REVIEW ON IMPLANTABLE DRUG DELIVERY SYSTEM

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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: Implantable 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 body. [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
	neous		cancer
	oral		geal cancer
Wafers	oral	ne (BCNU)	nalignantglioma
R	neous	e	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	nplant Type	Delivered	Indication
	ar	vir	nitis in AIDS patients
	ar	one	
	ar	ne, Alginic acid	le glaucoma
g (Durysta)	ar	ost	a

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	**nplant Type**	**Delivered**	**Indication**
(Jadellet)	neous	estrel	ption
Nexplanon	neous	trel	ption
	nal	trel, Ethinyl estradiol	ption
	nal		sal 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**
		uscle cells adhesion , hyperplasia
		emodelling , anti-inflammatory
	tin and fenofibrate	botic , anti-inflammatory & anti restenosis
graft	nole	dhesion.
graft	hasone and heparin	ulant, 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.

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