REVIEW ON IMPLANTABLE DRUG DELIVERY SYSTEM

Pratik K. Nidhalkar [1], Prasanna A. Datar [2], Sakshi N. Jagtap [3],

Mahesh S. Khedkar [1], Kajal Sonawane [1], Vaibhavi V. Sayam [1].

[1]*Student , Rajgad Dnyanpeeth's College Of Pharmacy , Bhor , Pune 412206 , India.*

[2]*Department of Medicinal Chemistry , Rajgad Dnyanpeeth's College Of Pharmacy , Bhor , Pune 412206 , India.*

[3]*Student , Bharti Vidyapeeth's College Of Engineering For Women , Bharti vidyapeeth , Pune 411046 , India.*

ABSTRACT:

The implantable drug delivery system is a revolutionary medication delivery method. Allows for regulated and sustained drug release. The sterile dosage form is administered subcutaneously or intramuscularly through minor surgery or implantable devices, such as big needles.

Implants can be prepared using a variety of techniques, including solvent casting, injection moulding, and 3D printing. Compression Melt Casting Hot-melt extrusion, etc. Conventional drug delivery systems have challenges such as first-pass mechanisms, GI fluid degradation, short-acting effects, drug fluction in plasma, and patient compliance. Implants provide an edge over the majority of conventional difficulties. The medicine is released at a steady pace over a set time period, resulting in no fluctuation. It provides both local and systemic action, reducing drug waste and toxicity to non-targeted organs.

Implants and implantable devices help enhance patient compliance by reducing the frequency of doses for chronic illnesses over time. It is commonly used for cancer treatment, contraception, dental therapy, and eye diseases.

Keywords*:- Implantable drug delivery , Implants , Zero order , Predetermined rate , Polymers , API.*

1. INTRODUCTION:

In 1861, Lafarge presented the concept of implanted medication systems for long-term release. Implants are small, sterile, solid compounds manufactured from highly purified drugs using compression, molding, or extrusion.(1)

They are implanted in subcutaneous or intramuscular tissue via minimal surgery or a large bore needle. It allows for continuous drug elutation at a steady zero order rate in the bloodstream or at a specific tissue site over time, without the need for repeated needle insertions or surgery. (2)

Thus, it's a more effective alternative to daily medication injections for pain relief and treating chronic diseases and disorders. It treats conditions such as osteoporosis, heart disease (CVD), refractory epilepsy, glaucoma, cystic fibrosis, and cancer. Diabetes (high glucose). (3)

1.1 Ideal Implants:

1. Environmentally stable: The best implants would not deteriorate in the presence of heat, moisture, light, or air.
2. Biostable: Should not deteriorate in gastrointestinal biofluids.
3. They should Non-irritant, Neither poisonous non carcinogenic. (4)
4. implantable devices should deliver medications at a consistent zero-order rate over a set period of time
5. Removal: Implantble should be easily detachable as required.

6. The implant should be simple to design and cost-effective. [5]
7. Should be simple to sterilise.
8. Implants can increase patient compliance by reducing the frequency of drug administration throughout treatment. [6]

1.2 Advantages:

1. Improve efficacy.
2. Reduces medication waste
3. Minimizes deleterious systemic adverse effects
4. Improve drug administration.
5. Drugs with short half-lives are suitable.
6. The drug was eluted in zero-order for a specified time.
7. Patient compliance improves as drug frequency decreases.
8. Implants are delivered to the intended
9. Avoid the initial pass.
10. Side effects were decreased.
11. Enhance medication stability and bioavailability within the [7]

1.3 Disadvantages:

1. The invasion of drugs is required.
2. The elimination of device failures is essential.
3. Termination of non-biodegradable drugs is required.
4. If a high concentration of dosage is administered, there is a chance of negative effects.
5. Biocompatibility issues: causes of foreign bodies. [7]
6. A limited-potency drug is used. [8]
7. There might be a risk of dose dumping if the device fails.
8. If any toxicity or poisoning occurs, then it's impossible to withdraw the drug from the body. [9]

2. MANUFACTURING METHODS:

2.1 Compression:

The compression approach is simpler and faster than the other ways. The material is shaped by applying force without heat or solvents, resulting in the desired shape. Implants generated through compression have an asymmetrical surface with many holes and channels, which can cause uneven drug release. These implants are highly dense. For example, protein and peptide implants are produced using this technology. [10,11]

2.2 Melt casting:

In melt casting, the polymer is melted, the drug is added, mixed, and then blended, after which the melt is poured into moulds to cool down and solidify. Melt casting is not appropriate for heat-sensitive pharmaceuticals (11).

2.3 Hot melt extrusion:

Hot melt extrusion involves melting, mixing, and forcing a polymer through a small aperture called a die. The extruder consists of a motor, heaters, and revolving screws in a barrel. Continuous heat and pressure are used to melt materials and create new products with homogeneous shape and density. (11, 12).

2.4 Casting solvent:

In solvent casting polymer and medication are mixed in an organic solvent to generate a solution. The mixture is then poured (cast) into the appropriate shape, shape and size to get correct shape. Finally, the solvent is evaporated, leaving a polymer residue of the required shape (usually a disc) behind. The downside of these methods is that they necessitate a substantial amount of solvent [10, 11, 12].

2.5 3D printing:

3D printing processes include laser sintering, powder-based 3D printing, stereolithography, fused deposition modeling (FDM), and others. The product is built with computer-aided design software, which provides numerous options. The implants shape and size can be customized. That is, it can be hollow, manufactured, or filled with API or materials homogeneously blended with drug, and then printed into the desired shape and size. (11, 12)

2.6 Injection moulding:

Here drug and excipients or polymers is heated to melt uniformly, the mixture then syring and pressure to inject in molten state into selected mould of specific shape. The mixture is then cooled down to set and solidify Heat labile drugs and polymers are not used in these method [10,11]

2.7 Other:

a. Photolithiography: Electronic components are fabricated using photolithography. This system is based on MEMS implantable technology. [12]

b. Electrospinning: There are two methods for electrospinning: solution and melting. Polymer dissolved in organic solvent in solution. In melting API and polymers melted, heat-sensitive compounds are avoided since they deteriorate. [12]

3. THERAPEUTIC APPLICATIONS:

3.1 Cancer:

The implantable medication delivery device has the ability to safely and effectively administer chemotherapy drugs to the affected side without producing any adverse effects. Brain, prostate, and bladder cancer are just a handful of the diseases for which implants are offered. [13]

Eg: The Gliadel wafer, which was approved as one of the first implanted brain cancer treatments to deliver chemotherapy directly to the tumor site, contains 7.7 mg Carmustine (alkylating agent). [14]

The Zoladex is biodegradable implantable rod for prostate cancer treatment contains 10.8 mg Goserelin acetate (GnRH Agonist). [15]

Table No 1: Cancer Implant Products

Product Name	Implant Type	Delivered	Indication
Zoladex	Sub-cutaneous	Goserelin	Prostate cancer
Oncogel	Intra-tumoral	Paclitaxel	Oesophageal cancer
Gliadel Wafers	Intra-tumoral	Carmustine (BCNU)	Primary malignantglioma
Prostap SR	Sub-cutaneous	Leuprolide	Prostate cancer

Device: Implantable Port or Port-a-cath:

First, the mass of the tumor is excised (usually via minimally invasive laparoscopic surgery), followed by intravenous (IV) or intraperitoneal (IP) chemotherapy using a platinum-based drug like cisplatin.

Intraperitonial patients are given 100mg/M2 of cisplatin solution via in-dwelling catheter once every three weeks for six cycles. During the cytoreduction procedure, the catheter and the subcutaneous port to which it is linked are inserted. Following the debulking of big visible tumors, two 5mm incisions are made in the upper and lower right quadrants of the abdomen The catheter is subcutaneously tunneled to an incision in the lower right quadrant of the abdomen, where it will enter the peritoneal cavity. The port is then placed through an incision in the upper right quadrant and subcutaneously sutured. [18,19]

2. Ocular:

Ocular implants or ocular inserts are used to treat chronic eye conditions such retinitis pigmentosa, diabetic retinopathy, age-related macular degeneration (AMD), and glaucoma. It contains several implants such as Lacrisert, a soluble ocular medication insert (SODI), Minidisc, and the most common Occusert. [20]

The Ocusert:

Occusert is a non-erodible inserts therapeutic system The inferior cul-de-sac, which exists between the sclera and the eyelid, is where this flat, flexible, elliptical device is supposed to be put. It releases pilocarpine continuously and steadily for seven days. The drug reservoir contains pilocarpin base and

alginic acid, with ethylene-vinyl acetate controlling the release rate. This device delivers pilocarpin at a rate of 20-40 micrograms per hour for a week. [21,22]

`**Table No 2:** Occular Implant Products

Product Name	Implant Type	Delivered	Indication
Vitrasert	Intra-ocular	Ganciclovir	CMV retinitis in AIDS patients
Retisert	Intra-ocular	Fluocinolone	uveitis
Ocusert	Intra-ocular	Pilocarpine, Alginic acid	Open angle glaucoma
BIM Ring (Durysta)	Intra-ocular	Bimatoprost	Glaucoma

Device: Passive MEMS for Occular Dieseases:

MEMS (microelectromechanical systems) devices with micron-scale structures are frequently manufactured for ocular dieseases. [23]
The device is surgically implanted, with the reservoir behind the conjunctiva (the membrane that surrounds the eye).Depending on the site of therapy, the cannula is inserted into the eye wall, with the medication dispensing tip terminating in either the anterior or posterior section. When the reservoir is mechanically triggered by the patient's finger, a specified dose of medication is given from the device. The medicine is forced down the confined microchannel within the transscleral cannula by the increase in pressure within the reservoir. Near the tip of the cannula, a flow-regulating check valve (one-way valve) was included. The check valve opens in response to the pressure rise, allowing medication to flow out of the device while preventing the backflow of physiological fluids into the device. [24,25]

3. Dental:

Dental polymeric implants are being developed for local, long-term activity against fluoride antibacterial and antibiotics. Stannous fluoride was mixed into various dental cements with copolymers hydroxyethyl methacrylate and methyl methacrylate for long-term fluoride release. The device, which was about 8 mm long and contained 42 mg of fluoride in the core, was affixed to the buccal surface of the maxillary first molar and was designed to release 0.5 mg of fluoride each day for 30 days [14,21].

Miniscrews: Titanium miniscrews are an alternate method for attaining anchoring. These gadgets are exceedingly tiny and can be implanted in places where other implantable devices cannot. Eg: some miniscrews , are so small that they can be put in bone between the roots of individual teeth. Similar devices are used in orthognathic surgery for osteotomy fixation, such as screws. [26, 27]

Miniplate: Using titanium miniplates has been one more method of combining implantable technology with orthodontic therapy. Miniplates are frequently used in orthognathic surgery for osteotomy fixation or in the fixation of fractures.[30,32]

Device: The Intellidrug implant:
The Intellidrug implant is placed in the buccal cavity, and the drug is released in a predetermined manner for a particular amount of time directly into the bloodstream, avoiding the first-pass effect.
The IntelliDrugt implant is based on an osmotic micropump, which includes a reservoir that retains the medication in the form of a solid tablet, a compressible polymer balloon (fluidic capacity), an electronically controlled microvalve, and a flow sensor. This illustration depicts the implant attached to a mandibular tooth so that saliva travels through the semipermeable membrane (saliva inlet) and dissolves the medicine, creating a hydrostatic pressure that drives the dissolved drug through the microvalve drug outlet for delivery. The flow sensor detects the medication using impedance measurement techniques and measures the flow rate and concentration of the dissolved drug solution to alert the user the concentration level falls below the predetermined rate.

4. CONTRACEPTIVE:
Norplant is FDA-approved. Approved contraception is applied subcutaneously to the upper arm in a fan design. [14] The device consists of six silicon membrane capsules, each containing 36 mg of levonorgestrel

(for a total of 216 mg), valid for 5 years.
Nestorone implants include derived progesterone, which provides contraception for up to two years.
Nomesgestrol implants are silicone reservoirs containing 55 mg of the steroid that offer contraception for up to a year. [15,21]

Table No 3: Contraceptive Implant Products :

Product Name	Implant Type	Delivered	Indication
Norplant (Jadellet)	Sub-cutaneous	Levonorgestrel	Contraception
Implanon Nexplanon	Sub-cutaneous	Etonogestrel	Contraception
Nuvaring	Intra-vaginal	Etonogestrel, Ethinyl estradiol	Contraception
Estring	Intra-vaginal	Estradiol	Menopausal symptoms

1. Copper-bearing IUDs: These are plastic IUDs with copper sleeves and copper wire on a polyethylene frame. Copper IUDs come in a variety of styles. Copper T, CuT380 A, and Multiload 375 are a few examples. [30]
2. Hormone-releasing IUDs: These are constructed of plastic and release modest amounts of progesterone and levonorgestrel (LNG) on a regular Like Mirena, Skyla, and Liletta work by releasing a small quantity of the progestin levonorgestrel (LNG). The major method of action is to render sperm deadly inside the uterus. It also helps to thin the endometrium. [31]
3. Inert or unmedicated IUDs: These IUDs do not include any bioactive ingredients. They are built of plastic or stainless steel, like the Lippes Loop, which is injected via the cervix in a cannula and takes a trapezoidal shape in the uterus, while Chinese stainless steel rings can deform and be inserted through the cervix. [38, 39]

5. CVD:

Drug-eluting stents and small-diameter vascular grafts (SDVGs) are two types of IDDS used to treat CVD. These IDDS are typically constructed from a polymeric matrix. These matrices not only allow for an increase in the upper limit of the medication quantity loaded or deposited onto these devices but also protect pharmaceuticals from enzymatic degradation or modulate the release rate.
Stents: first generation and second generation
The first generation was constructed from a non-biodegradable polymer. The disadvantage of the first generation is that it produces thrombosis, chronic inflammation, and neointimal hyperplasia. For example, sirolimus eluting stent (Cypher) and palcitaxel (Taxus) [12, 34].
Second-generation stents: Biodegradable polymers are used to make these stents. It eliminates the negative effects associated with non-biodegradable first-generation stents. Everolimus-eluting stent (XIENCEV) and zotarolimus-eluting stent (The Resolute) are a few examples. [34, 35]

Table No 3: CVD Implant Products

Type	Drug	Use
Stent	Sirolimus	smooth muscle cells adhesion , hyperplasia
Stent	Rutin	Cardiac remodelling , anti-inflammatory
Stent	Atorvastatin and fenofibrate	antithrombotic , anti-inflammatory & anti restenosis
Vascular graft	Dipyridamole	Platelet adhesion.
Vascular graft	Dexamethasone and heparin	Anticoagulant, anti-inflammatory & anti- fibrinogen

4. CONCLUSION:

IDDSs are a particularly appealing treatment method that avoids the restrictions of traditional medication administration routes. This technology aids in the introduction of new bioactive chemicals into clinical practice and aids in the development of new bioactive substances Repurpose drugs that are already marketed. To begin, implantable drug delivery systems must be sterile. As a result, they are either prepared in aseptic circumstances, increasing production costs, or they must be terminally sterile. The latter is less expensive, but terminal sterilisation procedures require the use of gamma radiation or

ethylene oxide, which may damage the qualities of the IDDS. To hasten the development of new IDDS, researchers have access to emerging technologies like machine learning. This technology can be used to forecast the performance of new gadgets, thereby shortening development periods and costs. IDDS was utilized to treat chronic disorders such as cancer, contraception, dental therapy, and eye diseases.

5. ACKNOWLEDGEMENT:

"I would like to acknowledge the valuable support and resources provided by Rajgad Dnyanpeeths College of Pharmacy, Bhor throughout the [REVIEW ON IMPLANTABLE DRUG DELIVERY SYSTEM]. Their commitment to excellence has greatly contributed to the success of this [REVIEW ON IMPLANTABLE DRUG DELIVERY SYSTEM]."

6. REFERENCES:

1. Martindel Valle EM, Galan MA, Carbonell RG. Drug delivery technologies: the way forward in the new decade. Industrial & engineering chemistry research. 2009 Mar 4;48(5):2475-86.
2. Chien Yie W. Novel drug delivery systems. Marcel Dekker Inc 1982; 1:1-816
3. Fitzpatrick D. Implantable electronic medical devices. Elsevier; 2014 Nov 5.
4. J. R. Robinson, Vincent H. L. Lee; “Controlled drug delivery: fundamentals & applications”; Second Edition; CRC Press; Page no: 481-516.
5. Vasant V. Ranade, Mannfred A. Hollinger, John B. Cannon; “Drug delivery systems”; Second Edition; CRC Press; Page no: 115- 140.
6. Solanki HK, Thakkar JH, Jani GK. Recent advances in implantable drug delivery. International Journal of Pharmaceutical Sciences Review and Research. 2010;4(3):168-77.
7. Ankaram A. S, Mali S. R. Implantable Polymeric Drug Delivery Devices: Classification, Manufacture and Clinical Applications. International Journal of Research Publication and Reviews. 2022 June. Vol 3.
8. Almoshari Y. Osmotic Pump Drug Delivery Systems—A Comprehensive Review. Pharmaceuticals. 2022 Nov 18;15(11):1430.
9. Pasupuleti P, Bandarapalle K, Neeraja G, Sandhya C, Afzal C, Venkataramana C, VenakataSai G. Implantable Drug Delivery Systems. Himalayan Journal of Health Sciences. 2023 Mar 16:1-9.
10. Bhivsane S. P, Shinde S. B, Wamne V. B, REVIEW ON: IMPLANTABLE DRUG DELIVERY SYSTEM International Journal For Research Trends And Innovation (IJRTI). 2022. Vol 7.
11. Holmberg.A, Developing an implantable drug delivery system for ecological studies on fish, approved by Spring term 2020
12. Magill E, Demartis S, Gavini E, Permana AD, Thakur RR, Adrianto MF, Waite D, Glover K, Picco CJ, Korelidou A, Detamornrat U. Solid implantable devices for sustained drug delivery. Advanced Drug Delivery Reviews. 2023 Jun 8:114950.
13. Exner AA and Saidal GM. Drug- eluting polymerimplants in cancer Therapy. Expert opin Drug Delivery 2008; 5:775-788.
14. Bharad VR, Sheikh AA, Kale RH, Biyani KR. IMPLANTABLE DRUG DELIVERY SYSTEMS: AN UPDATED REVIEW. International Journal of Pharmaceutical, Chemical & Biological Sciences. 2021 Sep 1;11(3).
15. Ameren S, Shahidulla SM, Sultana A, Fatima N. Implantable Drug Delivery System: An Innovative Approach. Journal of Drug Delivery and Therapeutics. 2023 May 15;13(5):98- 105.
16. Rock JA, Truglia JA, Caplan RJ. Zoladex (goserelin acetate implant) in the treatment of endometriosis: a randomized comparison with danazol. The Zoladex Endometriosis Study Group. Obstet Gynecol. 1993 Aug;82(2):198-205. PMID: 8336864.
17. Priyansha, Yadav M. K, Pal H, Yadav S. Short Review On: Implantable Drug Delivery Systems. Internationl journal of Creativity Reasarch Thoughts (IJCRT). 2021 July. Vol 9
18. Champeaux C, Weller J. Implantation of carmustine wafers (Gliadel®) for high-grade glioma treatment. A 9-year nationwide retrospective study. J Neurooncol. 2020 Mar;147(1):159-169. Epub 2020 Jan 23. PMID: 31974802.
19. Ye H. An intraperitoneal implantable drug delivery device for the treatment of ovarian cancer (Doctoral dissertation, Massachusetts Institute of Technology).
20. Cima.M.J, Ye. H, Carmen.M.D, Micheal, US Patent Application for medicament, method, and drug delivery device for treatment of ovarian cancer.
21. Y. W .Chien: Novel Drug Delivery System Second edition

22. Aj MZ, Patil SK, Baviskar DT, Jain DK. Implantable drug delivery system: a review. Int. J. Pharm. Tech. Res. 2012;4(1):280-92.
23. Fayzullin A, Bakulina A, Mikaelyan K, Shekhter A, Guller A. Implantable drug delivery systems and foreign body reaction: traversing the current clinical landscape. Bioengineering. 2021 Dec 9;8(12):205
24. Pollack IP, Quigley HA, Harbin TS. The Ocusert pilocarpine system: advantages and disadvantages. South Med J. 1976 Oct;69(10):1296-8. PMID: 982104.
25. Leinonen S, Immonen I, Kotaniemi K. Fluocinolone acetonide intravitreal implant (Retisert®) in the treatment of sight threatening macular oedema of juvenile idiopathic arthritis-related uveitis. Acta Ophthalmol. 2018 Sep;96(6):648-651. Epub 2018 Apr 14. PMID: 29655222.
26. Shankhapal1 R. S, Dalvi U. D, Sanap G. S, Implantable drug delivery system. Journal of Emerging Technologies and innovation research (JETIR). 2023 April. Vol 10.
27. Hilt JZ, Peppas NA. Microfabricated drug delivery devices. International Journal of Pharmaceutics. 2005 Dec 8;306(1-2):15-23.
28. Lo R , Li PY, Saati S, Agrawal RN, Humayun MS, Meng E. A passive MEMS drug delivery pump for treatment of ocular diseases. Biomedical microdevices. 2009 Oct;11:959-70.
29. Lo R, Kuwahara K, Li PY, Agrawal R, Humayun MS, Meng E. A passive refillable intraocular MEMS drug delivery device. In2006 International Conference on Microtechnologies in Medicine and Biology 2006 May 9.
30. Jaggi N, Bhutani R, Mehan P. Implantable Devices: A Review of Current Treatment Modalities. Int J Oral Implantol. 2012;3(1):31-5.
31. Costa A, Raffaini M, Melsen B. Miniscrews as orthodontic anchorage: A preliminary report. Int J OrthodOrthognathSurg 1998;13:201-09.
32. Sugawara J, Baik U, Umemori M, et al. Treatment and post treatment dentoalveolar changes following intrusion of mandibular molars with application of a skeletal anchorage system (SAS) for open bite correction. Int J Adult OrthodOrthognathSurg 2002;17:243-53.
33. Goettsche T. Intellidrug-controlled, oral drug delivery system as tooth implant (Doctoral dissertation, Dissertation, Albert-Ludwigs-Universität Freiburg, 2016).
34. Sivin I. Risks and benefits, advantages and disadvantages of levonorgestrel-releasing contraceptive implants. Drug Saf. 2003;26(5):303-35. PMID: 12650633
35. Gilbert BG. Contraceptive Implant Insertion and Removal. Prim Care. 2021 Dec;48(4):545-554. Epub 2021 Oct 7. PMID: 34752268
36. D'Souza RE, Bounds W, Guillebaud J. Randomized comparative emergency contraceptive study: GyneFix versus TCu380A and Nova-T. J Fam Plan RHC 2003; 29:23-29.
37. Grodstein F, Manson JE, Stampfer MJ, Rexrode K. Postmenopausal hormone therapy and stroke. Role of time since menopause and age at initiation of hormone therapy. Arch Intern Med2008;168:861-866.
38. Bilian X. Chinese experience with intrauterine devices. Contraception 2007; 75:S31.
39. .Lippes J. Contraception with intrauterine plastic loops. Am J ObstetGynecol 1965; 93:1024.
40. Masoud Adhami, Niamh K. Martin, Ciara Maguire, Aaron J. Courtenay, Ryan F. Donnelly, Juan Domínguez-Robles &EnekoLarrañeta (2023) Drug loaded implantable devices to treat cardiovascular disease, Expert Opinion on Drug Delivery, 20:4, 507-522.
41. Corduas F, Mancuso E, Lamprou DA. Long-acting implantable devices for the prevention and personalised treatment of infectious, inflammatory and chronic diseases. Journal of Drug Delivery Science and Technology. 2020 Dec 1;60:101952.
42. Prati F, Imola F, Corvo P, Cernigliaro C, Fouadi T, Ramazzotti V, Manzoli A, Pappalardo A, Cera M. The RESTART project: high-dose atorvastatin helps control restenosis After stenting procedures at high risk for restenosis. Results from a prospective study and a matched control group comparison. EuroIntervention. 2007 May;3(1):89-94. PMID: 19737690.
43. Magill E, Demartis S, Gavini E, Permana AD, Thakur RR, Adrianto MF, Waite D, Glover K, Picco CJ, Korelidou A, Detamornrat U. Solid implantable devices for sustained drug delivery. Advanced Drug Delivery Reviews. 2023 Jun 8:114950.
44. Mc Keage K, Murdoch D, Goa KL. The sirolimus-eluting stent: a review of its use in the treatment of coronary artery disease. Am J Cardiovasc Drugs. 2003;3(3):211-30. PMID: 14727933.