International Journal of Multidisciplinary Research and Growth Evaluation.

Implantable Drug Delivery System

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Article Info

ISSN (online): 2582-7138
Volume: 06
Issue: 01
January-February 2025
Received: 10-12-2024
Accepted: 12-01-2025
Page No: 1578-1582

Abstract
Implantable drug delivery systems [IDDS] provide a viable substitute for conventional medication delivery techniques. The most popular medication delivery methods, oral and injectable, frequently cause blood drug concentrations to peak and then fall. This calls for ongoing administration in order to sustain therapeutic medication levels. Oral medication distribution also has to contend with issues such first-pass metabolism and drug degradation in the gastrointestinal system. Conversely, IDDS allow for prolonged medication release, which makes them particularly useful for treating chronic illnesses where patients may find it challenging to adhere to traditional treatment regimens. These systems can be used for localized therapy, focusing on certain regions to optimize drug concentration at the site of action and reduce systemic exposure, even though they are usually utilized for systemic drug delivery.

DOI: https://doi.org/10.54660/.IJMRGE.2025.6.1.1578-1582

Keywords: implantable, medication, drug concentrations, chronic illness, localized therapy, therapeutic etc.

Introduction

The 1930s witnessed the first generation of implanted drug delivery devices (IDDS), despite their subsequent notable surge in popularity. The first IDDS was a hormone-containing pellet intended for subcutaneous implantation in cattle to promote growth and increase the productivity of meat output. The application of these devices to the treatment of women experiencing an early menopause was investigated in 1938, a few years later. Even though IDDS was created more than 90 years ago, interest in it has grown significantly during the last 20 years. Pharmaceutical corporations are becoming more and more interested in creating innovative drug delivery systems, demonstrating that this expanding interest is not limited to academics. The global IDDS market was estimated to be worth $10.09 billion in 2019 and is projected to increase at a pace of around 8% per year to reach $13.21 billion by 2027 [1].

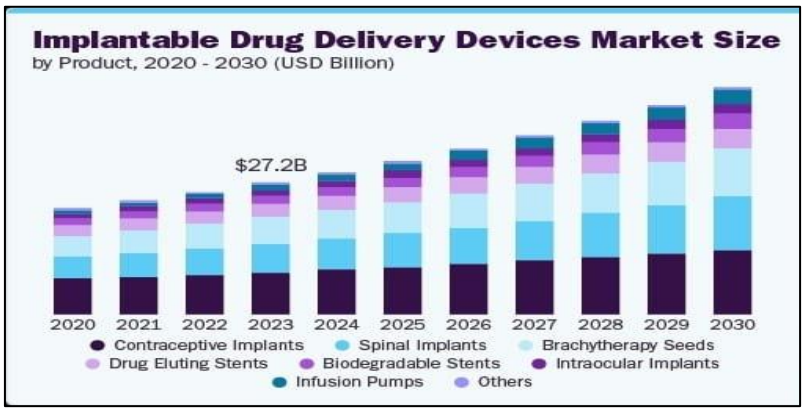

Fig 1: Implantable drug delivery devices market size

Desirable properties of implantable drug delivery system
Various ideal properties of implantable drug delivery system are given in the given below:

- Environmental stable
- Biocompatible
- Simple sterilization
- Drug release is controlled
- Manufacturing is simple
- Inexpensive and good mechanical strength [2]

Advantages

- Delivery of medication is long-term and under strict control.
- Improved patient compliance due to reduced dose frequency.
- There is a possibility of intermittent release and local administration.
- Prevents drug breakdown and first-pass metabolism in the GI tract.
- By lowering the required dosage drug side effects are can be reduced.
- Increased drug bioavailability and stability [2].

Disadvantages

- Invasive procedure: large implants necessitate surgery.
- Discontinuation: therapy is difficult to stop.
- Biocompatibility refers to the reaction of the host and the implant.
- Inflammatory response and infection of body implants.
- Device failure and implant dislocation are also risking.
- Cost: a drawback from a business standpoint [2].

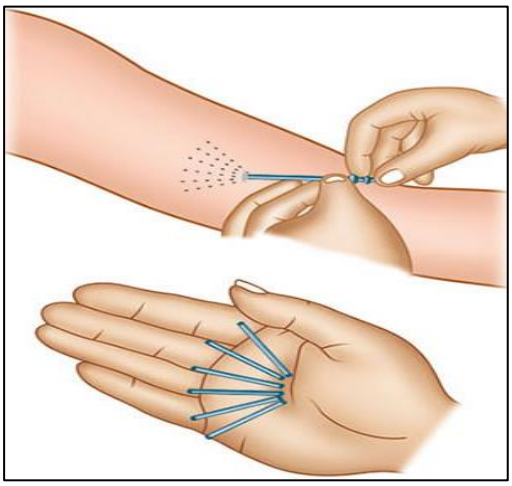

Fig 2: Norplant-long term contraceptive implant

Classification
Implanted drug delivery systems (IDDS) are generally classified into active and passive types. Passive implants rely on diffusion for drug release and can be biodegradable or non-biodegradable, typically made by mixing drugs with biocompatible polymers. These include monolithic and reservoir implants. Active implants, on the other hand, use energy-driven mechanisms to release drugs. Examples include osmotic pumps, which provide controlled release via osmotic gradients, and micro-electro-mechanical systems (mems), which use pumps and electric currents to manage drug flow.
Rapid advancements are being made in micro-reservoir devices, which include a capping membrane that is triggered to release the medicine. Fully biodegradable electrical components may now be included into these systems to initiate the release of drugs [2].

Fig 3: Types of dental implants

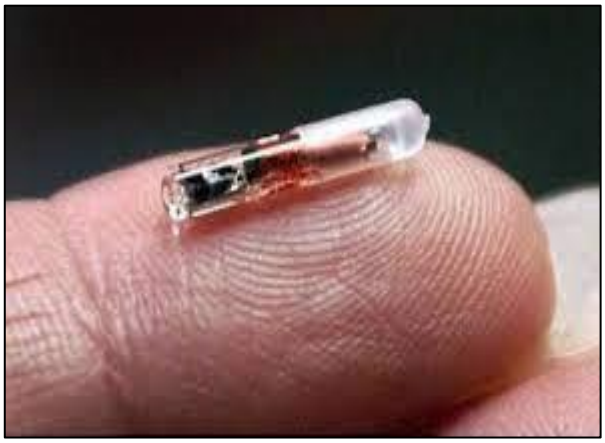

Fig 4: Microchip implant

Materials Used for Implantable Drug Delivery Systems (IDDS)
Natural Polymers
Natural polymers are derived from nature and typically offer excellent biocompatibility, non-cytotoxicity, and biodegradability. However, they do have some limitations, including unpredictable properties and low batch-to-batch consistency during production. Common natural polymers used in IDDS include cellulose, chitosan, alginate, collagen, gelatin, and silk protein [3].

1. **Cellulose** is a natural polysaccharide made up of β-d-glucopyranose monomers and is the most abundant organic compound on earth. It and its derivatives are widely used in drug delivery applications [4, 5].
2. **Chitosan** is produced by deacetylating chitin, a polysaccharide found in the cell walls of fungi. Chitosan is biocompatible, easy to process, and has controllable mechanical properties, making it suitable for drug delivery. However, it is hydrophobic and brittle, which limits its strength. It is often blended with other polymers to enhance its properties [3, 6].
3. **Alginate** is a linear polysaccharide derived from brown seaweed or algae. Its hydrophilic nature, solubility, biocompatibility, and biodegradability make it an ideal polymer for drug delivery. Alginate is capable of forming hydrogels and encapsulating molecules, and it can be used to create copolymers that add rigidity to drug delivery devices [6-7].
4. **Collagen** is a protein found in connective tissues of

animals and is known for its excellent biocompatibility and mechanical properties. Different types of collagen are sourced from various tissues (skin, tendon, bone, cartilage), each with unique properties. Collagen and its derivative, gelatin (a water-soluble protein obtained by partially hydrolyzing collagen), are frequently used in tissue engineering and implantable hydrogel drug delivery systems [4, 9].

5. **Silk protein**, sourced from silkworms, arachnids, and flies, boasts high mechanical strength due to the alignment of its protein chains. This versatile polymer is used in a range of medical applications, including subcutaneous implants and drug-eluting stents [10, 11].

Synthetic Polymers

Synthetic polymers, in contrast to natural ones, are known for their predictable properties and consistent batch-to-batch performance. They can be either biodegradable or non-biodegradable, making them suitable for various drug delivery applications [3].

Biodegradable Synthetic Polymers

1. **Polylactic acid (PLA):** a biodegradable polyester that degrades into lactic acid, which is safe for the body. PLA has two forms, PLLA and PLDA, with different properties. However, excessive lactic acid can cause inflammation. PLA generally degrades over 1–6 months [2, 11, 12].
2. **Polyglycolic acid (PGA):** similar to PLA but degrades faster, leading to glycolic acid production, which can cause inflammation, especially with large implants. It's often used in copolymers. [2,11,12]
3. **Poly (lactic-co-glycolic acid) (PLGA):** a copolymer of PLA and PGA, its properties and degradation rate can be adjusted, making it ideal for drug delivery. PLGA does not produce acidic degradation products and has been used in various medical applications, though achieving zero-order release is challenging [3, 12, 13].
4. **Polycaprolactone (PCL)**: known for its slow degradation (months to years) and lack of acidic degradation. It is biocompatible, hydrophobic, and widely used in drug delivery. It is also used in long-term implants and microspheres [3, 12, 13].
5. **Polyester amides**: these are used to create microspheres for slow, controlled drug release and can enhance the solubility of poorly water-soluble drugs [15].
6. **Polyphosphoesters (PPES)**: biocompatible and degrade in a controlled manner. PPES are similar to nucleic acids and have been used in gene delivery. Their degradation rate and hydrophobicity can be modified [6, 16].
7. **Polydioxanone (PDS)**: a slow-degrading polymer (9–12 months), used in microsphere and nanoparticle applications. Its degradation produces glycoxylate, which is safely excreted [6].

Non-Biodegradable Polymers

Non-biodegradable polymers, such as those used in contraceptive implants, are durable and cost-effective. They release drugs through diffusion, not degradation, and require removal after use [2].

1. **Polyurethanes (PUS)**: biocompatible, resistant to hydrolysis, and adjustable in rigidity, making them suitable for long-term implants [3, 6, 12].
2. **Poly (ethylene–vinyl alcohol) (PEVA)**: adjustable properties for various drugs; used in implants like contraceptives and ocular devices, though non-biodegradable, requiring removal [3].
3. **Poly (ether ether ketone) (PEEK)**: known for high strength and chemical resistance, commonly used in orthopedic implants, but hydrophobic and requires modification for better cell adhesion [17, 18].
4. **Poly (siloxanes)**: hydrophobic [19] and used for controlled drug release in implants like Norplant, though also non-biodegradable [20].
5. **Metals:** metals like stainless steel, titanium, and cobalt alloys are used for drug delivery systems. They offer high strength, corrosion resistance, and are typically used in stents and implants, often with coatings or as reservoirs for drug delivery [21].
6. **Ceramics:** ceramics, such as zirconia, calcium phosphates, and silicon, are used in drug delivery for their biocompatibility and slow biodegradability.[22] bioactive ceramics, like calcium phosphates, promote biological processes and are useful in tissue regeneration. Non-bioactive ceramics are strong but may cause tissue irritation [23].

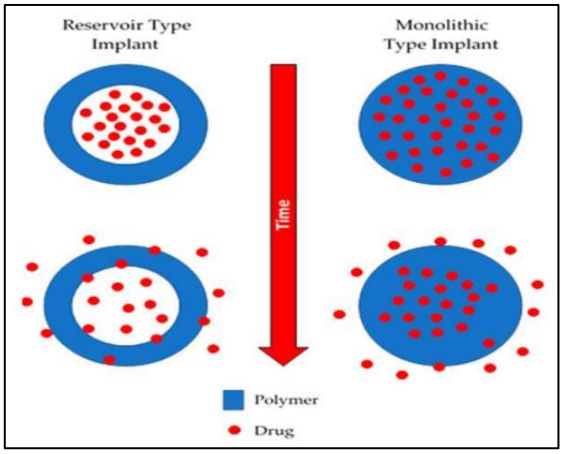

Fig 5: Reservoir type implant

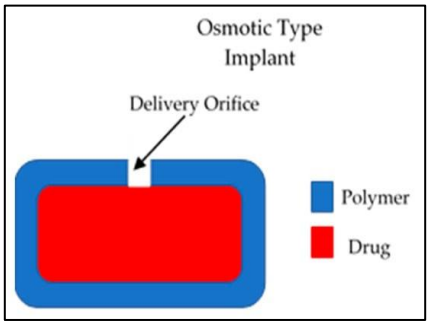

Fig 6: Osmotic type implant

Manufacturing Techniques Used for Implantable Drug Delivery Systems (IDDS)

1. **Hot-melt extrusion (HME):** a common method using heat to melt and mix polymers, avoiding solvents. It improves drug bioavailability and controls release but is unsuitable for heat-sensitive drugs [24, 25].
2. **Compression:** applies force to shape materials without heat or solvents. It's scalable and ideal for unstable drugs but can lead to faster drug release and surface irregularities [2, 23].
3. **Solvent casting:** uses solvents to dissolve and mold polymers, offering versatile shapes and uniform drug distribution. However, solvent toxicity and environmental concerns are drawbacks [3, 23].
4. **Injection moulding:** involves melting and injecting polymers into molds. It's versatile, scalable, and

provides good drug-polymer interactions but risks thermal degradation of drugs [3, 24, 26].

5. **Electrospinning**: creates ultrafine fibers using electrostatic potential. It allows various drug release profiles but may degrade heat-sensitive drugs or cause environmental/ cytotoxicity issues due to solvents [24, 26].
6. **3d-printing**: uses computer-aided design to print implants with custom shapes and drug blends. It's flexible and cost-effective but faces scalability and regulatory challenges [3, 24].
7. **Other techniques**: for metal or ceramic implants, methods like sintering and photolithography are used. Mems devices require specialized techniques for electronics manufacturing [28, 29].

Table 1: Implantable drug delivery devices used in the area of women's health

Product Name	Implant Type	Material	Drug Delivered	Indication
Norplant®	Sub-cutaneous	Silicone	Levonorgestrel	Contraception
Jadelle®				
Estring®	Intra-vaginal	Silicone	Estradiol	Menopausal symptoms
Nuvaring®	Intra-vaginal	PEVA	Etonogestrel, Ethinyl estradiol	Contraception
Implanon®	Sub-cutaneous	PEVA	Etonogestrel	Contraception
Nexplanon®				

Table 2: Implantable drug delivery devices used for anticancer therapy

Product Name	Implant Type	Material	Drug Delivered	Indication
Zoladex®	Sub-cutaneous	PLGA	Goserelin	Prostate cancer
Prostap®SR	Sub-cutaneous	PLGA	Leuprolide	Prostate cancer
Gliadel Wafers®	Intra-tumoral	Silicone	Carmustine (BCNU)	Primary malignant glioma
Oncogel®	Intra-tumoral	PLGA-PEG-PLGA	Paclitaxel	Oesophageal cancer
Vantas®	Sub-cutaneous	Methacrylate based hydrogel	Histrelin	Prostate Cancer
GemRIS®	Intra-vesical	ND	Gemcitabine	Non-muscle invasive Bladder Cancer

Table 3: Implantable drug delivery devices used to treat ocular diseases

Product Name	Implant Type	Material	Drug Delivered	Indication
Ocusert®	Intra-ocular	PEVA	Pilocarpine, Alginic acid	Open angle glaucoma
Retisert®	Intra-ocular	Microcrystalline cellulose, PVA, Magnesium stearate	Fluocinolone	Non-infectious uveitis
Vitrasert®	Intra-ocular	PVA, PEVA	Ganciclovir	CMV retinitis in AIDS patients

Table 4: Implantable drug delivery devices for pain management, infectious disease and central nervous system disorders

Therapeutic Indication	Product Name	Implant Type	Material	Drug Delivered	Indication
Pain	ND (Axxia Pharmaceuticals)	Sub-cutaneous	PU, PEG/PPG/PTMEG	Hydromorphine	Chronic neuropathic pain
	LiRIS®	Intra-vesical	Silicone	Lidocaine	Interstitial cystitis/bladder pain syndrome
	Probuphine®	Sub-cutaneous	PEVA	Buprenorphine	Opioid abuse
Infectious Diseases	ND	ND	PLGA	Isoniazid	TB
	ND	ND	PLGA	Isoniazid, Pyrazinamide	TB
Central Nervous System disorders	Med-Launch	Sub-cutaneous	PLGA	Risperidone	Schizophrenia
	ND	Sub-cutaneous	PU	Risperidone	Schizophrenia
	Risperdal consta®	Intra-muscular	PLGA	Risperidone	Schizophrenia

*ND=Not disclosed

Conclusion

Implantable drug delivery systems (IDDS) have made significant clinical and commercial progress in enhancing pharmaceutical treatments. However, it's essential to improve their performance, particularly regarding long-term biocompatibility and drug release kinetics. As noted, several commercial methods are close to achieving ideal zero-order release, and long-term in vivo kinetic studies of IDDS offer a feasible, profitable, and clinically viable alternative for continuous drug delivery to patients with chronic conditions.

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