

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: www.ijrpns.com



PARENTERAL CONTROLLED DRUG DELIVERY SYSTEM

M. Kalyani*¹, P. Surendra¹, V. Sirisha²

¹*Department of Pharmaceutics, Narasaraopet Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India.

²Department of Pharmaceutics, Narasaraopet Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), Andhra Pradesh, India.

ABSTRACT

Parenteral drug delivery systems are the preparations that are given other than oral route. (Para-outside, enteric-intestine). 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. These biodegradable injectable drug delivery system offer attractive opportunities for protein delivery and could possibly extend patent life of protein drugs. Parenteral drug delivery system seeks to optimize therapeutic index by providing immediate drug to the systemic pool in required quantity to treat- cardiac attacks, respiratory attacks. This article includes all the details of parenteral drug delivery system.

KEYWORDS

Parenteral drug delivery systems, Bio-availability, Pharmacoeconomic, Cardiac attacks and Respiratory attacks.

Author for Correspondence:

Kalyani M,
Department of Pharmaceutics,
Narasaraopet Institute of Pharmaceutical Sciences,
Narasaraopet, Guntur, Andhra Pradesh, India.
Email: kalyani.makanaboina@gmail.com

INTRODUCTION¹

With traditional administration, the drug active must remain between a maximum blood level value which may represent a toxic level and a minimum value below which the drug is no longer effective. With controlled administration, the blood levels are constant between the desired maximum and minimum for an extended period of time.

TRADITIONAL VS CONTROLLED RELEASE DRUG DOSING

Parenteral Controlled Drug Delivery System¹

The intra venous, subcutaneous, intra muscular, intraperitoneal and intrathecal routes are all examples of parenteral routes of drug administration.

- In developing controlled release parenteral dosage forms to have concentrated on the subcutaneous & intramuscular routes.
- Resulting in such products as aqueous and oil suspensions, oil solutions, and implants.
- Drug molecules will be released continuously from the reservoir at a rate determined by the characteristics of each formulation.
- This continuous release of drug molecules will result in a prolonged drug blood level.
- The rate of absorption and hence duration of therapeutic activities will be determined by the nature of the vehicle.
- 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 through the parenteral route of administration some disadvantages also present, to overcome those problems these controlled delivery system of parenteral dosage forms are used.

Disadvantages Over Conventional Parenteral Dosage Forms

- Parenteral route offers rapid onset of action with rapid declines of systemic drug level.
- It requires frequent injection, which ultimately leads to patient discomfort.
- Patient compliance.
- For the sake of effective treatment, it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range as long as a treatment calls for Continuous IV infusion.
- But it requires continuous hospitalization during treatment.

To overcome the disadvantages related to conventional dosage form controlled release formulations are using now a day.

The parenteral controlled drug delivery system consists of two types for the administration of drug.

Types of Parenteral Controlled Drug Delivery System

1. Inject able drug delivery
2. Implantable drug delivery system

Injectable Drug Delivery²

Approaches

Several formulation approaches are used for the preparation of parenteral controlled formulations. They are

- Use of viscous, water-miscible vehicles, such as an aqueous solution of gelatin.
- Utilization of water-immiscible vehicles, such as vegetable oils, plus water-repelling agent, such as aluminum monostearate.
- Formation of thixotropic suspensions.
- Preparation of water-soluble drug derivatives, such as salts, complexes, and esters.
- Dispersion in polymeric microspheres or microcapsules, such as lactide-glycolide homopolymers or copolymers.
- Co administration of vasoconstrictors.

Parenteral depot system

- Injectable preparations are prepared in the form of depot preparations.
- Depot: Long acting parenteral drug formulation is designed, ideally to provide slow constant, sustained, prolonged action.
- They may be classified based on the process used for controlled drug release are as follows....

Classification of Depot Preparations

1. Dissolution-Controlled Depot preparations

In this the drug absorption is controlled by slow dissolution of drug particles in the formulation.

2. Adsorption-type Depot preparations:

In this the drug absorption is based on the amount of drug unbounded.

3. Encapsulation-type Depot preparations

In this the rate of drug release is controlled by the rate of permeation across the permeation barrier.

4. Esterification-type depot preparations

The rate of drug absorption is controlled by the interfacial partitioning of drug ester from the reservoir.

Examples of few Injectable controlled release formulations

1. Long-acting Penicillin Preparations
2. Long-acting Vitamin B₁₂ preparations
3. Long-acting Adreno corticotropic Hormone Preparations
4. Long-acting Steroid preparations
5. Long-acting Antipsychotic Preparations
6. Long-acting Antinarcotics Preparations
7. Long-acting Contraceptive Preparations
8. Long-acting Insulin Preparations

Site of injection

1. For sub cutaneous

Injection Abdomen
Buttocks
Thighs
Upper arm

2. For IM injection

Upper outer quadrant of buttocks
Central upper hip
Central mid thighs

Biopharmaceutics of Controlled Release Parenteral Drug Products¹

- When a controlled drug formulation is administered parenterally in to a tissue space, muscle or adipose tissue.
- The drug can exert its therapeutic action.
- It must first be released from the formulation in to the general circulation and then to the site of drug action.

In many cases,

The rate limiting step is dissolution of drug particles in the formulation and

Partitioning of drug molecules from the vehicle to the surrounding tissue fluid.

Thus:

Factors that affect the dissolution step and / or the partitioning step will affect parenteral drug absorption.

For example

Subcutaneous absorption of the suspension of this drug in oil was

Predominantly by the distribution coefficient between the oily vehicle and the aqueous subcutaneous medium.

Effect of physicochemical properties^{3,4}

Rate of dissolution solids of drug solids in the formulation

Particle size and crystalline habit of drug solids

PH value of the formulation

Lipophilicity of the drug

Solubility of the drug

Presence of other ingredients

- Sustained and controlled release parenteral drug delivery systems include liposomes, microspheres, suspensions, gels, emulsions and implants.
- Such systems can be considered safer than conventional parenteral dosage forms.
- These parenteral dosage forms are usually selected when there are problems associated with oral delivery.
- The control release dosage forms are selected may be dependent on the desired effect. E.g. Long term

Aqueous solutions:

A. High viscosity products:

In this that by increasing viscosity of the vehicle the diffusion coefficient of the drug will be reduced.

For examples of such viscosity agents are: Methylcellulose, sodium carboxyl methyl cellulose and polyvinyl pyrrolidine.

B. Complex formation:

The complex formation can be achieved by forming a dissociable complex of a drug with macro molecules such as: Methyl cellulose, sodium carboxyl methyl cellulose and polyvinyl pyrrolidine.

Aqueous suspension

A suspension usually gives a longer duration of action than an aqueous solution when given intramuscularly or subcutaneously. The drug is continuously dissolving a situation that is not possible with aqueous solutions. The dissolution rate of a drug can be described by a modified form of the Noyes-Whitney equation.

$$\text{Mean dissolution rate} = \frac{A \cdot D \cdot (C_s - C)}{L}$$

Whereas A = Mean surface area for dissolution.

D = Drugs diffusion coefficient.

C_s = Saturation solubility of the drug.

L = Thickness of the diffusion layer.

Micro spheres

These are solid, spherical particles containing dispersed drug molecules either in solution or crystalline form

This delivery system has been applied to narcotic antagonists and anti Neoplastic agents.

The method consists of suspending the drug in a biodegradable.

Micro capsules

Micro capsules are spherical particles containing drug concentrated in the center core.

The coating material can be selected from a wide variety of natural and synthetic polymers.

These are depending on the material to be coated.

For examples of these polymers include Nylon, Dipolyacticacid, Albumin, and Cross-linked starch.

Oil solutions

This mechanism to achieve parenteral controlled release is through the use of oil solutions. Drug release is controlled by partitioning of drug out of the oil in to the surrounding aqueous medium. The equilibrium between drug in the oil phase and that in the aqueous phase with a characteristic constant. The apparent partition coefficient K is given by:

$$K = [D_o] / [D_w]$$

Where k = Drug concentration in oil / drug concentration in water.

Oil suspensions

Drug release from oil suspensions combines. In aqueous suspensions and oil solutions. The suspended particles acting as a drug reservoir. The process of drug availability consists of dissolution of drug particles followed by partitioning of drug from the oil solution to aqueous medium.

Emulsions

Emulsions use in topical drug delivery and also have been used as drug vehicles. More progress has been made with parenteral than with oral emulsions. For example: these have been administered intravenously in parenteral nutrition.

Liposomes

These are hydrated liquid crystals formed when phospholipids are allowed to swell in an aqueous media. Water or lipid-soluble substances can be entrapped within their aqueous or lipid phase. These

liposomes are intravenous carriers for enzymes such as amyloglycosidase & neuraminidase. As well as drugs such as penicillin G.

Nanoparticles

These are solid, colloidal particle, ranging from 10-1000nm in size. They consist of macromolecular materials.

Implants:^{1,5,6}

These are typically placed subcutaneously to sustain drug release via the mechanisms of drug diffusion, polymer dissolution or both. Non-biodegradable polymers: as poly dimethyl siloxane etc. biodegradable polymers: Investigated for controlled drug delivery are such as

Natural polymers: albumin, starch, dextran, gelatin, fibrinogen, hemoglobin. Poly anhydrides, poly (caprolactone), poly lacticacid. The drug release rate will be directly proportional to its physical dimensions

Infusion devices

A variety of infusion devices can be used to sustain and control drug delivery. These systems consist of a drug reservoir and a rate controlling unit (a pump).

The simple gravity-fed pump relies on gravity as an energy source. The syringe pump uses a synchronous motor to drive a plunger to meter drug in to the body. The non-volumetric peristaltic pump forces drug solution by external pressure through a continuous drug delivery.

Prodrugs

Prodrugs are agents that undergo bio transformation before exhibiting their therapeutic action. In this for a parent drug that is incompletely absorbed after intramuscular or subcutaneous administration.

Implantable Drug Delivery System⁸

In 1861 Lafarge developed a subcutaneously implantable drug pellet for long term continuous drug administration. In 1936 Deanesly and Parkes developed crystalline hormones in the form of solid steroid pellets for hormone substitution therapy.

Subcutaneous drug administration by pellet implantation has drawbacks

The release profile of drug from the pellet is not constant. Termination of the therapy is not possible.

Hence there was a development of novel implants with rate-controlled drug delivery to replace pellets. Later U. S. Naval Research Center developed a very small capsule-shaped implant using silicone polymer tubing to encapsulate thyroid hormone. In vitro release studies demonstrated that the silicone capsule releases thyroid hormone at a constant rate, day after day.

Approaches to the development of implantable drug delivery system

A number of approaches have been developed to achieve the controlled administration of drugs via implantation. These approaches are outlined as follows:

1. Controlled Drug Release by Diffusion

Membrane permeation-controlled drug delivery system using

- Nonporous membranes
- Porous membranes
- Semi porous membranes

Matrix diffusion-controlled drug delivery using

- Liphophilic polymers
- Hydrophilic polymers
- Porous polymers

Micro reservoir dissolution-controlled drug delivery using

- Hydrophilic reservoir in liphophilic matrix
- Liphophilic reservoir in hydrophilic matrix

Membrane-matrix hybrid-type drug delivery system

- Liphophilic membrane with hydrophilic matrix
- Hydrophilic membrane with liphophilic matrix

2. Controlled drug release by activation

- Osmotic pressure-activated drug delivery
- Vapor pressure-activated drug delivery
- Magnetically activated drug delivery
- Ultra sound activated drug delivery
- hydrolysis activated drug delivery

Levonorgestrel Sub dermal Implant (NORPLANT)

Norplant implants consist of sets of 6 identical silicone rods, 2.2mm in diameter and 34mm long, and impregnated with Levonorgestrel. Levonorgestrel Sub dermal implants are approved for use for 5 years.

Matrix diffusion-controlled drug delivery system

An example of this type of implantable drug delivery device is the compudose implant.

Micro reservoir dissolution-controlled drug delivery system

An example of this type of implantable drug delivery device is the Syncro-Mate implant. Osmotic pressure-activated drug delivery system: An example of this type of implantable drug delivery device is the Alzet osmotic pump.

Vapor pressure-activated drug delivery system

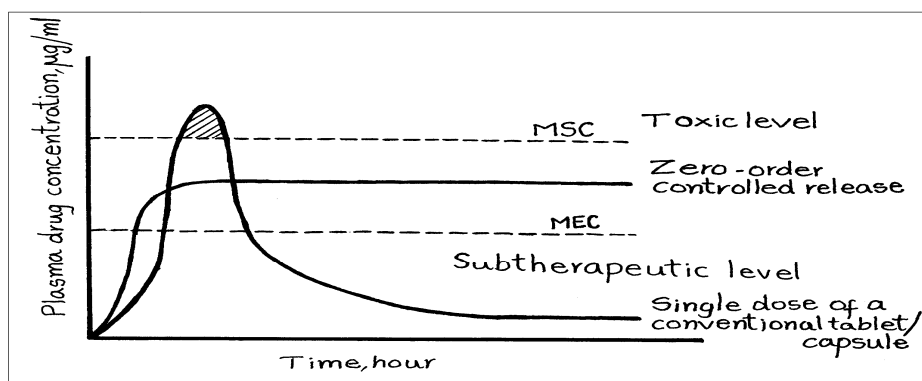


Figure No.1: Single dose vs. controlled drug delivery

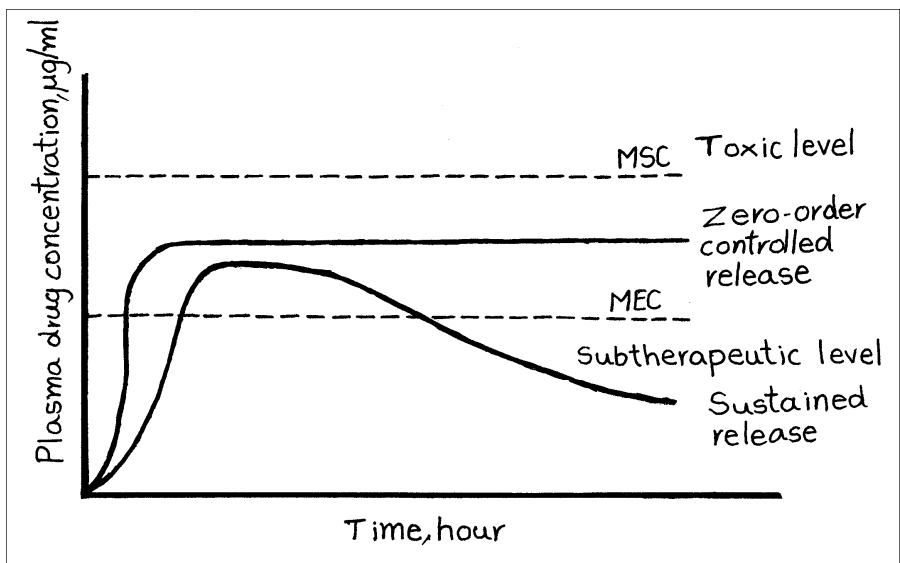


Figure No.2: Sustained release vs. controlled release

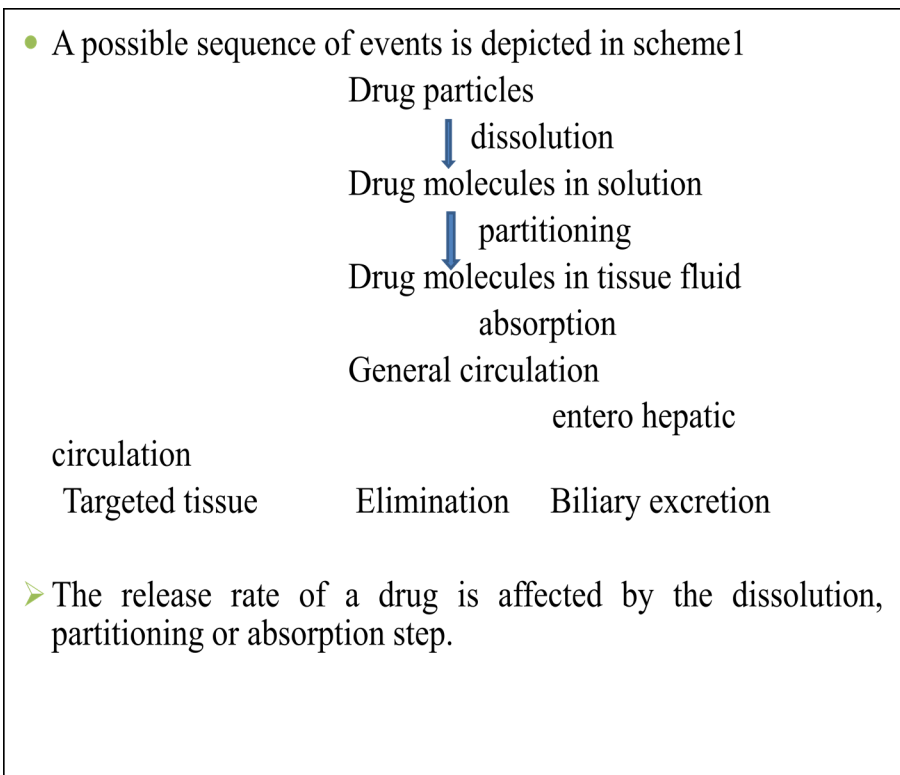


Figure No.3: Steps Involved in Drug Metabolism

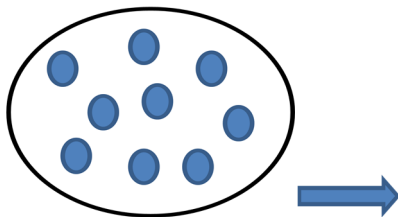


Figure No.4: Dispersed drug molecules in solution or crystalline forms.(Microsphere)

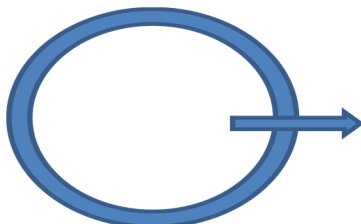
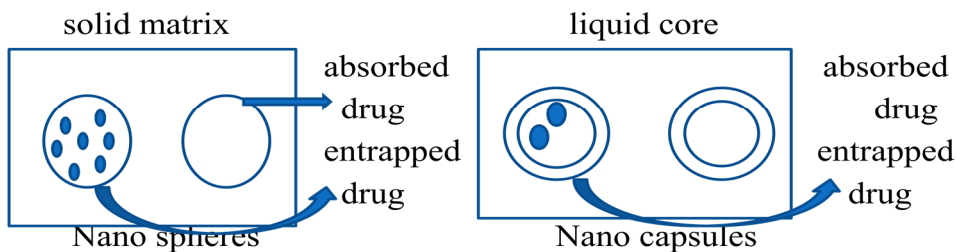


Figure No.5: Drug solution of suspension in the centre core. (Micro Capsule)

- Two types of nanoparticles can be obtained
- 1. Nanospheres and
- 2. Nanocapsules.
- 1) **Nanospheres:** They have a matrix type structure in which a drug is dispersed.



- 2. **Nanocapsules:** They exhibit a membrane-well structure with an oily core containing a drug.
- Reduction of particle size enables intravenous injection.

Figure No.4: Types of Nanoparticles



Figure No.6: Steps Involved in Parantral Drug Delivery

CONCLUSION

Extended release parenteral products are complex dosage forms, requiring careful development of test methods and acceptance criteria for the specifications. In particular, the in vitro release test method and acceptance criteria require rigorous scientific consideration and should be developed with an eye toward understanding the mechanisms of drug release. The final specifications need to ensure the safety, identity, strength, performance, and quality of the drug product at release and during storage through the end of its shelf-life. Major progresses in the development of parenteral sustained-release systems have been made in recent years as evidenced by the regulatory approval and market launch of several new products. Both the availability of novel carrier materials and the advances in method of fabrication have contributed

to these commercial successes. With the formulation challenges associated with biologics, new delivery systems have also been evolved specifically to address the unmet needs in the parenteral sustained release of proteins. The objective of parenteral controlled drug delivery system is to achieve a desired pharmacological response in a sustained manner at a selected site without undesirable interactions at the other sites. This is especially important in cancer chemotherapy, enzyme replacement therapy etc. It is achieved by two approaches. The first approach involves chemical modification of a parent compound to a derivative which is activated only at the targeted site. The second approach utilizes carriers such as liposomes, microspheres, nanoparticles and macromolecules to direct the drug to its site of action. Targeted and controlled drug release is an effective approach in

avoidance of hepatic first pass metabolism, rapid onset of action, better patient compliance, enhancement of bioavailability etc. Hence there is a need to develop novel drug delivery systems in order to achieve better drug performance.

ACKNOWLEDGEMENT

The authors are sincerely thanks to the Narasaraopet Institute of Pharmaceutical Sciences, Narasaraopet, Guntur (Dt), AP, India for providing the facilities to complete this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Chein Y W. Novel Drug Delivery Systems, New York, *Marcel Dekker Inc*, 2nd edition, 1992, 381-517.
2. Mahek Goel. parenteral controlled drug delivery system, pharमतutor-art-1477.
3. Brahmankar D M, Jaiswal S B. In: *Biopharmaceutics and Pharmacokinetics, A treatise*, 12th edition, 2007, 357-365.
4. Ijeoma F Uchegbu. In: *Parenteral Drug Delivery, J Pharm Sci*, 263(551), 1996, 355-358.
5. Leon Lachman H A, Liberman L K Joseph. In: *Theory and Practice of Industrial Pharmacy*, 3rd edition, 1991, 673-75.
6. Remington. In: *Pharmacy Practice*, 4th edition, 2001, 953-63
7. Patil S B, Kuchekar H S Mahajan. In: *Targeted Drug Delivery Systems. J Pharma Times*, 39(2), 2007, 19-21.
8. Vyas S P, Khar R K. In: *Controlled Drug Delivery Concepts and Advances*, 1st edition, 2002, 452-457.
9. Vyas SP, Khar RK. In: *Targeted and Controlled Drug Delivery*, 4, 2005, 213-215.
10. Shin Hyun, Bae Soo, Lee Myung. Pharmacokinetics of sildenafil after intravenous and oral administration in rats: Hepatic and intestinal first pass effects, *International Journal of Pharmaceutics*, 320(1-2), 2006, 64-70.
11. Heller J. Polymers for controlled parenteral delivery of peptides and proteins, *Advanced Drug Delivery Review*, 10(2-3), 1993, 163-204.

Please cite this article in press as: Kalyani M. et al., Parenteral controlled drug delivery system, *International Journal of Research in Pharmaceutical and Nano Sciences*, 2(5), 2013, 572-580.