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Review Article

A REVIEW ON SUSTAINED RELEASE INJECTABLE DEPOT DRUG DELIVERY SYSTEMS

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ABSTRACT

The proper management of some diseases has been shown to be dependent upon achieving consistent pharmacokinetic profiles, which is reliant on the timing of dosages, paired with the total compliance of the patient. For many specific patient populations compliance with daily oral dosing presents inherent complications. However, patients receiving continuous (i.e., extended release) therapies have been shown to have lower rates of relapse, because of the constant dosing of medication. Increasing the treatment length of a dose given by injection and finding preferential ways to deliver extended-release therapies are the basis for continued research in the formulation of extended or sustained-release injection products. In many cases, trying to avoid a parenteral (injectable) route of administration through oral dosing is not feasible or even desirable. Therefore, the development of many sustained-release drug products results in injection-based products. Extending the release of a drug may be achieved through the manipulation of physiochemical properties, the use of formulation technologies such as microspheres and nanospheres, and balancing the in vivo properties of the compound (such as half-life). This review will cover current options for developing extended-release pharmaceutical parenteral (injection) delivery systems including microspheres, traditional depots, and injectable implants that are currently approved or in-process of approval by the United States Food and Drug Administration. A detailed insight on the formulation of various injectable drug delivery systems is provided in this review along with an overview about the polymers and excipients mostly used in these formulations.

Key words: parenteral sustained release, depot preparations, microspheres, injectable implants.

1. INTRODUCTION:

In the administration of drugs and in the diagnosis of certain pathological conditions it is highly desirable, if not necessary, to affect a controlled release of one or more substances within the living organism, in particular within a mammalian host. For example, the controlled release of drugs over a period of time within a specified region or organ of the body can be used as a continuous dose, long-term delivery system. Devices for administering such a controlled release of drugs are generally referred to as "depots" or "implants". Continuous, long term drug delivery devices have distinct advantages over oral administration or direct injection of drugs since neither of these earlier developed modes can achieve a desired blood level of a drug in circulation for an extended period of time. Oral administration or direct injection bring about a pulse entry of the drug which may create drug concentrations beyond the capacity of the active centres to accept the drug, and may also exceed the capacity of the metabolic and excretory mechanism of the living organism. Thus, if the level of the drug remains elevated, tissues and/or organs may sustain detrimental effects. One technique for reducing excessive concentrations has been to modify the drug structure to provide a longer metabolic half-life; but this in turn has frequently demonstrated lowered therapeutic effectiveness. [1-5] To avoid the disadvantages of oral or direct injection administration of drugs, a number of modes of administration of continuous dose, long-term delivery devices have been used or proposed. These include devices based upon ingestion, injection, vaginal and uterine insertion, percutaneous application and subcutaneous implantation. While all of these routes of administration may be found useful less than one set of circumstances or the other, the use of subcutaneous implants offers a particularly desirable combination of properties to permit the administration of substances on a localized or systemic basis. To this end, subcutaneous implants serving as depots capable of slow release of a drug have been proposed. These implants suggest the possibility of attaining continuous administration over a prolonged period of time to achieve a relatively uniform delivery rate and, if desired, a static blood level. Since an excessive concentration of drug never enters the body fluids, problems of pulse entry are overcome and metabolic half-life is not a factor of controlling importance. [1-5]

Despite the advantages of administering drugs from implants, prior art devices designed for this purpose have possessed one or more disadvantages which limit their acceptability and efficacy. Among such disadvantages are non-biodegradability which may require a surgical procedure to remove them; non-biocompatibility which may result in the introduction of undesirable and even harmful substances into the body; antigenicity which gives rise to the production of unwanted antigen bodies in the system; and difficulty in controlling release rates of the drugs. [1-5]

Solid implant drug delivery system containing a drug incorporated in a thermoplastic or thermosetting biodegradable polymers have been widely used successfully. Such implants have to be inserted into the body through an incision which is sometimes larger than desired by the medical profession and occasionally leads to a reluctance of the patients to accept such an implant or drug delivery system. Such drug delivery systems include reservoir devices, osmotic devices and pulsatile devices for delivering beneficial agents. Injecting drug delivery systems as small particles, microparticles or microcapsules avoids the incision needed to implant drug delivery systems.[2-5] Microparticles, microspheres, and microcapsules, referred to herein collectively as "microparticles", are solid or semi-solid particles having a diameter of less than one millimetre, more preferably less than 100 microns, which can be formed of a variety of materials, including synthetic polymers, proteins, and polysaccharides. Microparticles have been used in many different applications, primarily separations, diagnostics, and drug delivery. In the controlled drug delivery area, molecules are encapsulated within microparticles or incorporated into a monolithic matrix, for subsequent release. A number of different techniques are routinely used to make these microparticles from synthetic polymers, natural polymers, proteins and polysaccharides, including phase separation, solvent evaporation, emulsification, and spray drying. Generally the polymers form the supporting structure of these microspheres, and the drug of interest is incorporated into the polymer structure. Exemplary polymers used for the formation of microspheres include homopolymers and copolymers of lactic acid and glycolic acid (PLGA). Microspheres produced using polymers such as this exhibit a poor loading efficiency and are often only able to incorporate a small percentage of the drug of interest into the polymer structure. Therefore, substantial quantities of microspheres often must be administered to achieve a therapeutic effect. [3-5] One disadvantage of the microparticles or beads currently available is that they are difficult and expensive to produce. Microparticles produced by these known methods have a wide particle size distribution, often lack uniformity, and fail to exhibit long term release kinetics when the concentration of active ingredients is high. Residual organic solvents could be toxic when administered to humans or animals. [2-5]

Microparticles prepared using lipids to encapsulate target drugs are currently available. Liposomes are spherical particles composed of a single or multiple phospholipids and cholesterol bilayers. Liposome technology has been hindered by problems including purity of lipid components, possible toxicity, vesicle heterogeneity and stability, excessive uptake and manufacturing or shelf-life difficulties.

Therefore, there is an on-going need for development of new methods for making microparticles, particularly those that can

be adapted for use in the separations, diagnostic and drug delivery area. Preferably, such improved microparticles would permit the sustained release of active agents in a predictable, consistent manner. 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. 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. Examples of extended release injectable formulations are given in Table.1 and the formulation details are given in Table.2.[1-5]

Table.1.Extended-Release Injectable Drug Products

Active Pharmaceutical Ingredient	Active Moiety	Release Mechanism	Formulation
Olanzapine Pamoate Monohydrate	olanzapine	Diffusion	Suspension
Fluphenazine Decanoate	fluphenazine	Prodrug	Sesame oil solution
Paliperidone Palmitate	paliperidone	Prodrug	Nano-suspension
Flupentixol Decanoate	flupentixol	Prodrug	Vegetable oil solution
Haloperidol Decanoate	haloperidol	Prodrug	Sesame oil solution
Risperidone	risperidone	Microsphere	Suspension
Naltrexone	naltrexone	Microsphere	Suspension
Leuprolide Acetate	leuprolide	Microsphere	Suspension
Octreotide Acetate	somatostatin analogue	Microsphere	Suspension
Lanreotide Acetate	somatostatin analogue	Diffusion	Supersaturated Solution
Methylprednisolone Acetate	methylprednisolone acetate	Diffusion	Suspension
Medroxyprogesterone Acetate	medroxyprogesterone acetate	Diffusion	Suspension
Testosterone Cypionate	testosterone	Prodrug	Cottonseed Oil Solution
Goserelin Acetate	goserelin	Diffusion	Polymer Implant
Exenatide	exenatide	Microsphere	Suspension

Table.2.Formulation Details of Extended-Release Products

Product	Dose[15]	Injection Volume [15]	Release Mechanism	Approval Date[15]
Olanzapine Pamoate Monohydrate	eq. 150 mg eq 210 mg eq 300 mg eq 405 mg	1.0 mL 1.4 mL 2.0 mL 2.7 mL	Diffusion	US- December 2009
Fluphenazine Decanoate	25 mg/mL	<5 mL	Prodrug	US- June 1972
Paliperidone Palmitate	39 mg 78 mg 117 mg 156 mg 234 mg	0.25 0.5 0.75 1.0 1.5	Prodrug	US- July 2009
Flupentixol Decanoate	20 mg/mL	1 or 2 mL	Prodrug	Canada-1976
Haloperidol Decanoate	50 mg/mL 100 mg/mL	1or 5 mL 1 or 5 mL	Diffusion	US- January 1986
Risperidone	12.5 mg 25 mg 37.5 mg 50 mg	2.0 mL	Microspheres	US- October 2003
Naltrexone	380 mg	4.0 mL	Microspheres	US- April 2006
Leuprolide Acetate	3.75 mg 7.5 mg 11.25 mg 15 mg 22.5 mg 30 mg	<2 mL	Microspheres	US- January 1989
Octreotide Acetate	eq 10 mg eq 20 mg eq 30 mg	5 mL	Microspheres	US- November 1998
Lanreotide Acetate	eq 60 mg eq 90 mg eq 120 mg	0.2-0.5 mL	Diffusion	US- August 2007
Methylprednisolone Acetate	20 mg/mL 40 mg/mL 80 mg/mL	5 mL 1, 5, 10 mL 1 or 5 mL	Diffusion	US-Before January 1982
Medroxyprogesterone Acetate	150 mg/mL 400 mg/mL	1 mL 2.5 mL	Diffusion	US- Before January 1982
Testosterone Cypionate	100 mg/mL 200 mg/mL	10 mL 1 or 10 mL	Prodrug	US- Before January 1982
Goserelin Acetate	eq 3.6 mg eq 10.8 mg	-	Diffusion	US- January 1996
Exenatide	Undefined	Undefined	Microspheres	US- Pending Approval

2. 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. 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. [6] 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. 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 maximum, 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).[6]

3. Types of depots drug delivery system:

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.

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. [7]

Polymer-based microspheres and in-situ forming: 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, and 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 crystallinity, glass-transition temperature, and hydrophilicity 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, and 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. [7]

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. 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 is solubilised 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. [8-10]

4. Drugs delivered as depots:

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) ; protein therapeutics such as the analog of glucagon-like peptide-1; recombinant human bone morphogenetic protein-2; superoxide dismutase; salmon Calcitonin; Insulin; gene delivery such as plasmid DNA; cancer therapeutic agents such as Bleomycin, Paclitaxel, Cisplatin, a peptide-like antineoplastic agent; postoperative pain therapeutic agents such as Ketorolac tromethamine; schizophrenia drugs such as Aripiprazole, Olanzapine; contraceptive peptide vaccine; drugs to treat alcohol dependence such as Naltrexone; and immunosuppressive drugs such as Rapamycin.[13-34] 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). [13-34]

5. Polymers used in depots:

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. Many microsphere research reports have demonstrated the usefulness of biodegradable polymers such as PLGA microspheres, PCL microspheres, polyanhydride microspheres, polyorthoesters microspheres, and polyalkylcyanoacrylate microspheres. [35-47]

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), (PEG). [48-52] Commercialized polymer-based injectable depot systems have used polymers or copolymers composed of monomers of lactic and glycolic acid. These polymers have the advantages of being semi permeable, biocompatible, and biodegradable, which makes them universally acceptable as injectable materials for drug-depot systems.[53]

6. Formulation of depots:

6.1. Microsphere depots:

The choice of the technique depends on the nature of the polymer, the drug, the intended use, and the duration of the therapy. The microencapsulation method employed must include the following requirements:[54-58]

i) The stability and biological activity of the drug should not be adversely affected during the encapsulation process or in the final microsphere product.

(ii) The yield of the microspheres having the required size range (up to 250 µm, ideally(125 µm) and the drug encapsulation efficiency should be high.

(iii) The microsphere quality and the drug release profile should be reproducible within specified limits.

(iv)The microspheres should be produced as a free flowing powder and should not exhibit aggregation or adherence.

6.1.1. Solvent evaporation and solvent extraction process [61-76]

6.1.2. Double (multiple) emulsion process[61-76]

6.1.3. Phase separation (coacervation) .[77-88]

6.1.4. Spray drying [89-100]

6.2. Implants and miscellaneous devices:

Preparation of drug-loaded implants from PLA or PLGA has been reported by many groups. Kunou et al. have designed nail-like Ganciclovir incorporated D,L-PLGA implant (length-5 mm, diameter-1 mm) for intraocular drug delivery to treat cytomegalovirus retinitis. Wang et al. have reported preparation (by compression) of 5-fluorouracil D,L-PLGA subconjunctival coated and uncoated implants/matrices (5 mg, diameter*2.5 mm, thickness*1.2 mm) using drug : PLGA ratio of 9 : 1, 8 : 2, and 7 : 3. Lin et al. and others have investigated the performance of various antibiotics loaded PLA and PLGA implants, beads and cylinders. Lemmouchi have reported in vitro and in vivo performance of drug-loaded rods of various polyesters prepared by the melt extrusion process [101-119]

6.3. In situ formed devices:

In an article, Schmitt et al. have reported preparation of amaranth incorporated pellets (diameter*3.7 mm, thickness*3.1 mm) from D,L-PLGA which was purchased from three different sources: DuPont, Birmingham Polymers, and Henley Chemicals. Tracy et al. prepared drug-free PLGA pellets by a similar method but used a Carver Laboratory Press instead. Schade et al. have described preparation of aqueous colloidal D,L-PLGA dispersion by a spontaneous emulsification solvent diffusion technique followed by drying of these dispersions to form biodegradable latex film. Preparation of low-density PLGA (85:15) foams having high interstitial void volume was reported by Hsut.*et al.* [101-119]

The traditional methods of preparing PLGA microparticles suffer from drawbacks such as:

(i) The microspheres need to be reconstituted (suspended) in an aqueous media, before they could be injected in the body,

(ii) The hazards and environmental concern associated with the use of organic solvents like ethylene chloride for the solubilisation of PLGA polymer, and

(iii) Residual organic solvents remaining in the final microsphere product.[120-141]

To improve patient acceptance, a novel implant system has been developed which is intramuscularly or subcutaneously administered as a liquid and subsequently solidifies in situ. First PLA or PLGA is dissolved by heating in a water-miscible, biocompatible solvent (this may also act as a plasticizer for the polymer). The polymer solution is then cooled under ambient condition and the drug is dispersed into it by homogenization or alternatively, the drug is dissolved in a solvent (like propylene glycol) which is miscible with the polymer solvent and water. This polymer-solvent-drug system has a viscous consistency but is sufficiently syringeable to be enabled to be injected intramuscularly or subcutaneously by conventional syringe and needle. When injected, it comes into contact with water from aqueous buffer (in vitro condition) or physiological fluid (in vivo condition) and as a result the polymer precipitates and forms a gel matrix (solidifies) entrapping the drug (in situ/in vitro or in situ/in vivo implant formation). The polymer solvent dissipates and diffuses out of the system and water diffuses into the polymer matrix. Due to water-insoluble nature of the polymer, it precipitates/coagulates to form a solid implant in situ, from which the drug is released in a controlled fashion. [120-141]

7. Depots under clinical trials:

A number of researchers have extensively employed the combination of a host of biocompatible solvents and biodegradable polyesters besides PLA and PLGA to deliver a variety of therapeutic drug classes. Although this implant system precludes the need for any surgery for its administration, it has a number of disadvantages: (i) the safety of solvents like NMP used to formulate these systems is questionable and not well documented, (ii) the injection of these liquid implant systems and their subsequent solidification produce non-uniform matrix implants having variable consistency and geometry, and (iii) due to formation of matrix implants having inconsistent texture, shape and size, the drug release from them is variable and unpredictable. (120-141). Jain et al. have described a novel method for in situ preparation of injectable biodegradable PLGA microspheres which did not involve the use of any unacceptable organic solvents [120-141].

The above novel microencapsulation process overcomes some of the disadvantages associated with other methods by excluding the use of unacceptable organic solvents like DCM or NMP and using acceptable vehicle mixture instead to prepare biodegradable PLGA microspheres.

Examples of injectable sustained-release drug delivery systems in clinical trials are given in Table 3 .[65-73]

Table.3.Some injectable sustained release products in clinical trials

Drug	Phase	Dosage form	Administration	Dosing frequency	Therapeutic area	Company
Progesterone	Phase I	Microspheres	IM	once a week	Hormone therapy	Productos Cientificos
Octreotide pamoate	Phase I	Microspheres	IM	once a month	Acromegaly	Novartis
Paclitaxel	Phase II	Oncogel (*in situ*-forming implant, ReGel)	injection directly into the tumor	every 4–6 weeks	Anticancer therapy	BTG
Aripiprazole	Phase III	IM depot	IM	once a month	Schizophrenia	Otsuka Pharm
Pasireotide	Phase III	Long-acting release formulation	IM	once a month	Acromegaly	Novartis
Bupivacaine	Phase III	SABER (*in situ*-forming implant)	at the surgical site prior to the wound closure	lasting 3 days	Postoperative pain	Durect

8. CONCLUSION:

As evident by the growing number of sustained-release injectable pharmaceutical products on the market, injectable depot systems are becoming one of the most effective systems for long-term drug delivery. Owing to the enhanced quality of life and cost of therapy supported by the advances in drug formulation and polymer science, more sophisticated injectable depot systems will be developed and commercialized in the near future. Moreover, the introduction of more potent drugs and protein/peptide drugs are particularly good candidates for formulation as long-acting parenteral depot systems. Polymer-based injectable depot systems for protein/peptide drugs have many advantages such as protection of sensitive proteins from degradation, prolonged or modified release, pulsatile release patterns, and enhancement of patient compliance. These important and unique advantages offer potential commercial success of future sustained-release injectable pharmaceutical products that have novel active pharmaceutical ingredients, including therapeutic proteins and peptides.

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