

Long Acting Injectables-An Overview

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Abstract

Recently conventional dosage forms of drugs are replaced by the new and the novel drug delivery systems. Among, these the controlled release/sustained release dosage forms create an interest in modern therapeutics. In recent years long acting injections have developed. These injections showed the prolong release of drug. Lesser frequency of dose, decrease in side effects and improved patient compliance are the uses received by controlled release of drugs. Parenteral drug delivery can achieve easy systemic circulation access with rapid drug absorption. It has more advantageous to achieve the release of drug in constant levels within the therapeutically concentration range of drug for obtaining the good treatment. With the help of polymers, the development in parenteral control release technologies has received huge boost up. So, many injectable control release products have received regulatory approval and launched in the pharmaceutical market. In the present review, efforts were put forth on the rationale and most recent progress done in the development and formulation of long acting parenteral drug release systems. The review focused on the current long-acting injectable formulation with special attention to marketed products.

Keywords: Long acting injectables, polymers, method, evaluation.

INTRODUCTION

Parenteral drug delivery with intravenous, subcutaneous, intramuscular, intraperitoneal, intrathecal injection now gains easy access to systemic circulation with fast drug absorption. This fast drug absorption is unfortunately also tended to be a rapid decline in the drug levels in the systemic circulation. In the case of chronic conditions, daily or weekly injections for months or years have resulted in poor patient compliance: 1) to control the rate of absorption of a drug or 2) to control the rate of excretion of a drug. In that controlling the absorption rate of a drug (by modifying dosage forms) is easier than controlling the excretion rate (by modifying physiology of body) of a drug. Continuous intravenous infusion has been recognized to maintain a constant and sustained drug level within a therapeutic concentration range for as long as required effective treatment. But it entails certain health random and therefore requires continuous hospitalization

and close medical supervision. The development of new injectable drug delivery system (parenteral depot formulation) has received considerable attention over the past few years¹. The main rationale behind the development of novel delivery systems is either to sustain the drug release or to maintain the effective drug concentration with reduced adverse effects. Suspensions, emulsions, liposome, micro particles and implants are identified as parenteral controlled release drug delivery systems².

TRADITIONAL VS CONTROLLED RELEASE PARENTERAL DRUG DOSING

Following are the some differences between control and traditional drug release of parenteral drug delivery dosing³.

Parenteral Drug Delivery	Controlled Release Parenteral Drug Delivery
Intravenous, subcutaneous, intramuscular, intraperitoneal, intrathecal routes are all examples of parenteral routes of drug administration.	Only intramuscular, subcutaneous routes are concentrated to develop control release parenteral drug delivery.
Aqueous, oil solutions, suspension can be given by this drug delivery system.	Aqueous, oil solutions, suspensions and implants can also be given by this drug delivery system.
Rapid onset of action can be achieved immediately after administration of drug.	Continuous release of drug molecule from the reservoir will results in prolonged drug blood level
This drug delivery system is considered the most efficient for drug delivery in case of poorly bioavailable drugs with narrow therapeutic window.	This drug delivery system is considered the most efficient for drug delivery in case of poorly bioavailable drugs with narrow therapeutic window for prolonged period of time.
This drug delivery system has some disadvantages are also present.	To overcome those problems controlled release parenteral drug delivery dosage forms are used.

MAJOR ROUTES OF PARENTERAL ADMINISTRATION

A) Subcutaneous: This route is mainly limited to non-irritating, water soluble drugs that are well absorbed, e.g. Insulin. To avoid local tissue damage and agglomeration of unabsorbed drug injection is rotated for chronically administered drugs. The amount of subcutaneous injection is limited to be 0.5-1.5 ml⁴.

B) Intramuscular: The best sites for intramuscular injection are gluteal, deltoid and vastus laterals muscles. It is important that the injection is deep in the muscle and away from the major nerves and arteries. To avoid tissue damage, the amount of intramuscular injection is limited less than 2ml. A polymeric membrane that is either impregnated with drug or surrounds the drug reservoir can be used as the drug delivery device⁵.

C) Intravenous: The intravenous route is infrequently use as a route of administration for sustained/ controlled dosage forms such as liposome, nanoparticles, and polypeptides. When drug was administered i.v, larger particles are either trapped in lungs or taken up by spleen or liver and smaller particles agglomerated in the bone marrow⁶.

Few advantages and disadvantages according routes of drugs administration for controlled release injectable delivery systems are showed in Table⁷.

Routes of Drug Administration	Advantages	Disadvantages
Subcutaneous	A) Water soluble drugs that are well absorbed. B) Generally limited to non-irritating	A) Adipose and connective tissue are poorly perfused with blood. B) The volume of injection is usually restricted to 0.5-1.5ml
Intramuscular	A) It is best route for control release parenteral drug delivery B) It is important that the injection deep in muscle and away from major nerves and arteries.	A) The volume of injection should not exceed 2ml. B) Tissue irritation may occur.
Intravenous	A) Used administered formulation such as liposomes, nanoparticles and polypeptide. B) Rapid onset of action can be achieved	A) This route is occasionally used for control release parenteral. B) Only particles with diameter between 0.1 and 7 µm.

ADVANTAGES AND DISADVANTAGES OF CONTROL RELEASE PARENTERAL DRUG DELIVERY

The most commonly used drug-delivery systems, which can release drugs longer than one week, are parenteral injections and implants. Advantages and disadvantages of parenteral controlled release over conventional drug delivery systems are discussed below⁸.

Some advantages and disadvantages of control release parenteral drug delivery are listed in table⁹.

Advantages	Disadvantages
Improved patient convenience and compliance.	The dosage form must be administered by trained personnel and require more time than those administered by other routes.
Reduction in fluctuation in steady-state levels.	Parenteral administration requires strict adherence to aseptic procedures, and some pain on injection is inevitable.
Increased safety margin of high potency drugs.	It is difficult to reverse its physiological effect.
Maximum utilization of drug.	The manufacturing and packaging requirements, parenteral dosage forms are more expensive than preparations of given by other routes.
Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing	Changes in formulation may occur to external environmental stimuli.

TYPES OF PARENTERAL CONTROLLED DRUG DELIVERY SYSTEM

Parenteral controlled release formulations are of following types¹⁰⁻¹²

A. INJECTABLES

1. Solutions
2. Colloidal Dispersions
3. Microspheres
4. Microcapsules
5. Nanoparticles
6. Noisome
7. Liposomes
8. Resealed erythrocytes
9. Polymeric Micelle
10. In situ forming implants
11. Injectable gels

B. IMPLANTS

C. INFUSION DEVICE

1. Osmotic pumps (Alzet)
2. Vapor pressure powered pumps (infusaid)
3. Battery powered

INJECTABLE GELS

Biodegradable injectable *in situ* gel forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot systems. It consists of biodegradable polymers dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using standard needles and syringes, it solidifies upon contact with aqueous body fluids to form solid implant. If a drug is incorporated into the polymer solution, it becomes entrapped within polymer matrix as it solidifies. Drug release occurs over time as polymer Biodegrades¹³.

MECHANISM OF ACTION

Drug delivery system consists of biodegradable polymers dissolved in biocompatible carriers. Pharmaceuticals may be blended into this liquid delivery system at the time of manufacturing or, depending upon the product, may be added later by the physician at the time of use. When the liquid product is injected into the subcutaneous space through a small gauge needle or placed into accessible tissue sites through a cannula, water in the tissue fluids causes the polymer to precipitate and trap the drug in a solid implant. The drug encapsulated within the implant is then released in a controlled manner as the polymer matrix biodegrades with time¹⁴.

POLYMERS USED AS INJECTABLE IN-SITU GELLING AGENTS

Materials that exhibit sol to gel transition in aqueous solution at temperatures between ambient and body temperature is of interest in the development of sustained release vehicles with *injectable in-situ* gelation properties. Some of the polymers used as *injectable in-situ* gelling agents are¹⁵⁻¹⁶

Method of Preparation	Polymers
Thermo Reversible <i>in Situ</i> Gelling System	A) Pluronics 1. Pluronic F68 2. Pluronic F127 3. Pluronic F128 B) Poloxamer C) Gellan gum D) Chitosan E) Cellulose derivatives 1. HPMC 2. Ethyl (hydroxy ethyl) cellulose 3. Xyloglucan 4. Tetronics
pH Sensitive <i>in Situ</i> Gelling System	A) Carbopol B) Carbomer C) Cellulose acetate phthalate latex(CAP) D) Polymethacrylic acid (PMMA) E) Polyethylene glycol(PEG) F) Pseudolatexes G) diethylaminoacetate (AEA)
Ion Sensitive <i>in Situ</i> Gelling System	A) Sodium Alginate B) Gelrite C) Hyaluronic Acid

THERMO REVERSIBLE *IN SITU* GELLING SYSTEM

The system of this polymer consists of a central polypropylene oxide surrounded by polyethylene oxide. At room temperature (25°C), this polymer is a viscous liquid and will then turn into a transparent gel when temperature increases (37°C). At low temperatures, this polymer will form a small micellar subunit in solution that will lead to increased viscosity leading to swelling to form a large cross-crossed micellar tissue. Examples of polymers for this system are poloxamers¹⁷.

pH SENSITIVE *IN SITU* GELLING SYSTEM

The mechanism is caused by electrostatic interactions or hydrophobic interactions, hydrogen bonding. This is an acidic molecule. When the polymer is dispersed into water, the carboxylic group of molecules will partially dissociate and form a coil. Because of the polymer sensitive pH, the increase of the pH of the solution results in polymer swelling. Polymer example with this system is carbopol¹⁸.

ION SENSITIVE *IN SITU* GELLING SYSTEM

The mechanism of this system is a monomer of alginate β -DMannuronic acid and α -L glucuronic acid arranged as an M-M block with a block that will cause a sequence change (M-G). After block G the polymer interacts with calcium moieties will result in homogeneous gel formation. Mechanical strength and hydrogel porosity depend on G: M ratio, cross linker type used and concentration of alginate solution. Examples of polymers used in this system are sodium alginate¹⁷

EXAMPLES OF DRUGS FOR CONTROLLED RELEASE INJECTABLE DELIVERY SYSTEMS

Few examples of drugs for controlled release injectable delivery systems are showed in Table¹⁹⁻²¹

Class	Drugs
Postoperative pain therapeutic agents	Ketorolac tromethamine
Recombinant human bone morphogenetic protein2	Superoxide dismutase, salmon calcitonin, insulin
Gene delivery	Plasmid DNA
Protein therapeutics	Analog of glucagon peptide1
Drugs to treat alcohol dependence	Naltrexone
Schizophrenia drugs	Aripiprazole, olanzapine
Immunosuppressive drugs	Rapamycin
Hormone therapy	Human somatropin
Cancer therapeutic agents	Bleomycin, paclitaxel, cisplatin

METHOD OF PREPARATION**PREPARATION OF *IN SITU* THERMO-REVERSIBLE GELLING SOLUTIONS****THE GEL-FORMING SOLUTIONS WERE PREPARED BY COLD METHOD**

The polymers were dispersed in cold water at 4° in a beaker and stirred on a magnetic stirrer at 500 rpm for 2 h. The dispersions were diluted to the required volume with cold distilled water and then stored at 4° to obtain clear solutions. PL127 and PL68 were used alone in concentrations²².

The polymers except pluronic F127 were completely dispersed in distilled water with continuous agitation at room temperature and cooled down to 4°C. Pluronic F127 was then slowly added to the solution with continuous agitation. The resulting solution was then left at 4°C until a clear solution was obtained²³.

CROSS LINKED POLYMER METHOD

Chitosan in variable concentrations of polymer solutions were prepared by dissolving chitosan in 1% dilute acetic acid into a glass vial. The vial was placed in a continuous shaker over night at room temperature to completely dissolve the polymer. Then propylene glycol as plasticizer was added into the polymer solution and mixed together. The formulations were clear, homogeneous solutions at room temperature. The mixture was stirred for 30 minutes at room temperature until it became increasingly viscous. The viscous solutions were left at room temperature to remove bubbles²⁴.

pH INDUCED GELLING SYSTEM

Acidic solutions of chitosan when subjected to alkaline pH form viscous gels. The *in situ* gel formation has been employed for controlled delivery of several drugs via oral or parenteral

routes. A polymer complex of polyethylene (PEG) and polymethacrylic acid (PMA) or polyacrylic acid (PAA) has also been known as a pH sensitive gelling system²⁵.

EVALUATION OF DRUG INCORPORATED GELLING SOLUTIONS**APPEARANCE AND CLARITY**

Visual looks of the formulation with respect to clarity is an important parameter for the drug solutions that are parenterally administered. The presence of granulated matter not only affects patient compliance but also can be a source of tissue irritation or may even be injurious. All the formulations were inspected for clarity by visual analysis against black and white background under a strong light²⁶.

GELLING STUDY

The viscosity and gelling capacity place a important role for *insitu* gelling system .the formulation should have a optimum viscosity such that it may be easy to administered by injection as a liquid which undergo sol-to-gel transition²⁷.

TEXTURE ANALYSIS

The firmness, agreeable and cohesiveness of formulation are analyzed by using texture analyzer which mainly indicates the syringeability of sol so the formulation can be easily administered *in-vivo*. Higher values of adhesiveness of gels are needed to maintain the genial contact with surfaces like tissues²⁸.

SOL-GEL TRANSITION TEMPERATURE AND GELLING TIME

For *in situ* gel forming systems embodied thermoreversible polymers, the sol-gel transition temperature may be defined as that temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at a specified rate. Gel formation is shown by a lack of movement of meniscus on tilting the tube. Gelling time is the time for first observation of gelation as defined above²⁹.

RHEOLOGY

This is an important parameter for the *in situ* gels, to be estimate. Viscosity and rheological properties of *in situ* forming drug delivery systems may be assesses using Brookfield viscometer. The viscosity of these formulations should be such that no difficulties are reflected during their administration by the patient, especially during parenteral administration³⁰.

IN-VITRO DISSOLUTION STUDY

In vitro release profile was studied using USP apparatus II at 37 ± 1°C with a rotating speed of 100 rpm in dissolution media namely, PBS pH 7.4. During the study, 5 ml of aliquots were removed at predetermined time intervals, the dissolution medium and replaced with fresh buffer to ensure sink condition and drug content can be determined by spectrophotometrically³¹.

IN VITRO DRUG RELEASE STUDIES

The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The sol form of the formulation is placed in the donor compartment. The arranged cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is assisted for the drug release using analytical technique³². For injectable *in situ* gels, the formulation is placed into vials containing receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analyzed³³.

CONCLUSION

Approximately, 15% of the current drug delivery market is injectable products. Long-acting parenteral drug formulation is designed ideally to provide slow, constant, and sustained release of drug over a prolong period, essentially to stimulate and replace the more hazardous, continuous intravenous infusion of a drug. Several chemosynthetic biodegradable and natural

polymers are used in the preparation of long acting injectable. These having more advantages compare to conventional method of drug administration. The long acting parenteral are prepared by various approaches like temperature dependent, pH sensitive, ion triggered method. Advances in the method of formulation and availability of novel polymers are resulting in commercial successes of controlled release products. To address the unmet needs in new drug delivery systems, the parenteral controlled release products have been evolved specifically.

REFERENCES

- 1] Bari H. A prolonged release parenteral drug delivery system—an overview. *Int J Pharm Sci Rev Res.* 2010 Jul;3(1):1-1.
- 2] Tejashree AG, Sagar CD, Ajit K S. A review on parenteral implants. *International Journal of Research and Reviews in Pharmacy and Applied science.* 2014;4(2):1056-72.
- 3] Kalyani M. et al. / *International Journal of Research in Pharmaceutical and Nano Sciences.* 2(5), 2013, 572- 580.
- 4] Muralidhar P, Bhargav E. Controlled release injectable drug delivery: an over view. *Asian Journal of Biomaterial Research.* 2017;3(1):6-15.
- 5] Pfeffer M, Smyth RD, Pittman KA, Nardella PA. Pharmacokinetics of subcutaneous and intramuscular butorphanol in dogs. *Journal of pharmaceutical sciences.* 1980 Jul 1;69(7):801-3.
- 6] Illum L, Davis SS. The targeting of drugs parenterally by use of microspheres. *PDA Journal of Pharmaceutical Science and Technology.* 1982 Nov 1;36(6):242-8.
- 7] *Controlled drug delivery, Second edition, Revised and Expanded, volume 20, by Robinson. Lee.*
- 8] Tipton AJ, Dunn R, In situ gelling system, in: *sustained release injectable product, Senior JH, Radomsky M, Interpharm press, Denver, 2000, 71-102*
- 9] Sheikh AA, Sheikh SR. Advanced injectable drug delivery system: A brief review. *System.* 2016;9:11.
- 10] Hollister LE, 1989, Site-specific drug delivery to central nervous system. *Neurobiology Aging,* 10; 628- 631.
- 11] Jantzen GM, Robinson JR. Sustained-and controlled-release drug delivery systems. *Drugs and The Pharmaceutical Sciences.* 1996;72:575-610.
- 12] Bechgaard H, Nielsen GH. Controlled-release multiple-units and single-unit doses a literature review. *Drug Development and Industrial Pharmacy.* 1978 Jan 1;4(1):53-67.
- 13] Pandya Y, Sisodiya D, Dashora K. ATRIGEL®, implants and controlled released drug delivery system. *Int J Biopharmaceutics.* 2014;5(3):208-13.
- 14] Hatefi A, Amsden B. Biodegradable injectable in situ forming drug delivery systems. *Journal of Controlled Release.* 2002 Apr 23;80(1-3):9-28.
- 15] Jansson PE, Lindberg B, Sandford PA. Structural studies of gellan gum, an extracellular polysaccharide elaborated by *Pseudomonas elodea.* *Carbohydrate Research.* 1983 Dec 10;124(1):135-9.
- 16] Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, Lu J, Li J, Du S, Liu Z. Research progress of in-situ gelling ophthalmic drug delivery system. *Asian Journal of Pharmaceutical Sciences.* 2019 Jan 1;14(1):1-5.
- 17] Chand P, Gnanarajan G, Kothiyal P. In situ gel: A review. *Indian Journal of Pharmaceutical and Biological Research.* 2016 Apr 1;4(2):11.
- 18] Deepti Singh*, A. Bhattacharaya, UVS Sara International Standard Serial Number (ISSN): 2319-8141
- 19] Packhaeuser CB, Schnieders J, Oster CG, Kissel T. In situ forming parenteral drug delivery systems: an overview. *European Journal of Pharmaceutics and Biopharmaceutics.* 2004 Sep 1;58(2):445-55.
- 20] Sheikh AA. *Injectable Controlled Release Drug Delivery Systems.* *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm.* 2016 Dec 21;10(04).
- 21] Heller J. Polymers for controlled parenteral delivery of peptides and proteins. *Adv Drug Deliv Rev* 1993;10:163-204
- 22] Vineetha K, Koland M. Investigation of a Biodegradable Injectable In Situ Gelling Implantable System of Rivastigmine Tartrate. *Asian Journal of Pharmaceutics.* 2017 Oct 1;11(4):S731-8
- 23] Sindhu SK, Gowda DV, Vishnu Datta S. Formulation and Evaluation of Injectable In-Situ Gelling Matrix System for Controlled Drug Release. *Ind J of Adv Che Scien.* 2014;2:89-92
- 24] Santhi Priya design and development of a weekly shot of injectable in-situ gel for an antipsychotic drug in the treatment of schizophrenia *ijrpc* 2017, 7(3), 221-23.
- 25] Sheikh AA, Sheikh SR. Advanced injectable drug delivery system: A brief review. *System.* 2016;9:11.
- 26] Vineetha K, Koland M. Investigation of a Biodegradable Injectable In Situ Gelling Implantable System of Rivastigmine Tartrate. *Asian Journal of Pharmaceutics.* 2017 Oct 1;11(4):S731-8.
- 27] Matschke C, Isele U, van Hoogevest P, Fahr A. Sustained-release injectables formed in situ and their potential use for veterinary products. *Journal of Controlled Release.* 2002 Dec 13;85(1-3):1-5.
- 28] Kashyap N, Viswanad B, Sharma G, Bhardwaj V, Ramarao P, Kumar MR. Design and evaluation of biodegradable, biosensitive in situ gelling system for pulsatile delivery of insulin. *Biomaterials.* 2007 Apr 1;28(11):2051-60.
- 29] Madan M, Bajaj A, Lewis S, Udupa N, Baig JA. In situ forming polymeric drug delivery systems. *Indian journal of pharmaceutical sciences.* 2009 May;71(3):242.
- 30] Patil PR, Salve VK, Thorat RU, Puranik PK, Khadabadi SS. Modern encroachment and provocation in nasal drug delivery system. *International journal of pharmaceutical sciences and research.* 2013 Jul 1;4(7):2569-75.
- 31] Singh K, Kaur H, Kumar SL. Design and development of sustained release injectable in situ gel of cytarabine. *Pharmacophore.* 2013 Nov 1;4(6).
- 32] Suisha F, Kawasaki N, Miyazaki S, Shirakawa M, Yamatoya K, Sasaki M, Attwood D. Xyloglucan gels as sustained release vehicles for the intraperitoneal administration of mitomycin C. *International journal of pharmaceutics.* 1998 Oct 15;172(1-2):27-32.
- 33] Chandrashekar G, Udupa N. Biodegradable injectable implant systems for long term drug delivery using poly (Lactic-co-glycolic) acid copolymers. *Journal of pharmacy and pharmacology.* 1996 Jul;48(7):669-74.