



A Detailed Review: Implantable Drug Delivery System.

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ABSTRACT:

The conventional routes of drug administration remain most popular and convenient methods with many Advantages. But it also has number of disadvantages and challenges, like Frequent dosing, Fluctuation in bioavailability, release date/time of drug. Over the last two Decades, Two major challenges in front of novel drug delivery. First is achieving sustained zero order release of drug for long period of time, and second one is controlled delivery of therapeutic molecule. To overcome these problems, there was essential need to develop new dosage form that release drug at controlled rate at targeted site. A promising alternative delivery method is the use of polymeric implantable devices that deliver drug molecules. It results in improvement of novel drug delivery system which optimizes therapeutic properties of drug. Implantable drug delivery system provides constant release rate, targeted delivery, reduced dosing with minimizing adverse effects. Currently various techniques of implantation are used for number of therapeutic applications like oncology, dentistry, ophthalmology, contraception, neurology, etc. In this review we discuss about these implants and their implantation techniques.

KEYWORDS: Implantable drug delivery system, implants, novel drug delivery system, controlled release drug delivery system

INTRODUCTION:

The idea of an implanted system for sustained release drug administration was first presented by "Lafarge" in 1861. For a prolonged supply, it was initially used to create solid implants that contained steroidal hormones. Implants are a single unit drug dosage form designed to administer a medication over an extended period of time to a chosen site of drug release at a therapeutically determined rate. Implants are small, solid, sterile devices made of highly purified drugs that are injected using large bore needles or placed in the body through subcutaneous or intramuscular tissue using a small surgical incision, past.

History:

This implantable medicine delivery device was created and trademarked by the Population Council in 1980, and it was first made accessible to the general public worldwide in 1983. As stated before, it was approved by the US FDA in December 1990, and US commercialisation began in February 1991. This form of contraception consists of six thin, flexible silicone capsules that contain 36 mg of the hormone levonorgestrel. It can offer up to five years of contraceptive protection when subcutaneously implanted, typically on the inside of the female user's upper arm. Its popularity and effectiveness can be gauged by the fact that it is authorised in 60 nations. Despite being removed from the US market in 2002, Norplant is still accessible in other nations and has been effectively used by almost 60 million women. A second implantable medication delivery method for contraceptive implants was authorised by the US FDA in 2006, the United States FDA approved a second implantable drug delivery technology for contraceptive implants. The implant is a single rod that is 4 cm in

length and 2 mm in breadth. Its PAVA core, or reservoir, contains 68 mg of etonogestrel, which is released over a period of three years. A PEVA membrane enclosing the rod regulates the pace of medication release. After removal and instant replacement with a new implant, the initial three years of protection against pregnancy can be prolonged. Implanon, which was created for simpler subcutaneous insertion and removal than Norplant, achieved excellent patient and physician acceptance.[1]

Ideal properties of implantables drug delivery system:

- Environmentally stable
- Biocompatible
- Easy to sterile
- Rate controlled release of drug
- Improve patient compliance
- Reduce dosing frequency
- Easy to manufacture
- Good mechanical strength
- Inexpensive

Advantages:

- Controlled DDS for long period of time
- Targeted DDS
- Bypass first pass metabolism
- Decrease side effects
- Improved stability and bioavailability
- Improved patient compliance

Disadvantages:

- Minimum surgery required
- Uneasy to simply discontinue the therapy
- Inadequate release
- Dose dumping
- Special equipment required for manufacturing so, expensive system
- May causes irritation or ulcer at site of implantation [2]

CLASSIFICATION OF IMPLANTABLE DRUG DELIVERY SYSTEM:

1. Rate programmed drug delivery system:

It works by controlling release rate of drug.

It is subdivided into three types, as following:

a) Polymer membrane permeation-controlled drug delivery system -

In this controlled drug delivery device, drug reservoir is totally encapsulated within a capsule shaped or spherical compartment.

A rate-controlling polymeric membrane encloses the entire apparatus.

The drug reservoir can be either solid particles or the dispersion of the solid particles in a liquid or solid dispersing medium.

The encapsulation of drug reservoir inside the polymeric membrane can be done by the encapsulation, microencapsulation, molding, extrusion, etc.

Ex. Norplant subdermal implant. [3]

b) Polymer matrix diffusion-controlled drug delivery system -

In this system implants containing drug reservoir is formed by dispersion of Solid drug into lipophilic or hydrophilic polymer matrix. Cross linking of polymer chains at room temperature to obtained liquid or semisolid polymer matrix in which solid drug dosage are dispersed. It also prepared by conservation or solid evaporation by dissolving the drug solid or the polymer in an organic solvent at an elevated temperature under a vacuum to form microsphere. Ex. Compu dose implant

c) Drug delivery device of the hybrid membrane matrix type

It is a hybrid form of polymer membrane permeation CDDS and polymer matrix permeation CDDS.

It follows constant drug release kinetics just like the polymer membrane permeation CDDS. therefore, it will reduce the chances of dose dumping from reservoir compartment.

In this system implantable devices were prepared by dispersion of drug solid particles uniformly throughout polymer matrix drug reservoir which then encapsulated within the rate controlling polymeric membrane.

It is a sandwich type implantable device.[3]

2. Activation modulated drug delivery system:

a) Osmotic pressure activated drug delivery system-

In this system drug solution is released through a specialized laser drilled delivery orifice at a constant rate under a controlled gradient of osmotic pressure.

Ex.- Alzet osmotic pump

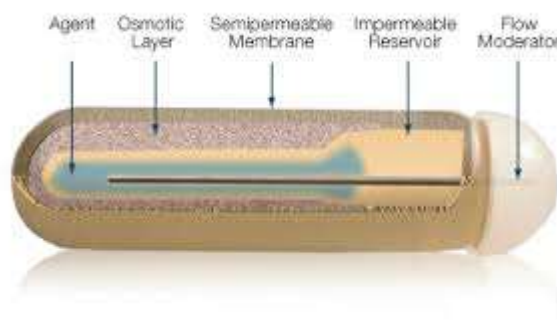


Fig.1 Alzet Osmotic Pump [4]

It is implanted subcutaneously or intramuscularly in which sterile, purified drug filled by compression.

Working:

Drug solution containing reservoir implanted which have additional components, stainless steel flow modulator in pump

Water from body tissues penetrate into semipermeable membrane of pump

Which create osmotic pressure with the help of osmotic agents

Results in compression of pump and finally drug released.

b) Vapor pressure activated drug delivery system-

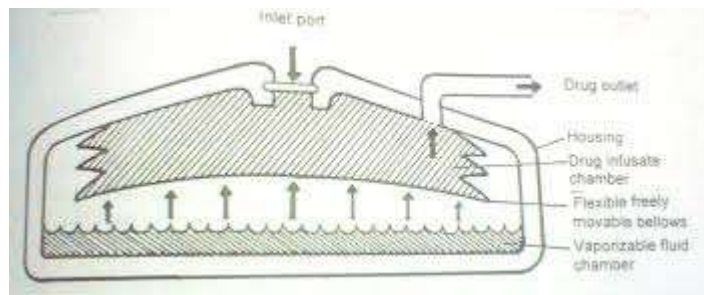


Fig.2 Vapor pressure pump [5]

It is a bist shaped device in which vapor pressure used as activating source.

It contains two chambers-

Infusate chamber- contains drug solution

Vaporizable fluid chamber- contains vaporizable fluid

Working:

After implantation at body temperature the vaporizable fluid present in vaporizable fluid chamber get evaporated

That vapors of fluid apply vapor pressure to infusate chamber drug solution

Which push drug solution outside the device and release the drug.

c) Hydration activated drug delivery system:

In this system fabricated hydrophilic polymers that in presence of water get swelled in body tissue and form microscopic pores from which drug released.

d) Hydrolysis activated drug delivery system:

The drug release by hydrolysis of biodegradable polymer by tissue fluid at implantable site.

APPLICATIONS:

1.Contraception:

Implant-based control is a widely used technique. One kind of subdermal implant used for birth control is called a norplant, which continually releases birth levonorgestrel. It consists of six silicon membrane units, each holding 36 micrograms of medicine. Birth control via implants is a common practice. A norplant is a type of subdermal implant that releases levonorgestrel continuously; it is used as a form of birth control. It is made up of six silicon membrane units, with 36 micrograms of medication contained in each. The capsules release 70 milligrams daily for the first three months, followed by 30 milligrams every day for approximately 800 days, and then five years of constant release. Progestasert is an ethylene vinyl intrauterine implant.

2. Ocular use:

Drugs designated for long-term ocular usage are commonly delivered by silicone, implanted devices, membrane-controlled devices, and infusion devices. A well-known example of a membrane-controlled device is the occusert, which has an ethylene vinyl acetate membrane enclosing an alginate-filled pilocarpine drug reserve. This device delivers a drug outburst at first, then a zero order release profile of the drug at an hourly rate of 20–40 milligrams for a week. It provides effective intraocular pressure (IOP) management with minimal side effects, and while it is accepted in adults, it is poorly tolerated in the elderly.

3. Cancer:

Prostate cancer can be effectively treated with silicone rod implants by administering testosterone propionic acid and ethinyl estradiol. Leuprolide acetate, which is structurally identical to gonadotropin-releasing hormone (GnRH), is released for a month with Lupron Depot. For one month, goserelin acetate is released from a biodegradable rod by Zoladex Depot, a medication used to treat prostate cancer.

4. Narcotic antagonism:

The implanted device of naltrexone hydrochloride has long-term opposing effects against narcotics. It comes in various kinds of polymers and formulations and releases its base from hydrochloride or palmitic acid salt.

5. Dental application:

Polymeric implants have been considered for a variety of dental uses, including as the local, sustained administration of antibiotics and fluoride antibacterial agents. To provide fluoride with a prolonged release, stannous fluoride was included into several dental cements. To be rate-limiting in drug release, another was distributed in the hydroxyethyl methacrylate and methyl methacrylate copolymer hydro gel coated with an outer layer of the same copolymer in a different ratio. The device was affixed to the buccal surface of the maxillary first molar and was designed to release 0.5 mg of fluoride every day for 30 days. It was around 8 mm long and contained 42 mg of fluoride in its core.

6. Other uses:

Insulin preparations are commonly supplied by implantable devices that function on biofeedback, releasing the insulin according to the body's pharmacological needs at a specific period of time. [6]

DRUG SELECTION CRITERIA:

All drug cannot be formulated as per implantable drug delivery system. The drug which are inappropriate for designing implantable formulation are-

- Drug having short or high half life
- Drug with low solubility
- Properties of drug that make it suitable for designing controlled drug delivery system includes-

Solubility of drug: low solubility

Partition coefficient : the drug should be have high partition coefficient.

Chemical stability: high stability

Molecular weight/size: less than 1000 D

Therapeutic index : drug with low therapeutic index are unsuitable for incorporation in implantable formulation. The drug should be have high therapeutic index.

pH : release of drug should not be influenced by pH.

Half - life : the half - life of drug is an index of its residence time in the body. The drug should not have short half life less than 2 hours or more than 8 hours. The medicine should ideally have a half-life of three to four hours.

Absorption rate : the absorption rate of implantable drug is low. In this system drug is slowly absorbed by diffusion mechanism.[7]

COMPOSITION:

1. Polymers : used to control drug release rates

a) Natural polymer : As these polymer are found in nature, they tend to exhibit excellent bioavailability, non cytotoxicity, and biodegradability.

Ex. Cellulose, chitosan, alginate, collagen, gelatin and silk protein.

b) Synthetic polymer :

-Biodegradable synthetic polymers -

Ex. Polylactic acid, polyglycolic acid, polycaprolactone (PCL), polyester amides, polyphosphoesters, polydioxanone.

-Non-biodegradable polymers –

Ex. Polyurethanes, poly(ethylene-vinyl alcohol), poly(siloxanes)

2. Penetration enhancer

Substance that improve the permeation of drug is referred as penetration enhancer.

They should be safe, nontoxic, pharmacologically and chemically inert, non irritant, and non allergic.

Ex. Cyclodextrin, benzalkonium chloride, dextran sulfate, sodium salicylate, Dimethylsulphoxide, Propylene glycol [8]

METHODS OF IMPLANT MANUFACTURING:

1. Hot melt extrusion –



Fig.3 Hot melt extrusion [9]

A suitable solvent is added to the drugs to cause it to dissolve and create a solution mixture. After that, the polymer is added slowly and given a 15 to 20 minute soak. After totally mixing the swelling product so it resembles dough, it is placed into an ejection cylinder and uses a showerhead to create a long rod-like structure. The product is allowed to air dry for the entire night before being cut to the proper size. In order to obtain the finished product, it is finally dehydrated at 41 °C. Extrusion can be done simultaneously, resulting in effective output. Thermoplastic polymeric materials, such as polyamide aliphatic polyesters like PLA, PGA, and PLGA, are necessary. Nonsolvent is necessary. However, heat-sensitive drugs may degrade as a result of this. This method yields devices similar to Implanon® and Zola Dex®.

2. Compaction:

The drug and polymer are combined to create a suspension, which is then lyophilized to create a cake. It is subjected to additional compaction in order to extract an implant using a Carver hydraulic machine that exerts a metric ton of force. It has the benefit of not requiring heating or solvents, making it perfect for creating implants with thermally stable materials, particularly proteinaceous content. The fast release characteristic of this implantable calls for stacking for optimization. Furthermore, the implants that are generated exhibit an uneven appearance with several cavities, which may further exacerbate the irregular discharge.

3. Moulding:

The polymeric material is heated, incorporated into the shape of a mold and allowed to solidify. The high heat used causes a drop in the polymers' relative molecular mass. Molecular mass and dispersibility can be decreased in a variety of ways, and this technique enhances the results. As a result, these implanted types disintegrated faster than implantables created in factories that were molded with maltreatment injections.

4. 3D Printing:

It is a low-cost, reliable, and adaptive process that may come in use later on, particularly for the rapid production of standard units for research needs. Although it isn't produced in large quantities, its use became advanced in 2015 when the FDA approved a particular substance. This method is mostly utilized to create implants and prostheses for usage in orthopedics and dentistry.[10]

EVALUATION PARAMETER:

Various parameters are implemented in the evaluation of implants after manufacture by any appropriate method. These are as follows

A. Shape and size: Under light, the size of an implant is confirmed with Vernier Calipers.

B. Uniform Thickness: With Vernier Calipers, the thickness of each individual implant as well as the differences between them can be measured. It is necessary to identify at least three specimens and determine the average value.

C. Uniform Weight: This test is designed to determine each implant's uniform weight. Twenty implants have been selected at random for the test, and each implant is weighed individually. A mean weight is found. Based on the findings, two implants cannot weigh more than the mean weight, and none of them can have a mean value that is twice as high as the others.[11]

D. Swelling Index: An hour includes putting a specimen in a swelling solution of phosphate buffer pH 7 in order to measure its weight. Gently wipe with a dry sheet to carefully remove any residual solution. The following formula determines the amount of swelling for each unit at any given time:

$$\text{Swelling index} = \frac{w_2 - w_1}{w_1} \times 100$$

where W1 and W2 stand for the specimen's mass in dry form and at a given moment, respectively.

E. In-vitro dissolution profile: The implant's in vitro dissolution profile is essential for evaluating drug dissolution and stability. The dissolving medium is placed in a container and the ideal parameters and rotational speed are set. The paddle turns once the implant is inserted into the vessel. Samples are removed at predetermined intervals of time. After that, the samples are analyzed using UV visible spectrophotometry at a certain wavelength. After at least three observations, the process is repeated, and the average value is recorded.

F. Stability testing: This test is used to identify variations in medication standards together with time and storage parameters such humidity, light, temperature, and shelf life.

G. Interaction analysis between polymer and drug: Drug-containing implants are subjected to FTIR analysis to determine the drug's compatibility and potential for interaction with other formulation ingredients.[12]

MARKETED EXAMPLES:

Table 1: Marketed Preparation of Implants. [13,14]

Brand name	Site of placement	Substance	Medication	Use
Implanon® Nexplanon®	subcutaneously	PEVA	Etonogestrel	contraceptive
Norplant® Jadelle®	subcutaneously	silicon	levonorgestrel	contraceptive
zoladex®	subcutaneously	PLGA	goserelin	Prostate adenocarcinoma
Iluvien	Vitreous cavity	PEVA	Fluocinolone acetonide	Diabetic macular odema
Probuphine	Subcutaneously	PEVA	Buprenorphine	Mylgia
vitrasert®	intraocular	PVA, PEVA	Ganciclovir	CMV retinitis in AIDS
Med launch	subcutaneously	PLGA	Risperidone	Schizophrenia
Oncogel®	intratumorally	PLGA+PEG PLGA	Paclitaxel	Oesophageal carcinoma
Prostap®SR	Subcutaneously	PLGA	Leuprolide	Prostate cancer
Gliadel wafers®	Intratumoral	Silicone	Carmustine	Primary malignant glioma

RECENT RESEARCH / ADVANCES:**❖ Titanium-Based alloys and composites for orthopedic implants Applications:**

Millions of people worldwide experience bone fractures and other damage each year as a result of illnesses, accidents, and military injuries. The experts applied scientific principles to enable such individuals to lead normal lives. If self-care fails, surgery by a competent professional may be necessary to repair any damaged or fractured bones. Some orthopaedic implants, such those for the legs, knees, hips, ankles, or joints, are permanent and need to function correctly for a long period. The four primary material categories employed in orthopaedic applications are metals, polymers, ceramics, and natural materials.

Metals have long been utilized extensively in orthopaedics; today, almost two thirds of implants are composed of metallic elements. At the moment, titanium (Ti)-based alloys (such as Ti-6Al-4V), cobalt chromium (Co-Cr) alloys, and 316L stainless steel are the materials used for these applications. compares the Young's modulus of each, an important property for orthopedic implants. Due to a variety of factors, including their high modulus in comparison to the substituted bone, limited wear and corrosion resistance, and lack of biocompatibility, the alloys have occasionally shown inclinations to fail over time. Given the 12- to 15-year duration of orthopaedic implants, a follow-up procedure is typically necessary at least once.[15]

❖ Dental implants significantly increase adjacent tooth loss risk due to root fracture

Dental implants are a common choice for replacing lost teeth because they provide long-term, sustainable function and aesthetics, with success rates above 90% and a 10-year survival rate. Despite the excellent survival percentage of teeth that are affixed to implants, issues like cavities, fractures, and hypermobility are common. Improper proximal contact between adjacent teeth can increase the risk of caries and periodontal disease. Furthermore, the size, form, and emergence profile of restorations supported by implants affect proximal embrasure morphology, which might impact the health of neighbouring teeth.

New research has shown that further work is need to reduce these iatrogenic dangers. Under eccentric occlusal forces, dental implants are more prone to crestal bone loss. This necessitates the use of occlusal load control techniques, which may mistakenly overload neighboring teeth and raise the risk of fractures or cracks^{7,8}. The reviewed retrospective cohort study by Chen et al.⁹ aims to investigate the risk and variables of tooth loss for teeth adjacent to dental implants compared to nonadjacent teeth, which is crucial for optimizing treatment outcomes and maintaining oral health. This is because there is limited evidence on how dental implants affect the outcomes of adjacent teeth.

According to the study, teeth next to dental implants were far more likely to have tooth loss, mostly as a result of root fractures. According to the research, dental implants may increase the likelihood of difficulties for adjacent teeth by acting as an iatrogenic factor. The conservative management of natural dentition should be given top priority, with a focus on efficient at-home care and strict periodontal surveillance. Prospective studies should be the main focus of future research in order to better understand these relationships improve clinical results.[16]

CONCLUSION:

An inventive method to achieve rate-controlled drug delivery at essential therapeutic concentrations is the implantable drug delivery system. This method clearly outperforms the conventional administration techniques in various aspects. There have been many developments in this field, and study is ongoing. Enhancing biodegradable and biocompatible materials, lowering the polymer's immunogenicity and toxicity during disintegration, improving the discharge profile, and then developing the devices that already exist are the main priorities. These devices have the potential to deliver superior zero-order drug release kinetic profiles in vivo over extended periods of time, rendering them appropriate for extended usage. These systems have a chance to decrease the requirement for frequent dosing, are generally economical, enhance medication efficacy, and boost patient compliance—all of which will ultimately make them more patient-friendly. The application of these cutting-edge gadgets will show to be an outstanding strategy in addressing the drawbacks connected with earlier drug administration systems, since many newer medications are constantly evolving from proteinaceous components that are inappropriate to be delivered orally.

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