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A 30-Year History of PLG Applications in Parenteral Controlled Drug Release

Poly(lactide-glycolide) has been used for drug-delivery applications because of its beneficial physicochemical properties, long safety record, and reliable commercial supply.

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 The history of poly(lactide-glycolide) (PLG) for drug-delivery applications can be told through the number of products that has steadily emerged on the market since the first product was launched in 1986. More than 35 commercial drug products have relied on the beneficial physical and chemical properties of PLG, its long safety record, and the reliable commercial supply of this polymer.

The first PLG drug delivery patent

US Patent 3,773,919 (1) was the first issued drug-delivery patent describing PLG/drug compositions. This patent, assigned to E.I. du Pont de Nemours and Company, was issued on Nov. 20, 1973. George Boswell and Richard Scribner were the groundbreaking inventors. They were experimenting with PLG-based drug delivery in the late 1960s, as indicated by the 1969 filing date. The patent describes the use of polylactide in drug formulations as a means of providing slow and sustained release of the drug over a controlled period. Pharmaceutical depot compositions described in the patent include injectable particles with sizes ranging from 0.1 to 1000 micron. The patent specification defines polylactides as polyesters generally derived from α-hydroxycarboxylic acids and specifically derived from lactic acid (α-hydroxypropionic acid). Polylactide, polyglycolide, and poly(lactide-co-glycolide) copolymers, therefore, are described. The patent specification lists many classes of drugs, including small molecules and peptides, but not proteins. The inventors interestingly foresaw the potential of this drug-delivery technology for antipsychotic agents, natural and synthetic hormones, narcotic antagonists, vitamin B12, and peptides such as bacitracin, polymyxin B sulfate, and sodium colistimethate. Emphasis was placed on the delivery of endocrine agents such as natural steroids and non-steroidal agents for fertility control, progestogens, estrogens, androgens, antiandrogens, corticoids, anabolic agents, and anti-inflammatory actives. Today, there are a number of PLG-based pharmaceutical products on the market that deliver many of the drug substances listed in the patent.

Long-acting contraceptives

In the 1970s, there was a lot of interest in controlled-release research for pharmaceutical applications. Much of this activity focused on the development of long-acting contraceptives. The goal was to develop formulations that released contraceptive steroids at a programmed rate for one month or longer following a single parenteral administration. Initially, researchers in the contraception field used non-biodegradable silicone materials as controlled-release excipients (2). PLG polymers were later found to have good biocompatibility and desirable bioabsorption properties; as a result, many investigators began to formulate contraceptive steroids with PLG as functional polymers. Various dosage forms, including injectable microparticles, implants, and fibers, were investigated for both systemic and local delivery (3).

With a global mission, the Program for Applied Research for Fertility Regulation (PARFR) funded several contraceptive programs. One of these programs involved injectable PLG microparticles for the release of norethisterone for one month and three months. The Southern Research Institute and the University of Alabama at Birmingham performed this program. Successful preclinical work led to the preparation of norethisterone microparticles for clinical trials, which represented the first use of PLG microparticles in human clinical trials in 1981 (4).

[2]
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Animal contraception work funded by Syntex in 1979 led to significant discoveries. This work involved the peptide drug nafarelin, an analog of luteinizing hormone-releasing hormone (LHRH). Naferelin was difficult to microencapsulate because of its good water solubility. Also at the time, little was known about the release profile of large, water-soluble molecules such as peptides from PLG polymers. A milestone occurred when a Southern Research Institute/Syntex team developed a phase-separation microencapsulation process for LHRH peptides that was much different from emulsion-based, solvent evaporation processes used to encapsulate steroids. This achievement opened the door to producing one-month formulations that showed sustained release of LHRH in animals (5, 6).

Debiopharm, a Swiss-based biopharmaceutical company, recognized that controlled-

release LHRH for the suppression of testosterone had greater potential for the treatment of prostate cancer than contraception. Having licensed triptorelin, another LHRH analog, Debiopharm contracted Southern Research Institute in 1981 to develop triptorelin microparticles with PLG. This effort led to the market launch of Decapeptyl SR (sustained-release triptorelin) in Europe in 1986, which was the first PLG injectable microparticle product on the market as well as the first injectable peptide-releasing product to be commercialized (7). It is still on the market today distributed by Ferring and Ipsen-Beaufour.

TAP, a joint venture of Takeda and Abbott, also used PLG microparticle technology for the one-month delivery of another LHRH analog, leuprolide. Again, the indication was prostate cancer. The product was launched as Lupron Depot (leuprolide acetate depot suspension) in 1989 (8), and it became a blockbuster drug with sales exceeding that of a liquid leuprolide product, which demonstrated the value of complex, extended-release parenteral products based on PLG excipients. Furthermore, because of the ability to tune the resorption rate of PLG polymers, TAP was able to extend the lifecycle of Lupron Depot with the launch of three-, four-, and six-month leuprolide microparticle products. Other LHRH/PLG microparticles emerged on the market as well, including Sanofi's Sprecur MP for the one-month delivery of buserelin and Watson's Trelstar Depot and Trelstar LA for the one- and three-month delivery of triptorelin pamoate, respectively.

Other extended-release microparticles

In the 1970s, the Sandoz drug-delivery group in Basel was actively developing extended-release, drug-delivery formulations with PLG polymers. First, Sandoz developed and launched Parlodel LAR (long acting repeatable bromocriptine). Parlodel LAR microparticles delivered bromocriptine for one month (9). With the goal to provide a more continuous drug-delivery pattern for their next extended release products, Sandoz developed a branched PLG polymer made with glucose as the initiator. This branched PLG or star PLG polymer was the basis of Sandostatin LAR, a successful product that releases octreotide, a somatostatin peptide, for four weeks. The product was launched in 1997 and is indicated for the treatment of acromegaly and carcinoid cancers (10). In 2014, Novartis launched another somatostatin

microparticle product with PLG--Signifor LAR, which delivers the peptide pasireotide for the same indication as Sandostatin LAR. Interestingly, these microparticles comprise a blend of PLG polymers. Ipsen-Beaufor has a somatostatin PLG microparticle product on the market as well, called Somatuline LA (lanreotide).

To date, Genentech is the only company that launched an extended-release PLG microparticle product for the delivery of a protein. This product, Nutropin Depot, releases recombinant human growth hormone for the treatment for growth hormone deficiency in pediatric patients. This product went on the market in 1999 (11).

Examples of other PLG microparticles on the market include Risperdal Consta (risperidone for antipsychotic indications), Vivitrol (naltrexone for alcohol addiction), and Bydureon (GLP1 peptide to treat type 2 diabetes).

Extended-release implants

In addition to PLG microparticles, PLG implants also played a role in controlled-release drug delivery of pharmaceutical products. A melt extrusion process, similar to fiber-spinning, is commonly used to make PLG implants. PLG drug-delivery implants are typically cylindrical rods about 1 cm long and 2 mm in diameter, with the drug dispersed within the PLG matrix core. Once an implant is injected, it can release the drug for weeks and months. After the drug is spent, the implant bioabsorbs.

While naferelin microparticles were being developed, ICI Pharma was working on a PLG implant for the one-month extended release of goserelin, another LHRH analog. This work led to the launch of Zoladex (goserelin) in 1990 by ICI Pharma. Sanofi's Profact Depot for the two- to three-month delivery of buserelin is another PLG/LHRH implant on the market.

Ozurdex (dexamethasone intravitreal implant) is the first PLG extended-release implant administered to the eye using a specifically designed applicator. The PLG implant releases 700 μg of dexamethasone for one month to treat macular edema and uveitis.

The most recent PLG implant introduced on the market is Scenesse developed by Evonik for the Australian company Clinuvel Pharmaceuticals. It releases the peptide afamelanotide, a photoprotective drug that protects against sunlight damage by increasing melanin in the skin. Scenesse is indicated for the treatment of erythropoietic protoporphyria, a severe skin disorder caused by the body's inability to protect itself from sunlight.

Local drug delivery

In the early 1980s, localized drug delivery was another novel concept pursued with PLG polymers. One program, funded by the US Army Institute of Dental Research, focused on the local delivery of antibiotics to treat battle wounds (12). The concept was for a soldier to apply a powder of controlled-release PLG/antibiotic microparticles directly into a wound. The microparticles would then slowly release the antibiotic and maintain a high level of drug at the wound site for 14 or 21 days to achieve efficacy without requiring daily, oral dosing.

OraPharm successfully brought the concept of local delivery to the market to treat bacterial infections using PLG excipient. Its Arestin (minocycline) PLG microparticles treat periodontal diseases. The dry microparticle powder is administered to the periodontal pocket using a cartridge system that is provided in the product's kit. Once administered, the microparticles stay in the pocket and release minocycline for two weeks. In addition to drug release, the PLG excipient plays a role in keeping the microparticles in the pocket.

In-situ forming drug delivery

In-situ forming PLG drug delivery was an approach invented by Southern Research Institute scientists. The concept involves administering a PLG polymer solution containing the drug substance such as the antibiotic doxycycline. The resulting liquid formulation is placed into a diseased periodontal pocket. Once in the pocket, the formulation solidifies due to solvent extraction, taking on the shape of the pocket and releasing antibiotic into the pocket for seven days (13). The key with this approach is that the formulation stays in the pocket during antibiotic treatment, especially as the pocket heals and decreases in size. The technology was licensed to Vipont Research Laboratories, which later became Atrix Laboratories. In 1999, Atrix successfully launched a periodontitis product branded as Atridox. Atrix also applied this *in-situ* forming technology to systemic delivery, for example in its Eligard product (leuprolide acetate injectable suspension) for the extended release of LHRH to treat prostate cancer (14).

Nanoparticles

PLG-based drug-delivery technology can be formed into nanoparticles (i.e., particles less than 1 μm in diameter). These nanoparticles can contain encapsulated drug, typically hydrophobic ones. Proteins, such as antibodies, and other moieties can be conjugated on the surface of the nanoparticles as a way of targeting them to specific cells.

Polymeric micelles represent a specific class of PLG-based drug-delivery nanoparticles, whereby a diblock of polylactide and polyethylene glycol (PEG) with hydrophobic and hydrophilic regions respectively allows for self-assembly of the polymer chains into 50-nm nanoparticles. The resulting core-shell constructs have PEG oriented on the surface. Moieties conjugated to the surface are used to target the nanoparticles to biological sites and to minimize toxicity. Genexol (paclitaxel) by Samyang is an example of a PLG polymeric micelle product on the market. Paclitaxol is encapsulated within the hydrophobic core of the polymeric micelle, and the product is indicated for the treatment of breast, lung, and ovarian cancers. The PLG polymeric micelle technology enhances the solubility of paclitaxel and allows significantly higher dosing of paclitaxel to patients without additional toxicity (15).

Vaccines

Researchers have investigated the use of PLG microparticles to encapsulate vaccine antigens. Microparticles of less than 10 μm in diameter are taken up by macrophages, dendritic cells, and Peyer's patches. The engulfed microparticles then release the vaccine antigen within these cells, triggering the cells to produce immunoglobulin antibody titers, which provide mucosal and T-cell responses.

The crucial role of commercial polymer supply

The supply of lactide/glycolide polymers plays a crucial role in the success of PLG-based drug-delivery products. Commercially manufactured PLG has been important in supplying the quantities needed for drug-delivery products, as well as ensuring that the PLG polymers have consistent and desired properties.

During early times, laboratories had to make their own PLG polymers and monomers. These polymers, especially polymers with high glycolide content (e.g., 50:50 lactide:glycolide polymers) had solubility challenges due to their long glycolide blocks. Also, polymer solubility varied from batch to batch, making it difficult to perform robust formulation processing and achieve reproducible drug-delivery performance from microparticles and implants. Resomer polymers offer more consistent properties with better and reproducible solubility.

The future for PLG drug delivery

The majority of biopharmaceutical drugs being developed today will require parenteral administration, and many of these compounds will require extended-release performance. Complex, parenteral drug-delivery technologies will meet these requirements. Safe and proven excipients, such as PLG polymers with consistent properties, will play a key role in formulation development.

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