ABSTRACT

Implant is an object or material inserted into the body for prosthetic, therapeutic, diagnostic or experimental purposes. Implants are one of the dosage forms used to achieve effective concentration for long time. Implant dosage forms are useful for patients having difficulty in taking drugs orally, and it allows the avoidance of frequent dosage by sustained supply. 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. Implantable 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 implantable parenteral drug delivery system.

Keywords: Implants, In situ forming implant, Solid implants, Bio-availability, Alzet osmotic pump, Injection-molding etc.
INTRODUCTION

Orally administered drug must be protected against denaturation in the gastrointestinal tract and should be capable of absorption across the wall of the stomach or the intestine. After absorption and upon reaching the portal circulation, it must be resistant to hepatic enzymes. The rate of drug absorption and elimination should ensure the blood levels within the therapeutic range. Moreover, the amount of intact drug that reaches the site of action should be sufficiently large to obtain desired therapeutic effect but insufficient to cause untoward side effects. \(^1\) A controlled drug action may be achieved by either chemically modifying the drug moiety or by formulating it in a specific way to control its release. Oral controlled release dosage forms can provide efficacy for about 24hrs. The main drawback of oral dosage form is the long transit time of approximately 12hrs through the GIT. If drug cannot be administered orally, a parenteral route of delivery is an alternative. Many proteins/peptides and other drugs, which are susceptible to the adverse conditions of GIT, are administered intravenously. Unfortunately, in intravenous drug administration, the duration of drug action is short for majority of therapeutically active agents and therefore frequent injections are required. The development of injectable controlled-release dosage forms is more likely to succeed commercially than alternative routes of delivery, assuming that these dosage forms provide the desired efficacy and safety \(^1\).

DEFINITION OF PARENTERALS

Parenteral preparation is sterile preparation containing one or more active ingredients intended for administration by injection, infusion, or implantation into the body. Parenteral preparations may require the use of excipients such as solvents, substances to enhance solubility, suspending agents, and buffering agents, substances to make the preparation isotonic with blood, stabilizers or antimicrobial preservatives. The addition of excipients is kept to a minimum. There must be no incompatibility between any of the components of the dosage form. Water for injections is used as the vehicle for aqueous injections.

**Parenteral controlled-release drug delivery systems**

Number of drug delivery systems has been developed over the years, parenteral drug delivery system being one of them. Parenteral drug delivery refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa. Conventional parenteral drug delivery systems, typically intravenous injection, occasionally cause a high plasma drug concentration, close to the minimum toxic concentration. Repetitive
administration is sometimes required due to the short duration of action from traditional systems. To avoid the problems from conventional systems, parenteral controlled-release drug delivery systems are designed to achieve consistent, predictable or desired drug release profiles. They can be administered via a parenteral route either by subcutaneous injection, intramuscular injection, or injection to other specific sites such as intra-articulate injection. Suspensions, emulsions, liposomes, micro particles and implants are identified as parenteral controlled release drug delivery systems. The systems are useful and necessary when drug candidates have poor absorption by other routes of administration and short half-lives, such as when peptides and proteins are used. The advantages of parenteral controlled-release over conventional drug delivery systems are: [2,3]

- To maintain a high drug concentration in the blood circulation or prolonging the duration of action.
- Improved drug pharmacokinetics.
- Enhancement of physical stability
- Reduction of side effects by maintaining a constant drug level via parenteral depot systems
- Increasing specificity and reducing systemic adverse effects for targeted drug delivery.
- An opportunity to control a precise drug release rate and
- Improvement of patient compliance by decreasing invasive administration and dosing frequencies.

Types of Parenteral Controlled Drug Delivery Systems

- Surgical implants
- Microspheres
- Liposomes

Implants

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 lactic acid. The drug release rate will be directly proportional to its physical dimensions [1,4,5,6].

**Microspheres**
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.

**Liposomes**
These are hydrated liquid crystals formed when phospholipids are allowed to swell in an aqueous medium. Water or lipid-soluble substances can be trapped 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.

**IMPLANTABLE PUMP SYSTEMS**
The primary characteristic that distinguishes a pump from other controlled-release systems is that the primary driving force for delivery by a pump is not the concentration difference of the drug but rather, a pressure difference [14]. The pump must be convenient to use by both the patient and the health professional, have long reservoir and battery life, easy programmability, and be implantable under local anaesthesia. There must also be a simple means to monitor the status and performance of the pump, and both the interior and exterior of the pump must be sterilizable [15].

![Fig.1: Duros osmotic pump (Alza -Mountain View, CA, USA).](image-url)
Table 1: Demonstration of Parenteral implants

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Company</th>
<th>Delivery technology</th>
<th>Polymeric carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decapeptyl SR</td>
<td>Triptorelin</td>
<td>Ipsen</td>
<td>Microparticles</td>
<td>PLGA</td>
</tr>
<tr>
<td>Nutropin Depot</td>
<td>Somatropin</td>
<td>Genetech</td>
<td>Microparticles</td>
<td>PLGA</td>
</tr>
<tr>
<td>Risperdal Consta</td>
<td>Risperidone</td>
<td>Janssen</td>
<td>Microparticles</td>
<td>PLGA</td>
</tr>
<tr>
<td>Sandostatin LAR</td>
<td>Octreotide</td>
<td>Novaris</td>
<td>Microparticles</td>
<td>PLGA</td>
</tr>
<tr>
<td>Trelstar Depot</td>
<td>Triptorelin</td>
<td>Watson Pharma</td>
<td>Microparticles</td>
<td>PLGA</td>
</tr>
<tr>
<td>Trelstar LA</td>
<td>Triptorelin</td>
<td>Watson Pharma</td>
<td>Microparticles</td>
<td>PLGA</td>
</tr>
<tr>
<td>Vivitrol</td>
<td>Naltrexone</td>
<td>Cephalon</td>
<td>Microparticles</td>
<td>PLGA</td>
</tr>
<tr>
<td>Profact Depot</td>
<td>Buserelin</td>
<td>Sanofi-Aventis</td>
<td>Solid implant</td>
<td>PLGA</td>
</tr>
<tr>
<td>Zoladex</td>
<td>Goserelin</td>
<td>AstraZeneca</td>
<td>Solid implant</td>
<td>PLGA</td>
</tr>
<tr>
<td>Gliadel</td>
<td>Carmustine</td>
<td>MGI Pharma</td>
<td>Targeting solid implant</td>
<td>Polifeprosan 20</td>
</tr>
<tr>
<td>Atridox</td>
<td>Doxycycline</td>
<td>Tolmar</td>
<td>In situ implant</td>
<td>PLA</td>
</tr>
<tr>
<td>Atrisorb-D FreeFlow</td>
<td>Doxycycline</td>
<td>Tolmar</td>
<td>In situ implant</td>
<td>PLA</td>
</tr>
<tr>
<td>Eligard</td>
<td>Leuprolide</td>
<td>Sanofi-Aventis</td>
<td>In situ implant</td>
<td>PLGA</td>
</tr>
<tr>
<td>Lupron Depot</td>
<td>Leuprolide</td>
<td>Abbott</td>
<td>In situ microparticles</td>
<td>PLGA</td>
</tr>
</tbody>
</table>

Table 2: Examples of parenteral controlled-release drug products (exceptional parenteral controlled-release based on biodegradable polymers)

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug</th>
<th>Company</th>
<th>Deliver technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambisome</td>
<td>Amphotericin</td>
<td>Gilead</td>
<td>Liposome</td>
</tr>
<tr>
<td>DaunoXome</td>
<td>Daunorubicin</td>
<td>Gilead</td>
<td>Liposome</td>
</tr>
<tr>
<td>Doxil</td>
<td>Doxorubicin</td>
<td>Johnson and Johnson</td>
<td>Liposome</td>
</tr>
<tr>
<td>Implanon</td>
<td>Etonogesterol</td>
<td>Organon</td>
<td>Implant</td>
</tr>
<tr>
<td>Plenaxis</td>
<td>Abarelix</td>
<td>Praecis</td>
<td>Carboxymethyl cellulose complex</td>
</tr>
<tr>
<td>Myocet</td>
<td>Doxorubicin</td>
<td>Elan</td>
<td>Lipid complex</td>
</tr>
</tbody>
</table>

Implantable Drug Delivery System

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 [8].

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: [9]
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 system
- Liphophilic membrane with matrix
- Hydrophilic membrane with liphophilic matrix

2. Controlled drug release by activation
- Osmotic pressure- activated drug delivery
- Vapour 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 derm 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 delivery system
An example of this type of implantable drug delivery device is the Syncro pressure-activated drug delivery system: example of this type of implantable drug delivery device is the Alzet osmotic pump.
Implants classified as following: [10]

1. Solid implants
Solid implants typically exhibit biphasic release kinetics, with initial burst of drug is usually due to the release of drug deposited on the surface of the implant although zero order kinetics may be achieved by. E.g. Coating the implant drug impermeable material Overall drug release may be controlled by varying polymer composition- an increase in the level of lactic acid in a polylactic acid co-glycolic acid copolymer retards drug release and increase in polymer molecular weight also retards drug release and prolongs drug effects.

2. In-Situ forming implants
Biodegradable injectable in situ forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot systems. The controlled release of bioactive macromolecules via (semi-) solid in situ forming systems has a number of advantages, such as:
1. Ease of administration,
2. Less complicated fabrication,
3. Less stressful manufacturing conditions for sensitive drug molecules.
From a manufacturing point of view, in situ forming depot systems offer the advantage that they are relatively simple to manufacture from polymers adapted for this approach. Compared with microspheres, which have to be washed and isolated after preparation, operating expenses for the production of in situ forming applications are marginal, thus lowering investment and manufacturing costs.

Classification of injectable in situ forming implants [11]

In situ cross-linked polymer systems
In situ polymer precipitation
Thermally induced gelling system

IMPLANTS FOR HEART
Percutaneous trans luminal angioplasty (PTCA) is used in the treatment of Coronary Artery Disease. Over the past decade, extensive research has been performed addressing the design of stents, which are commonly used for PTCA. Endoluminal metallic endoprostheses (stents) have reduced procedural complications in PTCA like elastic recoil of the vessel wall, balloon-induced dissection, and reoccurrence of restenosis. To overcome the restenosis issue, stents for local delivery of several drugs were established. First generation drug eluting stents (1GDES) consist of
a backbone stent (316 L stainless steel or Nitinol), a polymer (biodegradable or non-degradable), and drugs such as Paclitaxel or Sirolimus. This 1 G-DES was designed to reduce in stent neointimal formation and to minimize the appearance of restenosis.

**CYPHER STENT**

A stent is a permanent implant that remains in your artery. CYPHER® Stent is a small, expandable, slotted metal tube is inserted through a catheter into a coronary artery. There, it acts as a scaffold to help hold the artery open in order to improve blood flow to the heart and relieve the symptoms and dangers associated with artery blockage. The metal of the stent has a soft, plastic coating that contains the anti-rejection-type medicine Sirolimus. Eighty percent (80%) of the Sirolimus is released during the first 30 days. The rest is released by the end of 90 days.

---

**Fig. 2:** CYPHER Stent implant

**Fig. 3:** Metallic stent implant.

**Fig. 4:** Drug loaded stent inserted into coronary artery
TAXUS STENT

The TAXUS stent uses Translute™ Polymer, a proprietary polymer carrier technology, to control drug release. The durable Translute Polymer protects the drug and maintains coating integrity during preparation, delivery, and stent expansion. The polymer controls the release of paclitaxel, which may allow for consistent drug release and more uniform drug distribution.

Fig. 5: Taxus stent implant for heart

Fig. 6: Steps Involved in Parenterals Drug Delivery
ADVANTAGES OF IMPLANTABLE DRUG DELIVERY SYSTEM

The advantages of implantation therapy include [12]

Convenience
Effective concentration of drug in the blood can be maintained for longer period of time by techniques such as continuous intravenous infusion or repeated injections. On the other hand, under these treatments patients are regularly required to uninterrupted medical monitoring. A short-acting medicine worsens the condition, as the quantity of injections or the infusion rate need to be increased to maintain a therapeutically effective level of the drug. On the other hand, implantation treatment permits patients to get medication outside the hospital setting with marginal medical observation. Implantation treatment is also characterized by a lower occurrence of infection associated problems in comparison to indwelling catheter-based infusion system.

Improved drug delivery
The drug is distributed locally or in systemic circulation with least interference by metabolic or biological barriers. For example, the drug moiety bypassed the GIT and the liver. The by-passing effect is beneficial to drugs, which are either easily inactivated or absorbed poorly in the GIT and/or the liver before systemic distribution [1].

Compliance
By allowing a reduction, or complete elimination, of patient-involved dosing compliance is increased hugely. Patient can forget to take a medicine, but drug delivery from an implant is not dependent of patient input. Periodical refilling is involved in some implantable but despite this limitation the patient has less involvement in delivering the required medication.

Potential for controlled release
Implants are available which deliver drugs by zero order controlled release kinetics. The advantages of zero order controlled release are:

(a) Conventional therapy is avoided,
(b) Dosing frequency is reduced,
(c) Patient compliance is increased.

Potential for bio-responsive release
Bio-responsive release from implantable is an area of on-going research.

Potential for intermittent release
Intermittent release can be facilitated by externally programmable pumps. Intermittent release can facilitate drug release in response to such factors as:
Flexibility
In the choice of materials, methods of manufacture, degree of drug loading, drug release rate etc. considerable flexibility is possible. From a regulatory viewpoint, it is regarded as a new product and can lengthen the market protection of the drug for an additional 5 years (for a new drug entry) or 3 years (for existing drugs).

DISADVANTAGES OF IMPLANTABLE DRUG DELIVERY SYSTEM
The disadvantages of implantables include:

Invasive
To initiate therapy either a minor or a major surgical procedure is required to initiate therapy. Appropriate surgical personnel is required for this, and may be time-consuming, traumatic. This causes some scar formation at the site of implantation and surgery related complications in a very small number of patients. Uncomfortable feeling for the patient wearing the device.

Danger of device failure
There is no associated danger with this treatment that he device may for some reason fail to work. This again requires surgical involvement to correct \[^{13}\].

Termination
Osmotic pumps and non-biodegradable polymeric implants also are surgically recovered at the end of therapy. Although surgical recovery is not required in biodegradable polymeric implants. Its on-going biodegradation makes it difficult to end drug delivery, or to maintain the accurate dose at the end of its lifetime.

Limited to potent drugs
In order to minimize patient’s discomfort the size of an implant is usually kept small. Therefore most implants have a limited loading capacity so that frequently only somewhat potent medicines such as hormones may be appropriate for delivery by implantable devices.

Biocompatibility issues
Concerns over body reactions to a foreign substance often increase the issues of biocompatibility and safety of an implant.

Available online: www.ijipsr.com  September Issue
Possibility of adverse reactions

A high concentration of the drug delivered by an implantable device at the implantation site may produce adverse reactions.

CONCLUSION

Recently Implantable drug delivery is one of the technology sectors that often overlooked in the development of new drug delivery by the formulation, research and development in many pharmaceuticals. Implanted drug delivery technologies have ability to reduce the frequency of patient driven dosing and to deliver the compound in targeted manner. Many product utilizing implant delivery technologies are being utilized for many therapeutics applications such as, dental, ophthalmic, ontological disease. As with any implanted material, issues of biocompatibility need to be investigated, such as the formation of a fibrous capsule around the implant and, in the case of erosion-based devices, the possible toxicity or immunogenicity of the by-products of polymer degradation. 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 author would like to thanks to our honourable Principal Dr. Uma Maheswara Rao V and guide Mahalakshmi K for their valuable comments and guidance. I express a profound gratitude to my friend Sandeep Ankam for providing his unflinching support and valuable advices in each and every step which has helped me to complete this publication success. I would remain grateful to them and to their words of encouragement.

REFERENCES


Available online: www.ijipsr.com  

September Issue
2. Mahek Goel. Parenteral controlled drug delivery system, _pharmatutor-art-1477_.