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Sustained-Release Injectable Drug Delivery

A review on the current status of long-acting injectables, including commercially marketed products. This article is part of a special Drug Delivery issue.

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Reproducible sustained delivery of a drug at a target site is one of the main themes in controlled drug-delivery systems. The most commonly used drug-delivery systems, which can release drugs longer than one week, are parenteral injections and implants. Certain implant systems can deliver drugs for more than one year, and the longest drug delivery can be achieved by biodegradable or nonbiodegradable implant systems. Some examples of US Food and Drug Administration approved long-acting products are listed in Table I.

Table I: Examples of US Food and Drug Admistration-approved long-acting formulations on the

Drug	Brand name	Dosage form	Administration	Dosing frequency	Therapeutic
Fluoxetine hydrochloride (90 mg)	Prozac weekly	Capsule	Oral	once a week	Major depressive di
Alendronate sodium (70 mg)	Fosamax	Tablet/solution	Oral	once a week	Osteoporosis
Risedronate sodium (150 mg)	Actonel	Tablet	Oral	once a month	Osteoporosis
Ibandronate sodium (150 mg)	Boniva	Tablet	Oral	once a month	Osteoporosis
Ibandronate sodium (3 mg/3 mL)	Boniva	Injection	IV bolus	every 3 months	Osteoporosis
Zoledronic acid (5 mg/100 mL)	Reclast	Injection	IV infusion	once a year	Osteoporosis
Goserelin acetate (3.6 mg, 10.8 mg)	Zoladex	Implant	SC	every 1–3-months	Advanced prostate canc
Buserelin acetate (9.9 mg)	Suprefact depot	Implant	SC	every 3 months	Advanced prostate canc
Leuprolide acetate (72 mg)	Viadur	Implant	SC	once a year	Advanced prostate canc
Etonogestrel (68 mg)	Implanon	Implant	Subdermal	every 3 years	Hormone ther
Dexamethasone (0.7 mg)	Ozurdex	Implant	Intravitreal	every 2–3 months	Macular eden
Ganciclovir (4.5 mg)	Vitrasert	Implant	Intravitreal	every 5–8 months	Cytomegalovi retinitis
Fluocinolone acetonide (0.59mg)	Retisert	Implant	Intravitreal	every 30 months	Uveitis

* Does not include injectable sustained-release drug-delivery systems. IV is intravenous. SC is subcutaneous.

Table I: Examples of US Food and Drug Admistration-approved long-acting formulations on the market.*

Long-acting injectable formulations offer many advantages when compared with conventional formulations of the same compounds. These advantages include the following: a predictable drug-release profile during a defined period of time following each injection; better patient compliance; ease of application; improved systemic availability by avoidance of first-pass metabolism; reduced dosing frequency (i.e., fewer injections) without compromising the effectiveness of the treatment; decreased incidence of side effects; and overall cost reduction of medical care.

This review focuses on the current status and explores long-acting injectables with special attention to marketed products. Injectable routes, types of long-acting injectables (i.e., oil-based injections, injectable drug suspensions, injectable microspheres, and injectable *in situ* systems), drugs and polymers for depot injections, commercially available depot injections, and future injectable sustained-release drug-delivery systems are also discussed.

Types of injectable routes of administration

It is well recognized that the advantages of parenteral injections are immediate systemic drug availability and rapid onset of action. Another significant and unique advantage of parenteral injection is a long-term drug delivery by the formation of a depot or reservoir at the injection site after drug administration. As depicted in Table I, intravenous (IV) injection can be used for certain prolonged acting drugs due to the drugs' long half-lives in the body after IV

administration. The sustained release of drug from these preparations is a result of the long-acting property of drug and its residence in the bloodstream or the bone.

In general, there are two routes by which long-acting parenteral injections are most frequently administered: intramuscular (IM) and subcutaneous (SC). To determine the injectable route of administration for long-term delivery formulations, many factors should be considered such as safety profile, ease of administration, patient's limited mobility, area for target injection sites, quality of life and cost of therapy (1). In many cases, SC is the preferred route for administering a drug by injection because of greater area for target injection sites, use of shorter needles, ease of self-administration, less discomfort and inconvenience for patients, and better safety profile (1). Various insulin products are given SC, and this route of administration presumably continues to represent the primary route of delivery for protein-based drugs. However, the volumes of SC injection are usually limited to no more than 1–2 mL, and only nonirritant substances can be injected by a SC route because irritants can cause pain, necrosis, and sloughing at the site of injection. On the other hand, greater injection volumes (2–5 mL) can be given by the IM route. Mild irritants, oils, and suspensions can be injected by IM route in the large skeletal muscles (i.e., deltoid, triceps, gluteus maximus, and rectus femoris) because these muscles are less richly supplied with sensory nerves and are more vascular. Therefore, a few SC injections for long-term release can be found on the market (i.e., Depo-SubQ Provera 104, Pfizer (New York); Nutropin Depot, Genentech (South San Francisco, CA), and Eligard, sanofi-aventis (Paris), and many long-acting IM injections are available on the market (oil-based injections, injectable drug suspensions, and injectable microspheres).

Sustained-release properties of injectables

Sustained-release parenteral injections can be divided into several types: oil-based injectable solutions, injectable-drug suspensions, polymer-based microspheres and polymer-based *in-situ* formings. Oil-based injectable solutions and injectable drug suspensions control the release for weeks while polymer-based microspheres and *in-situ* gels are claimed to last for months (1, 7).

Oil-based injectable solutions and injectable drug suspensions. Conventional long-acting injections consist either of lipophilic drugs in aqueous solvents as suspensions or of lipophilic drugs dissolved in vegetable oils. The administration need for these long-acting formulations only takes place every few weeks or so. In the suspension formulations, the rate-limiting step of drug absorption is the dissolution of drug particles in the formulation or in the tissue fluid surrounding the drug formulation. Poorly water-soluble salt formations can be used to control the dissolution rate of drug particles to prolong the absorption, and olanzapine pamoate is an example of a poorly water-soluble salt form of olanzapine. Certain drugs for long-acting formulations are synthesized by esterification of the parent drug to a long-chain fatty acid. Based on its extremely low water solubility, a fatty acid ester of a drug dissolves slowly at the injection site after IM injection and is hydrolyzed to the parent drug. Once the ester is hydrolyzed intramuscularly, the parent drug becomes available in the systemic circulation. The release rate of paliperidone palmitate from long-acting injectable suspension is governed by this mechanism. In many formulations, a fatty acid ester of a drug is used to prepare an oil-based parenteral solution, and the drug-release rate from solution is controlled by the drug partitioning between the oil vehicle and the tissue fluid and by the drug bioconversion rate from drug esters to the

parent drug. However, several other factors such as injection site, injection volume, the extent of spreading of the depot at the injection site, and the absorption and distribution of the oil vehicle *per se* might affect the overall pharmacokinetic profile of the drug. Decanoic acid esters of antipsychotic drugs are widely used for these oil-based IM injections.

Polymer-based microspheres and in-situ formings. The development of polymer-based long-acting injectables is one of the most suitable strategies for macromolecules such as peptide and protein drugs. Advantages of polymer-based formulations for macromolecules include: *in vitro* and *in vivo* stabilization of macromolecules, improvement of systemic availability, extension of biological half life, enhancement of patient convenience and compliance, and reduction of dosing frequency.

Among the various approaches to deliver macromolecules parenterally, biodegradable microsphere systems are the most commercially successful. The most crucial factor in the design of injectable microspheres is the choice of an appropriate biodegradable polymer. The release of the drug molecule from biodegradable microspheres is controlled by diffusion through the polymer matrix and polymer degradation. The nature of the polymer, such as composition of copolymer ratios, polymer crystallinities, glass-transition temperature, and hydrophilicities plays a critical role in the release process. Although the microspheres structure, intrinsic polymer properties, core solubility, polymer hydrophilicity, and polymer molecular weight influence the drug-release kinetics, the possible mechanisms of drug release from microsphere are as follows: initial release from the surface, release through the pores, diffusion through the intact polymer barrier, diffusion through a water-swollen barrier, polymer erosion, and bulk degradation. All these mechanisms together play a part in the release process (2).

Another intensively studied polymeric injectable depot system is an *in-situ*-forming implant system. *In situ*-forming implant systems are made of biodegradable products, which can be injected *via* a syringe into the body, and once injected, congeal to form a solid biodegradable implant. This article will briefly summarize the types of *in situ*-forming implants because the topic has been intensively reviewed elsewhere (3–5). Biodegradable injectable *in situ*-forming implants are classified into five categories based on the mechanism of depot formation: thermoplastic pastes, *in situ* cross-linked polymer systems, *in situ* polymer precipitation, thermally induced gelling systems, and *in situ* solidifying organogels. The mechanism of depot formation of thermoplastic pastes is to form a semisolid upon cooling to body temperature after injection into the body in the molten form. Cross-linked polymer networks can be achieved *in situ* in various ways, forming solid polymer systems or gels. Methods for *in situ* cross-linked systems include free radical reactions, usually initiated by heat or absorption of photons, or ionic interactions between small cations and polymer anions. *In situ* formings can be produced by causing polymer precipitation from solution. A water-insoluble and biodegradable polymer are solubilized in a biocompatible organic solvent to which a drug is added which forms a solution or suspension after mixing. When this formulation is injected into the body, the water-miscible organic solvent dissipates and water penetrates into the organic phase. This leads to phase separation and precipitation of the polymer forming a depot at the site of injection. This method has been designed as Atrigel technology (QLT, Vancouver, Canada), which used as a drug-carrier system for Eligard. Thermally induced gelling systems show thermo-reversible sol/gel transitions and are characterized by a lower critical solution temperature. They are liquid at room

temperature and produce a gel at and above the lower critical solution temperature. *In situ* solidifying organogels are composed of water-insoluble amphiphilic lipids, which swell in water and form various types of lyotropic liquid crystals.

Drugs delivered as sustained-release injectables

Various drugs are investigated for sustained-release injectable delivery systems for controlled drug delivery as recently described by these authors (6). These systems include small molecular drugs and protein/peptide drugs. Examples of drugs for sustained-release injectable delivery systems include: hormone therapy (i.e., human somatropin) (7, 8); protein therapeutics such as the analog of glucagon-like peptide-1 (9); recombinant human bone morphogenetic protein-2 (10); superoxide dismutase (11); salmon calcitonin (12, 13); insulin (14–16); gene delivery such as plasmid DNA (17–19); cancer therapeutic agents such as bleomycin (20), paclitaxel (21), cisplatin (22), a peptide-like antineoplastic agent (23); postoperative pain therapeutic agents such as ketorolac tromethamine (24); schizophrenia drugs such as aripiprazole (25), olanzapine (26); contraceptive peptide vaccine (27); drugs to treat alcohol dependence such as naltrexone (28); and immunosuppressive drugs such as rapamycin (29).

Despite a number of parenteral depot studies using a variety of drugs, only drugs in limited therapeutic areas are available on the market. Antipsychotic drugs and hormones have been used for more than five decades in the field of schizophrenia and hormone replacement therapy. Since the first launching of microsphere formulation, Lupron Depot (Abbott, Abbott Park, IL) for the palliative treatment of advanced prostate cancer in 1989, several microsphere formulations and *in situ*-forming implants have been released on the US market. The therapeutic indications and drugs of commercialized products include: the palliative treatment of advanced prostate cancer (leuprolide acetate and triptorelin pamoate); the treatment of acromegaly (octreotide acetate and lanreotide acetate); the long-term treatment of growth failure (somatropin-rDNA origin); the treatment of schizophrenia (risperidone); and the treatment of alcohol dependence (naltrexone).

Polymers in injectable sustained release

As recently described by these authors (6), a variety of biodegradable polymers for controlled drug delivery intensively studied over the past several decades include polylactides (PLA), polyglycolides (PGA), poly(lactide-co-glycolide) (PLGA), poly(ε-caprolactone) (PCL), polyglyconate, polyanhydrides, polyorthoesters, poly(dioxanone), and polyalkylcyanoacrylates. Among the various approaches to deliver macromolecules parenterally, injectable biodegradable microspheres are the most successful systems (30). Many microsphere research reports have demonstrated the usefulness of biodegradable polymers such as PLGA microspheres (31–38), PCL microspheres (39), polyanhydride microspheres (40), polyorthoesters microspheres (41), and polyalkylcyanoacrylate microspheres (42, 43).

The Atrigel technology that is used in Eligard containing leuprolide acetate and PLGA is a once-monthly *in situ*-forming implant for the palliative treatment of advanced prostate cancer. Many reports have been published on novel biodegradable *in situ*-forming polymers such as multiblock poly(ether ester urethane)s consisting of poly-[(*R*)-3-hydroxybutyrate] (PHB), poly(ethylene glycol) (PEG), and poly(propylene glycol) (PPG) polymer (44), PEG-grafted chitosan polymer

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