved QoL during the first 6 months of therapy compared with CMF chemotherapy in both pre and perimenopausal ER positive patients [72]. Zoladex® without chemotherapy indicated reversible sexual dysfunction in premenopausal breast cancer patients [73]. Further, a trial to assess the feasibility of preventive treatment with goserelin and ibandronate combination for premenopausal women with increased risk for breast cancer was found to be ineffective [74]. Turner et al. reported the use of GnRH agonists to overcome chemotherapy induced infertility in young breast cancer patients, however the outcome was uncertain and requires further trials [75].

2.2.2.2. Decapeptyl®/Trelstar®/Pamorelin®. Trelstar®, a triptorelin containing depot formulation, is also marketed under the names of Decapeptyl® and Pamorelin® in Europe, Latin America and India. Decapeptyl® was introduced in the European market in 1986 as first injectable, depot of LHRH analog (leuprolide acetate). In 2000, Debiopharm group received the USFDA approval for Trelstar®, indicated for the palliative treatment of advanced prostate cancer which is currently available in 1-month (3.75 mg), 3-month (11.25 mg) and 6-month (22.50 mg) dosage forms [76].

Distribution and elimination of triptorelin after i.v. bolus administration, followed 3-compartment model and corresponding half-lives were approximately 6 min, 45 min, and 3 h. The pharmacokinetic study following a single i.m. injection of Trelstar® depot (3.75 mg) indicated \( C_{\text{max}} = 28.43 \pm 7.31 \text{ ng/mL} \) within 6 min, and AUC\(_{\text{0-28 days}} , 223.15 \pm 46.96 \text{ h ng/mL} \). The plasma concentrations declined up to 0.084 ng/mL after 4 weeks [77]. Trelstar® depot is supplied as a sterile, lyophilized biodegradable microgranule formulation, reconstituted in 2 mL of sterile water for injection utilizing a 21-gauge needle or using the single dose delivery system called as Mixject®. Unit dose formulation of 3.75 mg intended to provide 1-month sustained release contains peptide base equivalent to 3.75 mg, 170 mg PLGA, 85 mg mannitol, 30 mg carboxymethylcellulose sodium and 2 mg polysorbate 80 [78]. Trelstar® depot, 6-month formulation also received the USFDA...
approval that offers better patient compliance and requires only twice administration yearly.

2.2.2.3. Eligard®. Eligard®, depot developed by Atrix laboratories, received the USFDA approval for the treatment of prostate cancer in 2002. It is an extended-release biodegradable formulation of leuprolide acetate based on AtriGel® technology. AtriGel® is a novel delivery system that consists of a biodegradable polymer PLGA dissolved in the biocompatible and water miscible solvent such as NMP. The rate of release of leuprolide acetate is controlled by varying the MW of the polymer and the solvent concentrations. This unique feature of AtriGel® system gave rise to a range of Eligard® depot formulations such as 1 month (7.5 mg dose), 3 months (22.5 mg dose), and 6 months (45 mg dose). The 1-month formulation contains the PLGA with 50:50 M ratio of α,ω-lactide to glycolide with carboxyl end groups. The 3-month formulation of Eligard® contains the PLGA polymer in a molar ratio of 75:25 of α,ω-lactide to glycolide with hexanediol. The PLGA molar ratio for the 6-month formulation is 85:15 of α,ω-lactide to glycolide [79,80].

It is supplied as a two-syringe system, one of which contains leuprolide acetate powder and the other containing the AtriGel® polymer. Prior to administration, the two syringes are coupled and their contents are mixed to obtain a uniform suspension. When the polymer solution is injected into the body, the organic solvent dissipates into the surrounding tissue and the water permeates into the implant which leads to phase separation and subsequent coagulation of the polymer to form an implant in situ [81]. This implant then releases the leuprolide in a controlled manner as the polymer matrix biodegrades with time. The advantage of AtriGel® in situ implant system over microsphere system lies in the formation of single, relatively large sphere by AtriGel® which results in smaller surface area and less degradation of leuprolide acetate.

The 6-month depot formulation of Eligard® (45 mg) was evaluated for its safety and efficacy in a 12-month, open-label, multicenter study in patients with prostate cancer. The mean time required to reach castrate testosterone (T) levels (50 ng/dL) was 21 days. A total of 111 patients with different stages of prostate cancer were enrolled and 103 of them received two 6-month depot formulations. After 12 months, 99% of patients were reported with T levels of 50 ng/dL, and 88% of patients had T levels of 20 ng/dL. Mean prostate specific antigen levels decreased from 39.8 ± 21.5 ng/mL at baseline to 1.2 ± 0.3 ng/mL at 12 months. These attractive results along with practical advantages of less frequent visits to the physician and less number of injections required made it a more preferable alternative for the management of prostate cancer [82,83]. A comparative study of Eligard® 1-month, 3-month, and 6-month formulations was conducted in nine European countries to evaluate their efficacy, safety and cost effectiveness. Data suggested comparable efficacy and safety with all three formulations, but Eligard® 6-month formulation was found to be more cost effective due to less number of visits required for administration [84].

2.2.2.4. Profact Depot®/Suprefact Depot®. Profact Depot® or Suprefact Depot®, a buserelin acetate containing PLGA implant of Sanofi-Aventis Canada Inc., is used for the palliative treatment of advanced castrate resistant prostate cancer. Buserelin acetate is a synthetic peptide analog of the natural LHRH, formed by substitutions of glycine at the 6th position and glycaminad at the 10th position with δ-serine and ethylamide, and resulted in 20–170 times greater effect than natural LHRH on release of FSH and LH. Formulation is available as 2 and 3-month depot containing 6.6 mg and 9.9 mg buserelin acetate within prefilled syringe respectively [85,86].

In clinical pharmacology studies with 2-month depot formulation, maximum release was recorded on day 1, followed by an extended plateau phase that lasted for eight weeks. After this period, an accelerated biodegradation of the implant material was observed with a terminal half-life of release of 20–30 days. Single dose studies performed in healthy male subjects and in patients with benign prostatic hypertrophy showed a therapeutic release for eight weeks (dosage interval). After this period, a minimum therapeutic release rate of 4.95 μg/day was observed that was fully effective in maintaining testosterone levels in the surgical castration range. Further administration of the implant every two months ensured continuous suppression of testosterone secretion with no accumulation of buserelin after repeated dosing.

Release profile of 3-month formulation was biphasic and negligible initial release (Tmax < 1 day) was observed, followed by a phase of slow, steady release which continued for about 3 months. A second small increase in the serum buserelin concentration was detected between 12 and 16 weeks following which the median serum level of buserelin was far above the detection limit (0.05 ng/mL), indicating testosterone levels in the surgical castration range [87].

2.2.2.5. Suprecur® and Enantone® depot. Suprecur® and Enantone® depot are PLGA microparticle formulations of GnRH analog. Enantone® depot, a product of Takeda Pharmaceutical, containing leuprolide acetate, is available for the treatment of prostate cancer while, Suprecur® depot is an extended release PLGA microparticle formulation of buserelin acetate for the treatment of endometriosis in women. Marketed by Sanofi-Aventis, Suprecur® provides sustained delivery of buserelin acetate for 1 month.

2.2.3. Clinical products for growth hormone regulation

2.2.3.1. Sandostatin® LAR depot. Sandostatin®, a octreotide containing formulation, was approved in 1988 as an immediate release injection and in 1998 as sustained release LAR depot for the treatment of acromegaly [88]. Injections are available as sterile 1 mL ampoules with strengths of 50, 100, or 500 μg octreotide and sterile 5 mL multi-dose vials in 2 strengths of 200 and 1000 μg/mL of octreotide. The immediate release injections were meant to be administered by i.v. or s.c. route. These injectable formulations of octreotide increased its apparent plasma half-life up to 1.7 h as compared to 1–3 min for natural hormone somatostatin and resulted in peak concentration of 5.2 ng/mL (100 μg dose) within 0.4 h in healthy volunteers while 2.8 ng/mL (100 μg dose) within 0.7 h in acromegaly patients. However, these injections provided an immediate release profile with a variable response up to 12 h and thus to incorporate both immediate and sustained release characters in a single formulation, Novartis launched Sandostatin® LAR depot which received the USFDA approval in 1998. Sandostatin LAR is a long acting dosage form containing octreotide acetate encapsulated within PLGA microspheres. Copolymer has an average MW – 52 kDa and 55:45 M ratio of lactide to glycolide. Sandostatin LAR microspheres were of about 50 μm in size. Scanning electron microscopy revealed the spherical shape of these microspheres with compact structure and presence of minor pores. Mannitol, a component of Sandostatin LAR, was found in crystalline form, loosely connected to microspheres [89]. Sandostatin® LAR maintained all clinical and pharmacological characteristics of the immediate release Sandostatin® injection with the added feature of sustained release of octreotide at the site of injection. Pharmacologically, the depot works by imitating the action of somatostatin. Octreotide is a more potent inhibitor of growth hormone, glucagon, insulin and LH than somatostatin thus decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. These pharmacological actions make octreotide useful in the treatment of metastatic carcinoid tumors and vasoactive intestinal peptide secreting adenomas.

Pharmacokinetics was determined after a single i.m. injection of Sandostatin® LAR depot in a healthy volunteer. Serum octreotide concentration reached a transient initial peak of about 0.03 ng/mL/mg within 1 h, which progressively declined after 3–5 days to a level of <0.01 ng/mL/mg and again slowly increased, to reach a plateau concentration of 0.07 ng/mL/mg within 2–3 weeks. Plateau concentrations
were maintained for 2–3 weeks followed by slow decrease to 0.01 ng/mL/mg within 12 to 13th weeks. It was concomitant with the terminal degradation phase of the polymer matrix of the dosage form. Additional advantage of LAR depot over injection was reduced peak to trough variation in octreotide concentrations ranging from 44 to 68% (with LAR-depot), compared to the 163–209% variation encountered with the s.c. three times daily regimen of Sandostatin® Injection [89,90].

The efficacy of octreotide therapy in acromegalic patients as primary or secondary therapy was evaluated. Four acromegalic patients with macroadenoma were treated with octreotide 20 mg/28 days. Three patients received preoperative octreotide and one patient received octreotide post-operation. The concentrations of human growth hormone (HGH) and IGF1 were evaluated at 0, 6 and 12 months, while magnetic resonance imaging (MRI) was taken before treatment and after 12 months. Mean serum GH decreased from 53 ng/mL to 13 ng/mL while mean plasma IGF1 concentrations decreased from 502.5 ng/mL to 490.25 ng/mL at 3 months. After one year of therapy, tumor size decreased with a mean value of 22.58% in 75% of cases. No effect of dose increment was recorded [91].

2.2.3.2. Somatuline®. Somatuline® Depot (lanreotide depot) is an injectable, sustained release formulation of lanreotide acetate, an octapeptide somatostatin analog that inhibits insulin-like growth factor-1 (IGF-1) and growth hormone (GH) [92]. Lanreotide has a high affinity for human somatostatin receptors II and V that is the primary mechanism for GH inhibition. In 2007, Ipsen Pharma received the USFDA approval for Somatuline® which was indicated for long-term treatment of acromegaly patients with an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy are not an option [93–95]. Somatuline® Depot consists of lanreotide acetate PLGA microspheres that are supplied in pre-filled syringes with dose ranges of 60, 90 and 120 mg for deep s.c. injection. Formation does not require reconstitution, and was recently demonstrated in a 6-month clinical trial to be suitable for self or partner administration thus avoiding visit to a medical facility [96]. In healthy subjects, a single deep s.c. administration of Somatuline® Depot resulted in mean absolute bioavailability of 73.4, 69.0 and 78.4%, for the 60, 90 and 120 mg doses, respectively. Sustained release of lanreotide was observed with a half-life of 23 to 30 days and mean serum concentration of >1 ng/mL was maintained throughout 28 days for 90 mg and 120 mg doses while >0.9 mg/mL for 60 mg dose. Repeat-dose administration of Somatuline® Depot every 28 days resulted in steady-state trough serum lanreotide concentrations of 1.8 ± 0.3, 2.3 ± 0.9 and 3.8 ± 1.0 ng/mL at 60, 90 and 120 mg doses respectively. Limited initial burst effect and a low peak to trough fluctuation (81% to 108%) of the serum concentration were observed at the plateau. Somatuline is marketed as Somatuline® Depot within the US and as Somatuline® Autogel® in other countries [97]. In 2015, approval of Somatuline® Depot for neuroendocrine tumors associated indication in US and Europe resulted in €103.4 million sale and a 33.7% uplift in year-on-year performance [98].

2.2.3.3. Nutropin®. Nutropin® Depot, a collaborative project of Genentech and Alkermes, was approved in 1999, by the USFDA for the treatment of growth hormone deficiency (GHD) in pediatric patients. It is a long-acting formulation of micronized particles of recombinant human growth hormone (rhGH) embedded in biocompatible, biodegradable PLGA microspheres using ProLease® technology (described in detail in Section 3.4) [99,100]. ProLease technology involves encapsulation of freeze-dried protein within the PLGA matrix by atomization of freeze-dried protein, PLGA suspension and immediate freezing of droplets. These microspheres are available as dry powder and reconstituted immediately before use. Following s.c. injection, bioactive rhGH is released from the microspheres into the body initially by diffusion, followed by both polymer degradation and diffusion [101,102].

In GHD children, serum GH concentration–time profiles of single doses of 0.75 mg/kg and 1.5 mg/kg of Nutropin® Depot showed an initial rapid release followed by a slow decline in GH concentration. For the initial two doses, serum GH levels >1 µg/L was maintained for approximately 11–14 days however, no progressive accumulation of GH was recorded upon repeated dosing over 6 months. Relative bioavailability of single dose of Nutropin® Depot in GHD children was found to be 33% to 38% higher in comparison to single dose of Nutropin® AQ injection. A single dose of Nutropin® Depot 0.25–0.5 mg/kg in adults with GHD resulted in normalized insulin like growth factor-1 (IGF-1) levels for 14–17 days while GH released slowly over 56 days [103,104]. In an open-label study of 135 adults with GHD, Nutropin® Depot had similar effects on reduction of fat mass and an increase in lean body mass was observed on daily injections of GH [105]. In prepubertal children, Nutropin® Depot was administered in doses from 0.15 mg/kg to 0.75 mg/kg every two weeks. An increase in IGF-I levels was observed which was maintained until 16–20 days [106]. Nutropin® Depot was withdrawn from the market in 2004 because of manufacturing issues and business decision of Alkermes and Genentech [107].

2.2.4. Clinical products for the treatment of periodontal disease 2.2.4.1. Arestin®. Periodontal disease affects more than 50 million adults across many demographic categories. Clinical symptoms for the disease involve swollen and painful gums that may ulcerate, become necrotic and finally result in tooth loss [108]. In 2001, Ora Pharmaceuticals received the USFDA approval for Arestin®, a subgingival sustained release microsphere formulation of minocycline hydrochloride intended for the treatment of periodontal disease. Sustained release profile of Arestin® microspheres was achieved by incorporation of minocycline hydrochloride within biodegradable polymer PLGA where the ratio of PLA and PGA within copolymer played an important role to tailor the duration of release. Dose of Arestin® is variable and depends upon the size, shape, and number of pockets being treated. The unit dose cartridge of Arestin delivers minocycline hydrochloride equivalent to 1 mg of minocycline freebase. Insertion of Arestin® is painless, omitting the use of local anesthesia. Moreover, the biodegradable nature of polymer eliminates the need of surgical removal of inserts [109]. Study demonstrated the effectiveness of Arestin® as adjunctive with SRP in patients with chronic periodontitis. A total of 2805 patients suffering from chronic periodontal disease were given SRP at baseline with single application of Arestin® in all pockets ≥5 mm. A recall visit after 3 months involving second application of Arestin® and final assessment after 6 months resulted in reduction of pockets to ≤5 mm in 62% and 67% patients after one and two applications, respectively [110]. Arestin® was found to be efficacious in smoker patients and statistically significant pocket depth reduction was observed in these patients [111].

2.2.5. Clinical products for blood glucose regulation 2.2.5.1. Bydureon®. Bydureon® is a once-weekly extended release formulation of exenatide, a potent agonist of the GLP-1 receptor. Exenatide has been widely used as an adjunctive therapy to improve glycemic control in type II diabetes mellitus patients who are unable to achieve adequate glucose control using metformin and/or sulfonylurea [112, 113]. Exenatide was approved by the USFDA on April 28, 2005 and marketed as Byetta™ (Amylin Pharmaceuticals, San Diego, CA, USA). However, it has a plasma half-life of 2.4 h and an action time of about 8 h requiring its administration twice daily which is painful and inconvenient to patients [114]. Many efforts have been made to obtain a long acting formulation of exenatide and a once-weekly PLGA microsphere injection — Bydureon® was approved by the USFDA on January 27, 2012. Bydureon® is developed by Amylin Pharmaceuticals (Indianapolis, IN, USA) and the only long-acting exenatide product in the market [115].
The Bydureon® microspheres are prepared based on Medisorb® microsphere technology (Alkermes Inc.). The polymer used in microsphere preparation is Medisorb 50:50 DA4P, composed of lactide and glycolide monomers in a M ratio of 50:50. This polymer has a carboxylic end group and an inherent viscosity of approximately 0.4 dL/g. The microspheres contain 5 mg of encapsulated exenatide per 100 mg of microspheres. For the preparation of microspheres, exenatide is dissolved in a water phase then mixed with a dichloromethane solution containing polymer and sonicated for several minutes. After a coacervate formation, the embryonic microspheres are prepared with silicone oil and transferred into a heptane/ethanol solvent mixture to harden them [116,117]. The diameter of the microspheres is 0.06 mm with the typical pinched-raisin shape and dense surface layer. The only excipient in Bydureon® is sucrose, acting as pore former to modulate drug release and stabilizer to maintain peptide integrity during manufacturing. Mannitol was used as pore former in initial trials but it was eliminated from the final formulation due to undesired increase in initial phase release. Similarly, ammonium sulfate was added in an effort to increase exenatide release during the lag phase. However, the presence of ammonium sulfate also caused an undesired increase in initial phase release hence not included in final dosage form [115]. The optimal formulation resulted in extended release of exenatide at consistent therapeutic levels over the dosing interval, while also provided an acceptably low initial release.

Bydureon® is administered subcutaneously into the abdomen, thigh, or back of the upper arm. The dosing kit includes a vial of dry powder with a premeasured 2 mg dose of exenatide encapsulated in 40 mg of microspheres; a syringe prefilled with 0.65 mL of diluent; a vial connector; and needles for s.c. injection. Bydureon® can be taken any time of day, with or without food, in contrast to exenatide twice daily formulation (EBID) that must be administered, within 60 min before the two main meals of the day [117]. After s.c. injection of reconstituted formulation, exenatide microspheres hydrate in situ and adhere to one another to form an amalgam. A small amount of loosely bound surface exenatide (less than 1%) releases in the first few hours, whereas drug located in deeper interstices diffuses out more slowly. Following weekly administration of 2 mg prolonged-release exenatide, mean exenatide concentration exceeded the minimal efficacious concentration (>-50 pg/mL) in 2 weeks and increased gradually over 6 to 7 weeks to reach steady state (~300 pg/mL) concentration. Steady-state exenatide concentration was maintained during the 1 week interval between doses with minimal peak to trough fluctuation from this average therapeutic concentration. As the plasma exenatide concentration reaches the therapeutic range by 2 weeks and steady state by 6–7 weeks, this gradual approach to steady state seems to improve tolerability with reduced frequency of nausea with Bydureon® than EBID. Pharmacokinetic characteristics of exenatide are independent of the dose. The mean apparent volume of distribution following a single dose of exenatide is 28 L while the mean apparent clearance of exenatide is 9 L/h. Nonclinical studies have shown that exenatide is eliminated by glomerular filtration with subsequent proteolytic degradation. Further, the mean plasma exenatide concentrations fell below minimal detectable concentrations after 10 weeks of discontinuation of prolonged-release exenatide therapy [117,118].

The glucose-lowering efficacy of exenatide has been reported in many clinical trials which include one placebo-controlled study [119] and five comparative studies namely DURATION-1, -2, -3, -4 and -5 (Diabetes Therapy Utilization: Researching Changes in A1c, Weight and other Factors Through Intervention with Exenatide Once Weekly) [120–123]. Exenatide once weekly resulted in significant improvement in glycemic control than exenatide given twice a day, with no increased risk of hypoglycemia and almost similar reduction in body weight [124]. Exenatide administration may be associated with palpable skin nodules that generally resolve without further medical intervention [119]. In comparative trials, exenatide improved hemoglobin A1c more than EBID, sitagliptin, pioglitazone, or insulin glargine and reduced fasting plasma glucose more than EBID. Weight loss due to Bydureon® or EBID was similar. In comparison to Bydureon®, though EBID provides modestly better postprandial control for the two post-injection meals, advantage of Bydureon® includes greater ability to meet therapeutic HbA1c goals, better fasting glucose control, a lower incidence of gastro-intestinal upset, more flexible dosing, and less frequent injections [117].

2.3. Poly(lactic acid)–poly ethylene glycol (PLA–PEG)

2.3.1. Genexol®–PM

Genexol®–PM (Cynviloq™) developed by the South Korean company Samyang Corporation, is a sterile, lyophilized polymeric micellar formulation of paclitaxel that employs a colloidal carrier system to allow intravenous delivery of paclitaxel without the use of cremophor EL. These micelles are 20 to 50 nm in size and consist of two block copolymers: PEG that is useful as a non-immunogenic carriers and the core-forming PLA that allows the solubilization of the hydrophobic drug [125]. Preclinical in vivo studies have shown that compared with free paclitaxel, the bio-distribution of paclitaxel administered as Genexol®–PM was 2–3 times higher in various tissues, including the liver, spleen, kidneys, lungs, heart and tumor. Moreover, Genexol®–PM demonstrated 3-fold increase in the maximum tolerated dose (MTD) and a significantly increased antitumor efficacy compared to free paclitaxel [10].

In phase I studies, no acute hypersensitivity reactions occurred in patients at the MTD 390 mg/m² administered every 3 weeks or 120 mg/m² weekly [126]. Phase II studies have demonstrated the safety and efficacy of Genexol®–PM with high response rates in patients with metastatic breast cancer and advanced pancreatic cancer. However, in patients with metastatic breast cancer, hypersensitivity reactions were seen in 19.5% of patients [127,128]. Genexol®–PM administration enhanced response rates when given to patients who were not responsive to standard taxane therapy (paclitaxel/carboplatin) [129]. Moreover, Genexol®–PM plus cisplatin combination chemotherapy showed significant antitumor activity that allowed administration of higher doses of paclitaxel, compared to the cremophor EL formulation, in patients with advanced non–small-cell lung cancer [130]. Genexol®–PM is also an effective treatment option for gemcitabine-resistant pancreatic ductal adenocarcinoma, a lethal disease, with overall tumor response rate <25% and median survival <6 months. Cell line study showed similar IC₅₀ for gemcitabine treated and gemcitabine resistant cells when treated with Genexol®–PM. In vivo Genexol®–PM treatment resulted in a greater percent reduction in tumor size, less metastatic spread and longer survival compared with treatment with gemcitabine alone [131]. Genexol®–PM also completed phase I or II trials in metastatic breast cancer, non–small cell lung carcinoma, pancreatic cancer, ovarian cancer, and bladder cancer. Studies are now being conducted for the treatment of several malignancies, including phase III and IV studies in patients with recurrent breast cancer. In 2013, Sorrento Therapeutics, Inc. and Igdrasol acquired exclusive distribution rights from Samyang Biopharmaceuticals to market Cynviloq™ in the U.S. and several countries of the European Union.

2.3.2. OncoGel™

OncoGel™ is a chromophore free, paclitaxel formulations of tri-block copolymer (PLGA–PEG–PLGA), intended for local tumor management. It is based on ReGel® technology, ReGel® is a thermosensitive, water-soluble implant, designed to undergo a reversible thermal transition from a water soluble low viscosity solution (sol-state) at temperatures between 2 and 15 °C to a viscous, water insoluble biodegradable controlled-release gel (gel-state) at body temperature [132,133].

ReGel®, being a non-ionic surfactant, spontaneously forms polymeric micelles containing a hydrophobic core. In solution state of ReGel, hydrophobic drugs show greater affinity for its hydrophobic...
core. At body temperature, ReGel transition occurs from sol to gel and hydrophobic drugs become associated with the hydrophobic constituents of ReGel thus forming a controlled-release depot. It also provides a vehicle to solubilize poorly soluble drugs [more than 400-fold (>10 mg/mL) solubility enhancement for paclitaxel]. OncoGel™ was administered by intralesional injection or placed into the tumor cavity following resection hence, it was used as part of combination therapy in cancer treatment. Drug release was observed over 50 days with complete degradation over 6–8 weeks in vitro [134].

A phase I clinical trial was performed on patients with inoperable solid tumors to study the toxicity, pharmacokinetics, and antitumor activity of OncoGel™ injected directly into tumors. For this purpose, 16 patients received OncoGel™ injections with paclitaxel dose ranging from 0.06 to 2.0 mg/cm³. OncoGel™ was well tolerated up to a dose of 2.0 mg paclitaxel/cm³ and paclitaxel remained localized at the injection site. Major side effects reported were injection site pain, erythema, muscle spasm, post-procedural discharge and injection site bruising. No dose-limiting response was observed at the highest dose evaluated for this study (2.0 mg/cm³) [135]. However, OncoGel™ failed to show any impact in a phase Ib study designed to assess its presurgical potential in patients with esophageal cancer.

3. Marketed technologies for injectables

Drug delivery technologies evolved over the past decades. This section emphasizes upon the marketed technologies specifically developed for the preparation of injectable sustained release formulations (Fig. 2). Each technology offers its unique characteristics in an attempt to optimize drug delivery by protecting the unique properties of active agent while minimizing its drawbacks [136,137].

3.1. Medisorb™ technology

Medisorb™ is Alkermes’ proprietary technology that involves encapsulation of drug in microspheres made of PLGA copolymer. Upon injection, the microspheres begin to absorb water immediately that leads to swelling of the microspheres and breakdown of polymer over time with sustained supply of medication. This technology provided two successful products namely Vivitrol® and Risperidal® Consta®, approved to treat alcohol/opioid dependence and psychotic disorders respectively. This technology offers the ability to achieve a customized extended-release profile lasting from days to months [59,60].

3.2. ReGel® technology

ReGel® is a Macro-Med’s proprietary drug delivery systems, characterized by thermally induced sol to gel conversion of formulation. ReGel® technology makes use of thermally reversible gelling polymers that offer a range of gelation temperature, degradation rates and release characteristics as a function of MW, degree of hydrophobicity and polymer concentration. PLGA–PEG–PLGA copolymer, a thermally reversible gelling material, was used to encapsulate the paclitaxel and brought a formulation OncoGel™ until clinical phase. This formulation remains in sol form at room temperature, which upon injection in the body undergoes a reversible phase transition to form water insoluble, biodegradable gel depot. The formulation successfully completed phase I trial however, failed to give any superior result in phase II trial performed over esophagus cancer patients [133,138]. hGHD-1 is another injectable depot formulation of human growth hormone utilizing ReGel® drug delivery system for the treatment of patients with hGHD deficiency [139].
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<tr>
<td>7.</td>
<td>A clinical trial of paclitaxel loaded polymeric micelle in patients with taxane-pretreated recurrent breast cancer</td>
<td>Recurrent breast cancer</td>
<td>To evaluate the response rate in patients with taxane-pre-treated recurrent breast cancer receiving paclitaxel loaded polymeric micelle (Genexol®-PM)</td>
<td>NCT01689194</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>8.</td>
<td>Efficacy study of Genexol®-PM and cisplatin in locally advanced head and neck cancers</td>
<td>Advanced head and neck cancers</td>
<td>To evaluate the efficacy and safety of induction chemotherapy using Genexol®-PM + cisplatin for locally advanced head and neck cancers</td>
<td>NCT01770795</td>
<td>II</td>
<td>Completed</td>
</tr>
<tr>
<td>9.</td>
<td>A phase II trial of Genexol®-PM and gemcitabine in patients with advanced non-small-cell lung cancer</td>
<td>Non-small-cell lung cancer</td>
<td>To evaluate the efficacy and safety of Genexol®-PM (PEG-polymeric micelle formulated paclitaxel) and gemcitabine in untreated metastatic NSCLC patients</td>
<td>NCT02234115</td>
<td>III</td>
<td>Recruiting</td>
</tr>
<tr>
<td>10.</td>
<td>Safety, efficacy, and pharmacokinetic behavior of leuprolide mesylate in subjects with advanced prostate carcinoma</td>
<td>Advanced prostate carcinoma</td>
<td>To evaluate the safety and efficacy of leuprolide mesylate in treatment of subjects with advanced prostate carcinoma upon twice yearly administration</td>
<td>NCT01556425</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>11.</td>
<td>The separate and combined effects of Vivitrol® and opioid abstinence reinforcement in the treatment of opioid dependence</td>
<td>Opiate dependence</td>
<td>To evaluate extended release naltrexone (Vivitrol®) and employment-based reinforcement of opiate abstinence in promoting opiate abstinence and reducing risky injection behavior in recently detoxified, opioid-dependent, injection drug users</td>
<td>NCT02537574</td>
<td>III</td>
<td>Recruiting</td>
</tr>
<tr>
<td>12.</td>
<td>Naltrexone for use in conjunction with buprenorphine in adults with opioid use disorder prior to first dose of Vivitrol®</td>
<td>Opioid use disorder</td>
<td>To evaluate the safety, effectiveness and tolerance of low doses of oral naltrexone along with buprenorphine to treat opioid use disorder prior to the first injection of Vivitrol®</td>
<td>NCT01246401</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>13.</td>
<td>Naltrexone for opioid dependent released human immunodeficiency virus positive (HIV+) criminal justice populations (new hope)</td>
<td>HIV; AIDS; opioid dependence; drug dependence</td>
<td>To study the extent of release-naltrexone (XR-NTX) among HIV infected prisoners meeting diagnostic statistical manual I.V. criteria for opioid dependence who are transitioning from the structure of a correctional setting to the community</td>
<td>NCT02508636</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>14.</td>
<td>Trial of radiotherapy with leuprolide and enzalutamide in high risk prostate cancer</td>
<td>Prostatic neoplasms</td>
<td>To evaluate efficacy, safety, toxicity, and feasibility of the addition of enzalutamide to leuprolide (Lupron Depot®) for a total duration of 24 months in patients with very high-risk prostate cancer or pelvic node positive disease receiving radiotherapy</td>
<td>NCT00667069</td>
<td>III</td>
<td>Recruiting</td>
</tr>
<tr>
<td>15.</td>
<td>Triptorelin and radiation therapies in treating patients who have undergone surgery for intermediate-risk stage III or stage IV prostate cancer</td>
<td>Prostate cancer</td>
<td>To compare the immediate adjuvant radiotherapy associate with hormonal therapy of LH-RH analog (Decapeptyl® LP) vs. delayed radiotherapy until biochemical relapse associated with hormonal therapy of LH-RH analog (Decapeptyl® LP) in patients with operable prostate cancer</td>
<td>NCT01352091</td>
<td>III</td>
<td>Recruiting</td>
</tr>
<tr>
<td>16.</td>
<td>Adjuvant AI combined with Zoladex®</td>
<td>Breast cancer</td>
<td>To compare the efficacy of Zoladex® combined with Aromidex® after SERMs (tamoxifen and Fareston®) as an adjuvant therapy for 2–3 years</td>
<td>NCT02409849</td>
<td>II</td>
<td>Not yet recruiting</td>
</tr>
</tbody>
</table>
| 17. | Octreotide LAR as maintenance treatment for patients with NEC | Gastro-entero-pancreatic carcinoma | To determine the efficacy of octreotide LAR as maintenance treatment after first-line chemotherapy for patients with unresectable or metastatic gastro-entero-pancreatic or esophageal neuroendocrine carcinomas | (continued on next page)
release of the drug from the polymer matrix can be tailored by selection of appropriate polymer and manipulation in polymer properties. The hydrophobic poly(D,L-lactide-co-caprolactone) resulted in very low release and hence lag phase can be seen in these release mechanisms that depend on dissolution of the drug, diffusion of the dissolved drug out of the microspheres, hydrolysis and weight loss of the polymer to create pores for continuous release of the dissolved drug from the microsphere matrix. Glass transition temperature (Tg) of polymer/hydrated microspheres plays an important role to modulate the release. If the Tg is lower than the temperature at the injection site, the polymer may plasticize and the microsphere porosity may be reduced significantly. In such cases, any subsequent release depends on hydrolytic degradation of polymer to create new channels for drug diffusion. Further, hydrophobicity of polymer, localization of drug within microsphere and a highly dense polymer matrix may result in very low release and hence lag phase can be seen in these release profiles [143,144]. Nutropin® Depot, approved for the treatment of growth hormone deficiency in pediatric patients, was formulated using ProLease® technology [145].

4. Clinical trials

Various clinical trials involving PLA and its copolymer based marketed products in combination with other agents/therapies are covered in this section (Table 3). Combination of recently approved therapeutic agents with already existing products in the market covers a major part of recent clinical trials. These combinations are also explored for other indications.

5. Conclusion

PLA and its copolymers are known for their multifaceted application and are still the major hydrophobic polyesters. They continued to show enormous prospect for development of drug delivery depots. PLA or PLGA copolymerized with PEG self-assembles to form micelles instantly that can be tailored to form in situ hydrogels. This unique thermo-

Table 3 (continued)

<table>
<thead>
<tr>
<th>SN</th>
<th>Title</th>
<th>Condition</th>
<th>Purpose</th>
<th>NCT no.</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Combination of everolimus and octreotide LAR in aggressive recurrent meningiomas</td>
<td>Aggressive recurrent meningiomas</td>
<td>To determine the antitumor effect of combination of everolimus and octreotide in recurrent and/or aggressive meningioma growth with limited adverse effects</td>
<td>NCT02333565</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>19</td>
<td>A pilot study of pre- and post-operative uses of Somatuline® Depot</td>
<td>Acromegaly</td>
<td>To evaluate pre- and post-operative use of Somatuline® Depot. Initial treatment (3 months before surgery) was scheduled to see any reduction in complication of surgery and any improvement in remission following surgery. Second phase, which includes a 3–12 month post-surgery is only for people who do not go into remission after the operation to assess the possible remission of acromegaly after resuming the drug treatment for an additional 3 to 9 months</td>
<td>NCT01861717</td>
<td>IV</td>
<td>Recruiting</td>
</tr>
<tr>
<td>20</td>
<td>Treatment of inoperable and/or metastatic Merkel cell carcinoma by somatostatin analogs (PHMC-Merkel)</td>
<td>Merkel cell carcinoma</td>
<td>To evaluate the efficacy of lanreotide on locally evolving and/or metastatic MCC in a national prospective multicenter phase II study. The lanreotide treatment (Somatuline® LP 120 mg injected s.c. every 28 days) will be provided and an ancillary immunohistochemistry study on somatostatin receptors II, III, and V, dopamine receptors I and II and polymavirus MCPyV will be performed</td>
<td>NCT02351128</td>
<td>II</td>
<td>Recruiting</td>
</tr>
<tr>
<td>21</td>
<td>A 12/24-week, open, multicenter, phase IV study on safety and efficacy of 2 mg exenatide once weekly (Bydureon) in T2DM patients</td>
<td>Type II diabetes mellitus</td>
<td>To provide additional information regarding safety and efficacy of Bydureon, exenatide once weekly for injectable suspension, in the Korean population</td>
<td>NCT02533453</td>
<td>IV</td>
<td>Recruiting</td>
</tr>
<tr>
<td>22</td>
<td>Effects on re-endothelialization with Bydureon treatment in type 2 diabetes subjects</td>
<td>Atherosclerosis, diabetes, restenosis</td>
<td>To study the effect of exenatide long-acting release (LAR) (Bydureon) to minimize vascular remodeling and neointima formation after percutaneous coronary intervention and to accelerate stent endothelialization</td>
<td>NCT02621489</td>
<td>IV</td>
<td>Recruiting</td>
</tr>
<tr>
<td>23</td>
<td>Exenatide once weekly, cardiovascular risk and type-2 diabetes</td>
<td>Type II diabetes mellitus</td>
<td>To evaluate the effect of exenatide once-weekly formulation on cardiovascular risk markers related to subclinical atherosclerosis, endothelial dysfunction, oxidative stress and atherogenic lipoproteins</td>
<td>NCT02380521</td>
<td>IV</td>
<td>Recruiting</td>
</tr>
<tr>
<td>24</td>
<td>New onset type 1 diabetes: role of exenatide</td>
<td>Type 1 diabetes</td>
<td>To study the effect of exenatide long-acting release (LAR) (Bydureon) for improving the after meal sugars in people with new onset type 1 diabetes</td>
<td>NCT01269034</td>
<td>IV</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>
responsive feature of PLA copolymers stimulated the research directed to PLA injectable formulations. Apart from academia, the pharmaceutical companies have also taken initiative, and last two decades have witnessed the arrival of many PLA and its copolymer based products in the market. Remarkable properties of PLA and its copolymers made its way from bench to the clinic and hopefully are well on their way to improve the length and quality of life for patients suffering from various diseases. However, in spite of the great achievements, there is still a long way to go which is justified with cases of Nutropin® Depot, OncoGel™ and many more. Nutropin®, a sustained release depot formulation of Genentech’s human growth hormone, was developed using Alkermes’ ProLease® technology. It was approved in 1999 by the USFDA as a treatment for growth hormone deficiency in pediatric patients. Nutropin® Depot performed well in preclinical and early clinical studies, and it successfully delivered a larger macromolecule, ~22,000 kDa than the previous USFDA approved microparticle depot systems. However, the product was discontinued in 2004 by a joint agreement of both companies due to unmet expectation in terms of market revenue. These issues are also encountered by other growth hormone products and, to some extent, by several protein-based microparticle formulations. This example highlights some of the post-market challenges faced by microparticle formulations that need to be addressed in order to remain competitive. OncoGel™, a cremophor free Paclitaxel formulation for local tumor management, also faced challenges during its clinical phase development. Recognizing what we are missing is the first step toward moving in the right direction to solve many problems that remain. Sincere efforts to address many issues are still required to find new products for various indications.

References

F.G. Hutchinson, B.J.A. Furr, Biodegradable polymers for the sustained release of Zoladex® (10.8 mg Goserelin Acetate Implant), 2003.


