Available online at www.elixirpublishers.com (Elixir International Journal)

Pharmacy

Elixir Pharmacy 69 (2014) 23710-23715

ISSN: 2229-712X

# Recent advances in parenteral drug delivery system

Debjit Bhowmik[1,*], S.Durai Vel[1], Rajalakshmi A.N[2] and K.P.Sampath Kumar[3]
[1]Nimra College of Pharmacy, Ibrahimpatnam, Vijayawada, Andhra Pradesh.
[2]Mother Theresa Post Graduate And Research Institute of Health Sciences, Puducherry.
[3]Department of Pharmacy, Coimbatore Medical College, Coimbatore.

**ARTICLE INFO**

**Article history:**
Received: 8 November 2013;
Received in revised form:
20 April 2014;
Accepted: 28 April 2014;

**Keywords**
Parenteral drug delivery systems,
Narrow therapeutic index,
Bio-availability.

**ABSTRACT**

Drug delivery is a multidisciplinary field. Researchers recently developed a drug-delivery system to mitigate some problems associated with jet-injection drug delivery, and also improved on the design and operation of microscale actuators as a possible drug-delivery methodThe Parenteral administration route is the most common and efficient for delivery of active drug substances with poor bio-availability and the drugs with a narrow therapeutic index. But parenteral route offers rapid onset of action with rapid declines of systemic drug level. For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for.Parenteral drug delivery systems are the preparations that are given other than oral route. (Para-outside, enteric–intestine). Parenteral drug delivery systems are most preferred drug delivery systems as they meet many benefits over other dosage forms in many cases such as unconsciousness, nausea, in emergency clinical episodes. The Parenteral administration route is the most common and efficient for delivery of active drug substances with poor bio-availability and the drugs with a narrow therapeutic index. But Parenteral route offers rapid onset of action with rapid declines of systemic drug level. For the sake of effective treatment it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for. It requires frequent injection, which ultimately leads to patient discomfort. For this reason, drug delivery system which can reduce total number of injection throughout the effective treatment, improve patient compliance as well as pharmacoeconomic.



## Introduction

Parenteral preparation are the sterile solution or suspension of drug in aqueous or oily vehicle meant for introduction into the body by means of an injectable needle under or through one or more layers of skin or mucous membrane. Injection should be sterile, isotonic and free from foreign particles, such as dust, fibers etc. They should be introducing through the same route for which they are intended. The parenteral route of administration is the most effective route for the delivery of the active pharmaceutical substances with narrow therapeutic index, poor bioavailability especially for those drugs, prescribed to unconscious patients. To maintain a therapeutic effective concentration of the drug, it requires frequent injections which ultimately lead to patient discomfort. In parenteral drug delivery, major progress has been done in the field of formulation technologies so as to provide a targeted and sustained release of drug in predictable manner. The present article reviews recent patents and major advancements in parenteral drug delivery systems along with general introduction. This article also deals with importance of novel systems in drug delivery to overcome the problems associated with conventional parenteral drug delivery systems.

## Advantages of Parenteral Administration

1.An immediate physiological response can be achieved if necessary, which can be of prime consideration in clinical condition such as cardiac arrest, astharna and shock .
2.Parenteral therapy is required for drugs that are not effective orally or that are destroyed by digestive secretions such as insulin other hormones and antibiotics.
3.Drug for uncooperative, nauseous or unconscious patients must he administered by injection.
4.When desirable, parenteral therapy gives the physician control of the drug since the patient must return for continued treatment, also in some cases the patient cannot be relied upon to take oral administration.
5.Parenteral administration can results in local effect for drugs when desired., as in dentistry and anesthesiology.
6.In case in which prolonged drug action is wanted, parenteral Forms are available, including the long intrartially and the long acting penecillins administered deep intra muscularly.
7.Parenteral therapy provides the means of correcting serious disturbances of fluid and electronic balances.
8.When food cannot be taken by mouth, total nutritional requirement can be supplied by the parenteral route.

## Disadvantage of Parenteral Administered

1.The dosage form must be administered by trained personnel and require more time than those administered by other routes.
2.Parenteral administration requires strict adherence to aseptic procedures, and some pain on injection is inevitable.
3.It is difficult to reverse its physiological effect.
4.The manufacturing and packaging requirements, parenteral dosage forms are more expensive than preparations of given by other routes.

Tele:
E-mail addresses: debjit_cr@yahoo.com

**In process quality control test**

In Process Quality control (IPQC) is a procedure or set of procedures intended to ensure that a manufactured product or performed service adheres to a defined set of quality criteria or meets the requirements of the client or customer or a standard.

**IPQC Testing for the parenteral product**

The responsibility of the QC department comes in three general areas

1st incoming stock

2nd Manufacturing

3rd Finished Product (it is not included in IPQC testing it is final product testing)

It involves three main things

1. Raw Material (Active Ingredient)
2. Vehicle
3. Additives

**Raw Material:**

Mainly the raw material is in the sterile form but it is the duty of QC department to check the sterility of the raw material.

**Vehicle:**

Mainly water is use as a vehicle for the parenteral but in some instances we use non-aqueous vehicles.

For testing of the vehicle we generally perform

i. Conductivity Test
ii. Amount of Solid Content Testing
iii. Test for Dissociative & Undissociative Organic & Inorganic Substances
iv. Pyrogen Testing

**Conductivity Test**

Conductivity of the water for injection or any other vehicle used is checked by the quality control department to check the amount of ionic substances. So the conductivity of the vehicle should not increase the specified limit given by the production department. If it increases or decreases the limit given by production department discard the vehicle.

**Amount of Solid Content Testing**

Amount of the solid present in water for injection is checked by the QC personnel's and it should be in the limit specified.

**Test for Dissociative & Undissociative Organic & Inorganic Substances:**

Some dissociative and Undissociative substances are also present. Undissociative such as pyrogens, however could be present in absence of ions and could not be checked by the above test there for contaminants other than ions, additional test are performed.

**Pyrogen test:**

The current USP clearly outlines the pyrogen assay. USP XIX considers a solution to be pyrogenic when 10 m1/kg is injected into a rabbit and there is a rise of temperature of 0.6 C or more for any rabbit, or a total rise of more than 1.4 C for three rabbits in a three rabbit test group. The official rabbit method requires considerable time, expense, training, and experience to master. There are few shortcuts. The consequence of not testing for pyrogens could be even more costly in terms of patient reactions and drug recalls.

**Pyrogen Assay - Limulus Amoebocyte Lysate**

Many laboratories conduct pyrogen assays by means of the limulus Amoebocyte lysate (LAL) test method. The LAL method is useful especially for screening products that are impractical to test by the rabbit method. Products best tested for endotoxins by LAL techniques are: radiopharmaceuticals, anesthetics, parenterals and many biologicals. Essentially, the LAL method reacts hemolymph (blood) from a horseshoe crab (Limulus polyphemus) with an endotoxin to form a gel. The quantity of endotoxin that gels is determined from dilution techniques comparing gel formation of a test sample to that of a reference pyrogen, or from spectrophotometric methods comparing the opacity of gel formation of a test sample to that opacity of a reference pyrogen. The LAL test is considered to be specific for the presence of endotoxins and is at least a hundred times more sensitive than the rabbit test. Even picnogram quantities of endotoxins can be shown by the LAL method. Although LAL is a relatively new pyrogen testing method, there has been shown a wide variety of polysaccharide derivatives that give positive limulus test results and also show fever activity. It is also a fact that some substances interfere with the LAL test even when pyrogens are present.

Some firms use the LAL test for screening pyrogens in raw materials, and follow up with pyrogen testing on the final product by means of the USP rabbit assay. The LAL test for pyrogens in drugs requires an amendment to the NDA on an individual product basis. LAL test reagents are licensed by the Bureau of Biologics. For devices, a firm must have its protocol approved by the Director, Bureau of Medical Devices, before it can substitute the LAL assay for the rabbit. \10\ the future of LAL testing appears promising in that it is being considered for inclusion in the USP, but it is not an official method at this time.

**Additives:**

Sometimes additives are necessary parenteral product like Antioxidents & agents to maintain tonicity.

***Antioxidants***

- Prevent the oxidation by being oxidized faster than the drug or by blocking oxidization
- Water soluble: acid, sodium bisulfate, sodium metabisulfite, sodium sulfite
- Oil soluble: Butylated hydroxytoluene (BHT), Butylated hydroxyanisole (BHA)
- Displacing the air.

***Buffers***

- Added to maintain the pH
- Result in stability
- Not overwhelmed by Physiological buffer
- Effective range, concentration, chemical effect
- Examples:
  - Sodium Citrate and citric acid
  - Sodium Acitate and Acetic acid
  - Sodium Benzoate and Benzoic acid
  - Sodium tartrate and tartaric acid
  - Sodium Phosphate (Monobasic Sodium hydrogen phosphate (NaH2PO4 and Dibasic Sodium Hydrogen Phosphate)
  - Sodium Bicarbonate

***Tonicity Agents***

- Reduce pain of Injection
- Can include buffers
  - Sodium chloride
  - Potassium chloride
  - Dextrose
  - Mannitol
  - Sorbitol
  - Lactose

**Test Before Filling**

Generally tests are perform to check the efficacy of the product before filling which include following

i. Volume Check
ii. Strength
iii. pH

iv. Turbidity
v. Color
vi. Sterility
vii. Pyrogenecity

**Volume Checking:**

Volume of the parenteral finished stock is checked either it is enough to fill the requirements of the batch or it can tell us about the loss of product during the preparation.

**Strength:**

Strength of the final to be checked .Either whole of the prepared material have the same concentration of the active or not in this we can check the amount of the active in preparation we usually use HPLC to check the strength.

**PH:**

PH of the final solution is checked by the QC department either it is complied with the requirement of the Production Department .If it is not with in the limits batch should be discarded.

**Turbidity:**

There should be no turbidity in the final product if there is any the batch is rejected.

**Color:**

Color of the final product should be complied with the requirements of the production department.

**Sterility:**

Sterility of the final product is also checked.

**Pyrogenecity:**

Test for pyrogen is performed on Lab animals to check the Sterility of the final product.

**Final Product Testing:**

It generally performs the following tests after the preparation has been packed.

i. Sterility test
ii. Pyrogen test
iii. Clarity test
iv. Leakage test
v. Assay

**Sterility Test**

The tests for sterility are intended for detecting the presence of viable forms of micro-organisms in or on pharmacopeial preparations. The test must be carried out under conditions designed to avoid accidental contamination of the product during the test. Precautions taken for this purpose should not adversely affect any micro-organisms which should be revealed in the test.

The working conditions in which the tests are performed should be monitored regularly by sampling the air and surfaces of the working area and by carrying out control tests. The tests are based upon the principle that if micro-organisms are placed in a medium which provides nutritive material and water, and kept at a favorable temperature, the organisms will grow and their presence can be indicated by turbidity in the originally clear medium.

**Pyrogen Testing:**

Pyrogen testing defines a process used by drug manufacturers to determine if bacterial toxins are present in vaccines and drugs that might cause fever when used on humans. It determines if microbes or their metabolites are present in intravenous solutions during the manufacturing process. The most common and oldest form of pyrogen testing consists of injecting drugs into rabbits to determine if a fever develops. A newer test uses blood from the horseshoe crab to test for toxins.

The rabbit pyrogen testing method surfaced in the 1940s after some patients became ill from intravenous drugs. Hypodermic devices at the time proved useful for administering drugs directly into the bloodstream for patients who were unable to tolerate oral medications. Even though hypodermics devices were sterile, the drugs were not always safe.

The human body fights exposure to bacterial toxins in the environment through the skin. When contaminated drugs are injected into the bloodstream, toxins bypass normal defense mechanisms. White blood cells begin releasing another form of pyrogen that causes high fever, which might lead to shock and death.

**Clarity Testing:**

Injectable solutions including solutions constituted from sterile solids must essentially be free from particles of approximately 50 µm or more that can be observed by inspection with the unaided eye.

For the purpose of this test particulate matter is defined as extraneous mobile, undissolved substances, other than gas bubbles, unintentionally present in injections. The test need not be done where particles in an injectable solution can be observed on visual inspection. The limits do not apply to multiple dose injections, to single dose small volume parenterals and to injectable solutions constituted from sterile solids.

The preparation meets the requirements of the test if it contains particles within the maximum limits shown in Table 1.

**Table 1 – Permitted limits of particulate matter**

| Particle size in µm (Equal to or larger than) | Maximum number of particles per ml |
|---|---|
| 10 | 50 |
| 25 | 5 |
| 50 | Nil |

**Leaker Test**

**Definition**

Leakage occurs when a discontinuity exists in the wall of a package that can allow the passage of gas under the action of a pressure or concentration differential existing across the wall. Leakage is mathematically defined as the rate at which a unit of gas mass (or volume) .goes into or out of the leak under
Specific conditions of temperature and pressure.

A method of testing the integrity of ampules containing a liquid therein for leakage comprising the steps of:

(a) Immersing the ampules in an aqueous solution of a water soluble salt of a dye,

(b) Applying negative pressure or a vacuum to the top of the solution containing the dye to generate a pressure differential between said solution and the liquid within the ampules at least once, and releasing said pressure or vacuum,

(c) Removing the ampules from the solution or draining the solution from the container,

(d) Decontaminating the ampules by removing any solution containing dye adhering to the external surface thereof.

(e) Color testing the ampules to detect faulty ampules into which dye has leaked,

(f) Rejecting said faulty ampules, if any, and subsequently.

**Assay**

Assay is performed according to the method given in the monograph of that parenteral preparation in the pharmacopoeia. Assay is done to check the quantity of medicament present in the parenteral preparation.

**Recent advances in parenteral drug delivery system**

The Parenteral route of administration is the most common and effective for the delivery of several therapeutic agents for quick response. Reduction in number of injections throughout the drug therapy will be truly advantageous not only in terms of compliance, but also in terms of side effects associated with conventional Parenteral drug delivery. Recently controlled-release, targeted delivery, and needle-free delivery technologies are being introduced to alleviate the problems associated with conventional parenteral therapy. Controlled and targeted drug delivery systems include implants, oily injections, or particulate systems such as microparticles, nanoparticles, liposomes, micelles etc. Surface modification of these carriers (e.g. antibodies, aptamers) are used for drug targeting to pathogenic tissue. Improved delivery devices such as pre-filled syringes, pens, auto-injectors and needle-free devices are continuously increasing in the market to promote self-administration and improve patient compliance. Moreover, the explosion of biological based drugs and vaccines have offered additional challenges for drug delivery experts to develop a standardized injectable for optimum pharmacological response. The Parenteral route of administration is the most effective route for the delivery of the active pharmaceutical substances with narrow therapeutic index, poor bioavailability especially for those drugs, prescribed to unconscious patients. To maintain a therapeutic effective concentration of the drug, it requires frequent injections which ultimately lead to patient discomfort. In Parenteral drug delivery, major progress has been done in the field of formulation technologies so as to provide a targeted and sustained release of drug in predictable manner. Controlled and targeted drug delivery via Parenteral route is advantageous in treatment of various disorders but the safety issues and lack of regulations are the major hurdles in their development. Injectable devices aid to improve patient compliance, reduce invasiveness of therapy, prevent needle-stick injuries, provide added therapeutic value and reduce the cost of treatment. A fundamental understanding of formulation development and device engineering can further be explored to meet patient's need and circumvent the challenges of conventional injectable drug delivery systems.

**Conventional Drug Delivery**

**Suspension:**

Injectable suspensions are marketed either as already to use injection or require a reconstitution prior to use. Suspensions are aid to improve controlled drug release, resistance to hydrolysis as well as oxidation, and escape from hepatic first pass effect.

**Emulsion:**

It is heterogeneous system which can be stabilized by emulsifying agents. Emulsion stability and limited number of approved emulsifier are the major challenges in their development. Reduced pain and irritation, better stability, improved drug solubility, reduced toxicity and targeted drug delivery are the potential advantages of injectable emulsion.

**Oil solution:**

Drug release can be controlled by partitioning of drug between oil and the aqueous phase. The drug available for absorption can be controlled by the partition co-efficient and the ratio of the volume of two phases.

**Injectable devices:**

Advancement in the field of injectable inspires the researchers to develop the next generation devices which can overcome the limitation of conventional delivery devices.

**Prefilled syringe:**

Syringe containing single-dose of drug and fixed needle is known as prefilled syringe. It provides numerous benefits like, minimization of cross-contamination, reduction in drug wastage, elimination of container preparation, reduction in medication error, and improved patient compliance. These devices evolved from biological drugs and vaccines to critical components for enhancing manufacturer and patient acceptability.

**Injectable pen:**

Injectable pens are more convenient to transport, repeatedly deliver accurate dosages, easier to use for those with visual or fine motor skills impairments, reduce injection pain. Disposable pen for single use, fixed dose and manual insertion have been recently marketed. Re-usable pen can be utilised for self-administration by periodic replacement of drug cartridge.

**Auto-injector**

These spring driven systems are popular due to simple, accurate and rapid drug administration, automatic operation, rugged construction, and prevention of needle contamination. Re-usable auto-injectors are a cost-effective for frequently administered products. Single-use disposable auto-injectors, and next generation re-usable auto-injectors are recently commercialized.

**Needle-free injectors**

Spring or high-pressure gas drives the drug product through a small orifice into the skin. Flexibility in formulation and dosing, no needle stick hazard, easier disposal, speed up in injection cycle, and improved bio-availability of biological are the potential advantages of needle-free injectors.

**Self-flushing infusion bag**

It can overcome the disadvantages associated with conventional infusion bags. It enhances the safety of patients and healthcare professionals alike, improves therapeutic efficacy and reduces hazardous waste and global costs. Different drug- and flushing-volume requirements can be adapted in such types of systems.

**Liposomes**

Liposomes are formed by the self-assembly of phospholipid molecules in an aqueous environment. The amphiphilic phospholipid molecules form a closed bilayer sphere in an attempt to shield their hydrophobic groups from the aqueous environment while still maintaining contact with the aqueous phase via the hydrophilic head group. When suitably dispersed they consist of a series of concentric bilayers alternating with aqueous compartments. Water or lipid soluble substances can be entrapped within their aqueous or lipid phase respectively. Depending on the phospholipids used and the ionic composition of the medium,liposomes of various sizes and shapes can be obtained.Furthermore,antibodies can be covalently coupled to liposomes to enhance their cell specificity.

**i) Liposomal anticancer agent**

The use of liposomes as anticancer drug delivery systems was originally hampered by the realization that liposomes are rapidly cleared from the circulation and largely taken up by the liver macrophage. It was observed that doxorubicin loaded stealth liposomes circulate for prolonged periods accumulate and extravagate within tumours & also improve tumoricidal activity in mice. In one study it has been reported that in patients, liposomal doxorubicin accumulates within Kaposi's sarcoma lesions and produces a good therapeutic response. Liposomal doxorubicin is now licensed as Caelyx for the treatment of Kaposi's sarcoma.

This formulation is currently in clinical trials for ovarian cancer and could be approved shortly for use in ovarian cancer patients who have failed to respond to paclitaxel and cisplatin.

**ii) Liposomes as vaccine adjuvants**

Liposomal vaccines can be made by associating microbes, soluble antigens, cytokines or deoxyribonucleic acid (DNA)with liposomes, the latter stimulating an immune response on expression of the antigenic protein. Liposomes encapsulating antigens, which are subsequently encapsulated within alginate lysine microcapsules to control the antigen release and to improve the antibody response. Liposomal vaccines may also be stored dried at refrigeration temperatures for up to 12 months and still retain their adjuvanticity.

**iii) Liposomal anti-infective agents**

Liposomal amphotericin B (Ambisome) used for the treatment of systemic fungal infection. This is the first licensed liposomal preparation It was observed in one study that liposomal amphotericin B, by passively targeting the liver and spleen, reduces the renal and general toxicity of the drug at normal doses.

**Niosomes**

Niosomes are unilamellar or multilamellar vesicles, where in an aqueous solution is enclosed in highly ordered bilayer made up of nonionic surfactants with or without cholesterol (chol) and dicetyl phosphate and exhibit a behavior similar to liposomes *in-vivo*They can be used in the treatment of cancer and also used as vaccine adjuvant. Some of its applications are discussed here.

**i) Anticancer niosomes**

Anticancer niosomes, if suitably designed will be expected to accumulate within tumours. For example niosomal encapsulation of methotrexateand doxorubicin increases drug delivery to the tumour and tumoricidal activity. It was reported that doxorubicin niosomes having size 200nm with a polyoxyethylene (molecular weight 1,000) surface are rapidly taken up by the liver and accumulate to a lesser extent in tumour, this technology may prove advantageous for the treatment of hepaticneoplasms. It was also observed that the activity of other anticancer drugs, such as vincristine, bleomycin plumbagin and a plant derived anticancer agent are improved on niosomal encapsulation.

**ii) Niosomes at targeted site**

Uptake by the liver and spleen make niosomes ideal for targeting diseases manifesting in these organs. One such condition is leishmaniasis and a number of other studieshas shown that niosomal formulations of sodium stibogluconate improve parasite suppression in the liver spleen and bone marrow. Niosomes may also be used as depot systems for short acting peptide drugs on intramuscular administration.

**iii) Niosomes as vaccine adjuvants**

It was studied that niosomal antigens are potent stimulators of the cellular and humoral immune response The formulation of antigens as a niosome in water-in-oil emulsion further increases the activity of antigens and hence enhanced the immunological response.

**Nanoparticles And Microparticles**

Nanoparticles and microparticles are usually prepared by the controlled precipitation of polymers solubilised in one of the phases of an emulsion. Precipitation of the polymer out of the solvent takes place on solvent evaporation, leaving particles of the polymer suspended in the residual solvent. For particulate dispersions, the required particle size of nanoparticles lies between the range of 30-500nm while for microparticles in excess of 0.5micron. Their applications in management of diseases are discussed below.

**Tumor targeting nanoparticles and microparticles**

The accumulation of non-stealth doxorubicin nanoparticles within the Kupffer cells of the liver may be used to target hepatic neoplasms indirectly this is achieved by providing a depot of drug for killing nearby neoplastic tissue. Microparticles may also be injected directly into tumours. It was observed that the direct injection of microparticles into solid tumours increases the tumoricidal activity of the drugs 5-fluorouracil and doxorubicin.

**Vaccine adjuvants**

Nanoparticles have also been used as vaccine adjuvants. It was reported that antigens, which adsorbed onto the surface or entrapped in the matrix of polymethylmethacrylate nanoparticles induces an enhanced immunological response. For example polymethylmethacrylate nanoparticles containing the influenza antigen may protect people against disease to a greater extent than the antigen alone.

**Microspheres**

Microsheres are solid, spherical particles containing dispersed molecules either in solution or in crystallineform. Numerous biodegradable polymers have been investigated for preparation of microspheres as depot formulation. Since drug release from this system is rate limited by dissolution of the matrix, so it is find that small polymer matrices released drug at a faster rate than larger ones. The application of biodegradable microspheres to deliver small molecules, proteins, and macromolecules using multiple routes of administration has been widely investigated and several products have been brought to market in the last 10–20 years. The method of preparation consists of suspending the drug in a biodegradable polymer, followed by reducing the mixture toparticles of the order of 600 μm,which are then injected as a suspension in carboxymethyl cellulose solution. For peptide or protein containing microspheres mainly three processes were studied more intensively, namely the w/o/w –technique phase separation methods and to some extent spray drying and by w/o/w emulsion-solvent evaporation method. The microsphere release drug in a zero order fashion over 1 to 3 months after intramuscular or subcutaneous injection into animals. PLGA microsphere had been also used for delivery of glycoprotein (GP) IIb/IIIa antagonist, plasmid DNA, Interleukin-1αandprolidaseenzyme.

To prolong the circulation, nanoparticles should be small enough. By taking an advantage of their rapid uptake by the RES and sequestration by liver kuffer's cells. The RES consist of phagocytic cells designed to cleanse unwanted cell debris and foreign particles E.g. Nanoparticles loaded with radioisotope technetium-99n can be used to image hepatic pathologies.

**Magnetic Microspheres**

Magnetic microspheres were developed to minimize reticuloendothelial clearance and to increase target site specificity. They can be used to entrap a wide variety of drugs .Magnetic microspheres can be prepared from albumin and magnetite. They are about 1.0μm in size,which is small enough to allow them to inject intravenously. These are relatively non-toxic and non-reactive with blood components.

Typically, Magnetic microspheres are infused into an artery supplying a given target site.A magnet of sufficient field strength is then externally placed over the target area to localize microspheres at the capillary bedin this region.

**Conclusion**

Oral drug delivery in which the systemic bioavailability of a drug is often subjected to variations in gastrointestinal transit and biotransformation in the liver by "First Pass" metabolism. Parenteral drug delivery, especially intravenous injection, can gain easy access to the systemic circulation with complete drug absorption and therefore reach the site of drug action Rapidly.The intravenous, subcutaneous, intramuscular, intraperitoneal, and intrathecal routes are all examples of parenteral routes of drug administration. For a variety of reasons, the most notable being physiological and anatomical constraints, not all of these are useful as routes for controlled drug delivery. Up to the present, efforts in developing controlled release parenteral dosage fortes seem to have concentrated the subcutaneous and intramuscular routes, resulting in such products as aqueous and oil solutions, and implants.There are currently a number of injectable depot formulation on the market.

**Reference**

1. Leon Lachman, H. A. Lieberman, The Theory and Practical of Industrial Pharmacy
2. Josep R. Robinson and Vincent ILL-Lee, Controlled drug delivery fundamental and application, Matcel Dekker Inc, New York, 1987; 29.
3. Remington,The science & practice of pharmacy, Lippineolt,Williams K_,Parenteral Preparation, ISE publication, Phelabelphia; 2000; 20(1): 804.
4. D.M Brahmankar & Sunil B.Jaiswal, A Textbook of Biopharmaceuitics & pharmacokinetics, Valibh Prakashan, 2002; 301: 360.
5. B.M.Mital, Textbook of Pharmaceutical Formulation, Vallabh Prakation, 1999; 276.
6. G.K. Jani, Textbook of Pharmaceutics-l, B.S. Shah Publications, 1997-1998; 2: 33.
7. N.K.Jain, Advances in controlled and Novel Drug Delivery System, C13S Publishers and Distributors, 2001; 190(1): 408-42.
8. Antal E.S., Disk C.F., WrightC.E., Welshman I.R., comparative bioavailability of two medroxy progesterone acetate suspensions, Int. .1. Pharma. Sci., 1989; 54: 33-39.
9. Alfred Martin, Physical Pharmacy, Fourth edition, BA, Waverly Pvt.Ltd. NewDelhi, 1997; 519-520.
10. Gilbert S. banker and Cristopher T. Rhodes, Morden Pharmaceutics Drug and Pharamaceutical science, Inc., New York, 1996; 72(3) : 638-596.
11. Liberman. A., Martin, Rieger M. and Banker Gilbent's Pharmaceutical Dosage firms Dispersed systems vol-2 Marcel Dekker 1996; 285.
12. Avis Kenneta E, " Theory and Practice of Industrial Pharmacy", Varghese publishing Bombay, 1976; 3: 654.
13. Arky R., Physician's Desk Reference 48M ed, Medical Economics Data Production Company, Montavale N.J. 1994; 2417.
14. Nyamrk, M and frank, K.F. "Journal of Pharamceutical science" Sep. 1999; 88: 861.
15. Chien, Yiew. W., " Journal of parenteral science and technology" May/June 1981; 35: 106.
16. Harvey, se "Journal of Ph: ramceutical science" Feb. 1998; 87: 175.
17. Chien Y. W., Novel drug delivery system, 1982; 381.
18. Arky R., Physician's Desk Reference, Medical Production Company, Montavale N.J. 1994; 48: 2170.
19. James Swarbrick and James C. Boylen, Encylopedia of pharmaceutical technology, 3-5: 389.