WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 8, 984-1002. Review Article ISSN 2277– 7105

IMPLANTABLE DRUG DELIVERY SYSTEM: AN INNOVATIVE APPROACH

Tithee Patel*[1], Nagesh Modi[1], Mona A Gupta[2]* and Dr. C. N. Patel[3]

[1]Student of M. Pharm, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana-384001, Gujarat, India.

[2]Assistant & Professor, Department of Pharmaceutics, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana-384001, Gujarat, India.

[3]Principal & Professor, Department of Pharmaceutical Chemistry & Quality Assurance, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana-384001, Gujarat, India.

Article Received on
02 March 2024,

Revised on 22 March 2024,
Accepted on 12 April 2024

DOI: 10. 20959/wjpr20248-32035

***Corresponding Author**
Tithee Patel
Student of M. Pharm, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana-384001, Gujarat, India.

ABSTRACT

This paper provides an in-depth discussion on the manufacturing methods and therapeutic applications of implantable drug delivery devices. Various manufacturing techniques such as hot melt extrusion, solvent casting, compression, injection molding, and 3D printing are explored in detail. The therapeutic applications of implantable drug delivery systems in ocular implants, dental implants, cancer therapy, infectious diseases, contraceptive implants, and pain management are also examined, with examples of devices and drugs provided for each application. Additionally, the paper delves into the mechanisms of drug release from implantable systems, including diffusion-controlled release, chemically controlled release, bioerosion, swelling-controlled release, and osmotically controlled release. The advantages of implantable drug delivery systems in improving patient compliance and efficiency are highlighted, along with the limitations such as the risk of adverse reactions and the need for surgical intervention for implantation.

KEYWORDS: Implantable drug delivery, Osmotic pump, controlled release, Hot melt extrusion, cancer therapy, 3D printing, Application.

1. INTRODUCTION

A medical device known as an implantable drug delivery system (IDDS) can be surgically inserted into a patient's tissues to administer a therapeutic substance and enhance its safety and effectiveness by regulating the medication's rate, location, and timing of release inside the body. Between the drug storage and the biological target, this mechanism serves as a clever interface. Combination items, such as pharmaceuticals, medical devices, or biological products that work together as a single entity, are considered IDDSs for regulatory reasons.[1] Deansby and Parkes introduced the idea of IDDS in 1937 when they reported on the effects of crystalline estrone pellets inserted subcutaneously on the development of brown leghorn capons. Folkman and Long proved the benefits of extended systemic medication delivery by implantation in the 1960s. Early research on the diffusion of low molecular compounds resulted in the creation of a broad class of passive implants, which include the medication and nonbiodegradable implants composed of a biocompatible material. The kind and concentration of the drug, together with the surface and material characteristics of the reservoir, all influence how quickly the drug releases. An explainable medication administration system for the treatment of several kinds of chronic illnesses, including diabetes, cancer, spasticity, and chronic pain.[2] For several medication classes, it is very appealing, especially those that need site-specific dosage, cannot be administered orally, or are absorbed irregularly by the digestive system.[3] Clinical application encompasses a broad range of implanted devices, such as intracerebral implants, vaginal rings, ocular implants, and subdermal implants.[4] The advantages of implantable devices include the capacity to generate large local medication amounts, similar to those seen with chemotherapy medications, as well as consistency in treatment response and delivery accuracy. Due to these benefits, many therapy regimens benefit best from local, implanted medication administration.[5]

1.1. Ideal properties of implantable drug delivery systems[6,7]

- It should to be stable in the environment.
- Biodegradable.
- Reduce the frequency of medicine delivery during treatment to increase patient compliance.
- Good mechanical strength.
- The implant needs to be sufficiently strong mechanically and be safe, stable, and effective.
- It should be simple to sterilise the implanted device.

- The device should be Non-toxic and Non carcinogenic.
- It must have to provide inexpensive therapy.

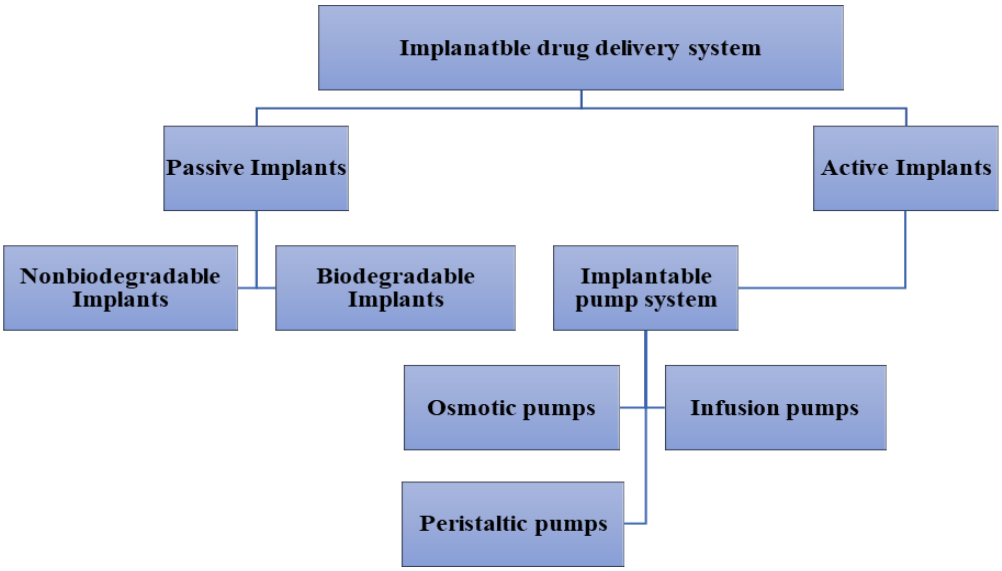
Table 1: Advantages and Disadvantages of Implantable drug delivery system.[8,9]

Advantages	Disadvantages
Provide linear delivery for long periods of time, from a few weeks to many months.	Chances of adverse reactions due to the local high concentration of drug at site of implantation
Patient compliance may be improved.	Predicted danger of device failure
Continuous small amounts of drug may be less painful than several large doses.	Interactions between host and implant
Improved efficiency.	Insertion of big size implants requires surgical interventions which can be unpleasant
Avoid the first-pass metabolism.	Therapy cannot be simply discontinued.
Improved bioavailability of drugs	Inadequate release of active pharmaceutical ingredient

1.2. Limitations of Implants[10]

- Toxicity may be possible.
- Having trouble turning off the release when needed.
- Pain is a possible outcome.
- Microsurgery is required to implant the system.

2. CLASSIFICATION OF IMPLANATBLE DRUG DELIVERY SYSTEM



The process for developing an implantable drug delivery system (IDDS) is complex, and there are many hybrids and exceptions that fall under several headings. The two primary

categories of IDDS are Active or Dynamic Implants and Passive Implants. There are two types of passive implants: nondegradable and degradable. On the other hand, active systems use an energy-dependent technique to supply a positive driving force to control the release of drugs. Osmotic pressure gradients and electromechanical drives are examples of devices that are part of an active system.

2.1. Passive Implants

These are generally basic devices that release drugs by passive diffusion; they do not have any moving parts. Usually, pharmaceuticals are enclosed in biocompatible polymer molecules to create them. The release profile may be controlled by adjusting parameters like: including the drug type and concentration, the kind of polymer, the implant design, and the surface characteristics.

2.1.1.Non-Biodegradable implants

Polymers like silicone elastomer, polyurethanes, polyacrylates, or copolymers like polyethylene vinyl acetate are frequently used to manufacture non-biodegradable implants.[11,12] Devices come in two varieties: reservoir-type implants and monolithic implants. Implants of the monolithic kind are composed of a polymer matrix containing uniformly distributed medication. Conversely, implants of the reservoir type have a small drug core encased in a non-biodegradable membrane that is permeable. The drug's permeability through the membrane and the thickness of the membrane will control the release kinetics.

Contraceptive delivery has made substantial use of implanted, non-biodegradable medication delivery methods. Over their lifespan, these devices maintain their structural integrity and robustness. Considering this, the primary disadvantage of non-biodegradable implants is their requirement for removal after their medication load has been exhausted. These devices' components have strong long-term biocompatibility, although occasionally they can result in infections, tissue injury, or aesthetic deformity.[13]

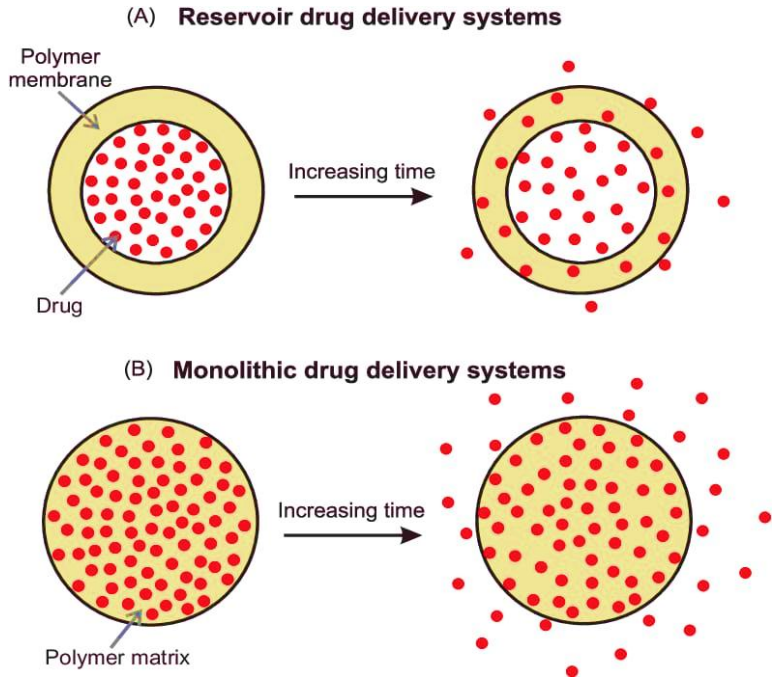


Figure 1: Reservoir drug delivery system and Monolithic drug delivery system.[14]

2.1.2.Biodegradable implants

Biodegradable systems based on polymers like poly (lactic acid), poly (lactic-co-glycolic acid), poly (caprolactone), or their block copolymer versions with other polymers have been developed to overcome the limitations of nonbiodegradable implants. The biocompatible polymers used to create these delivery systems eventually break down into harmless metabolites that the body may either absorb or excrete, which is one of the main benefits of biodegradable systems.[15] In addition, their formulation is more complex than that of nonbiodegradable ones. Several considerations are used when formulating them. For sustained drug release, the body's polymeric base disintegration profile must remain steady. It is preferable to use a flattened slab-like architecture with zero order profile and no edge erosion to provide more consistent and uniform medication release.[16]

2.2. Active or Dynamic Implant

Drug release is enabled and controlled by active or dynamic implant devices, which use a positive driving force. Because of this, they can usually regulate medicine dosages and delivery rates far more accurately than passive systems. Nevertheless, this is more expensive in terms of gadget cost as well as complexity.[3]

2.2.1. Implantable pump systems

The distribution rate and amount of several different medications must be under external control. Other than magnetic delivery techniques, neither biodegradable nor nondegradable delivery methods provide for this kind of control. In these cases, the necessary control has been provided using pump systems. Recent advances in microtechnology have made it feasible to develop pump systems that are tiny enough to be implanted subcutaneously for the administration of drugs.[17] This eliminates the requirement for an external pump system by enabling the patient to maintain control over medicine release. Pump systems' medication delivery technique sets them apart from other implanted systems. Drugs are released via pump systems via a gradient created by pressure differences, which allows for controlled bulk drug flow rates.[18] There are three different kinds of implanted pump systems: peristaltic, infusion, and osmotic.

2.2.1.1.Osmotic pumps

The most often used kind of implanted medication delivery devices is osmotic pumps. The gastrointestinal therapeutic system, sometimes referred to as Oros or the osmotic pump, was initially introduced for use by Alza Corporation after being initially described by Theeuwes and Yum. This pump is made of a semipermeable membrane around a medication reservoir. Through the process of osmosis, the surrounding membrane permits a constant inflow of biological fluid and water into the reservoir. The medication is released gradually from the drug portal a hole in the membrane due to the hydrostatic pressure that builds up because of this inflow. Until all the medicine in the reservoir has been used, the rate of drug release is zero-order or constant. These systems cannot have their drug delivery rates changed unless the semipermeable membrane's structure is altered, which necessitates system disassembly. It has been demonstrated that the consistent, extended release of medication is beneficial in the management and treatment of chronic pain.[19]

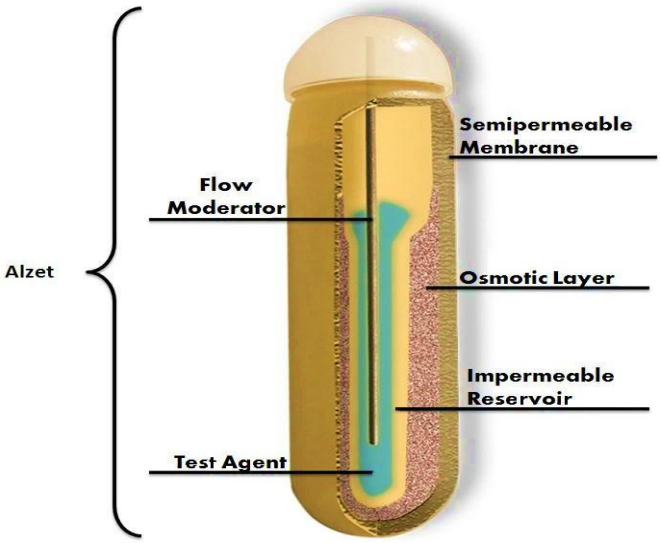


Figure 2: Schematic diagram of Alzet Osmotic pump.[20]

2.2.1.2.Infusion pumps

The instruments that run a fluorocarbon propellant to deliver the medication in vivo are called infusion pumps. These methods were put in place to provide diabetic people their insulin. These kinds of systems include MiniMed, SynchroMed, and Infusaid. The Infusaid system consists of a titanium disc-shaped canister and a foldable welded bellow.[21] The canister's interior is divided into two chambers by this bellow; the first chamber houses fluorocarbon propellants, while the second chamber houses the insulin formulation. There is also a flow restrictor in the system. At a constant temperature, the propellant's vapour pressure continuously generates a pressure source. medication dosage in the pump reservoir can be changed to change the medication delivery rate. This method is used to administer opioids intrathecal.[22]

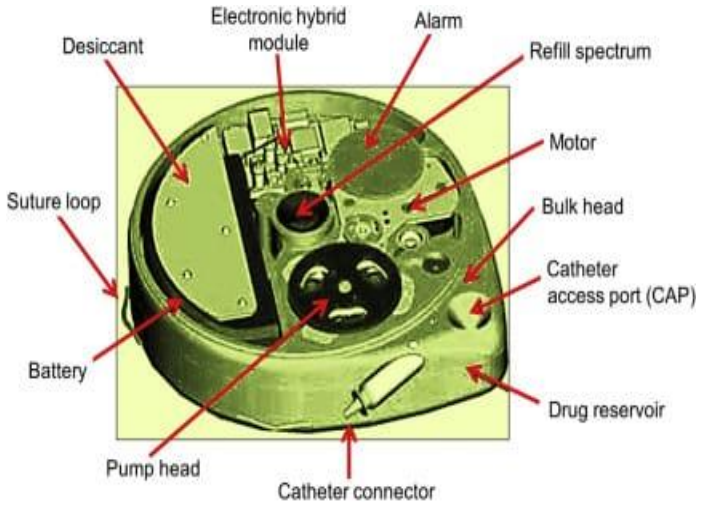


Figure 3: Diagram of Infusion pump.[22]

2.2.1.3. Peristaltic pumps

Many peristaltic pumps are of the rotating solenoid type. The battery, electronics, and pump are housed in titanium chambers that have been laser-welded. For enhanced biocompatibility, silicone polymer coating of the chambers is important. The drug reservoirs are deflated silicone rubber pouches with walls that are around 0.5 mm thick and capable of withstanding pressures more than 6O psi. Via a silicone rubber septum in the medication reservoir, the pouches are percutaneously replenished. Additionally, the medication reservoir and pump are connected by silicone rubber tubing. A low-pressure valve at the end of a catheter made of silicone rubber tubing strengthened with a stainless-steel helix is used to stop biological fluids from flowing backward. Next, the drug's flow rate and dosage are adjusted by manipulating the pump rate using an electronic external remote control.[23]

3. MECHANISM OF DRUG RELEASE FROM IDDS

3.1.Diffusion controlled release[24]

One key mechanism in many controlled release systems is diffusion. Because molecules collide randomly with one another, they move in a random manner, or as a molecule would at any given time. The drug molecules' transition from higher concentrations to lower concentrations is explained by their Brownian motion. As a result, a material diffuses throughout the concentration gradient.

The explanation for the Brownian movement of particles is,

$$\sim \sqrt{Dt}$$

Here, D = Diffusion coefficient

t = time

3.2. Chemically controlled release

The drug release rate is regulated by a chemical retort using the polymer as part of the chemically controlled mechanism. With this method, the polymer is liquefied first and subsequently absorbed by the body, obviating the need for surgery to remove the device after medication delivery is complete.[25]

3.2.1. Bioerosion

Polymeric monolithic devices erode due to assault by release medium elements, particularly water, which breaks down the covalent bonds within the polymeric matrix.[22] The

degradation rate of hydrolytically labile bonds is significantly influenced by the accessibility of water. Bond hydrolysis can be catalysed by an acid or a base. Should such be the case, it is susceptible to a limited concentration of both donors and acceptors of protons. In polyesters and PLGA, the chain end supplies acidic protons.[26]

3.3. Swelling Controlled release

Swelling is caused by an increase in polymer volume and water absorption via a polymer structure. Three circumstances might cause swelling

- When a polymer and water are incompatible.
- When a polymer bond has been formed via cross-links.
- When there is a long polymer chain.

Osmosis and swelling progression are similar in that water enters the polymer quickly, while polymer dissolution in water is sluggish because the polymer chains must be untangled. Swelling is dependent on density and hydrophilicity of the polymer, among other things.[27]

One process that initiates the release of a restricted medication is swelling. Diffusion of the drug over the expanded polymer becomes the dominating route for drug release in cases of fast swelling. However, if the swelling happens slowly, the mechanism controlling the amount of medication release takes over.[28]

3.4. Osmotically Controlled Release

The process known as osmosis occurs when an osmolyte's aqueous solutions are separated by a membrane. While it is impermeable to other solutes, this membrane absorbs water. To balance the concentration of nonpermeable solutes on each side of the membrane, water passes through a semipermeable membrane. Most of the time, diffusion is what allows the water to pass through the membrane. The difference in the chemical potentials of the water on each side of the membrane might be the determining factor. The thermodynamic compatibility of water with osmolytes and their concentration determine the difference in chemical potentials. The concentration of the osmolyte determines the osmotic pressure if the osmolytes are tiny molecules, such as salts.[29] A push-pull pump, an elementary osmotic pump, and an Alzet micro-osmotic pump are a few examples of osmotically regulated systems. The tissue of the animal has an Alzet micro pump put in it. In this case, it administers the medication in exact amounts. The medication is placed into a flexible wall reservoir with an impermeable barrier that is sealed using an osmotic agent. A strong

cellulose acetate membrane further seals this environment. Water passes through the cellulose acetate membrane osmotically in an aqueous environment. The agent is forced out of the hole by the tension this place on the reservoir walls.[30]

4. MENUFACTURING METHODS OF IMPLANT

A variety of factors such as cost, efficiency, and variations in the features of the implants produced, must be taken into consideration when selecting a manufacturing process for implanted drug delivery systems. There are several methods for producing implants, including as compression, solvent casting, and hot melt extrusion.

4.1. Hot melt extrusion

A suitable solvent is added to the medicine to cause it to dissolve and create a solution combination. After that, the polymer is added gradually and given a 15-20 minutes soak. After completely mixing the swelling product until it resembles dough, it is placed into an ejection cylinder and uses a showerhead to create an extended rod-like structure. The product is allowed to air dry for the entire night before being cut to the proper size. To achieve the finalised product, it is finally dehydrated at 41°C. Extrusion can be done concurrently, resulting in effective output. Thermoplastic polymeric materials, such as polyamide aliphatic polyesters like PLA, PLGA, and PGA, are necessary. To make products like Depot-Profact®, Implanon®, and Zoladex®, melt extrusion is used.[31]

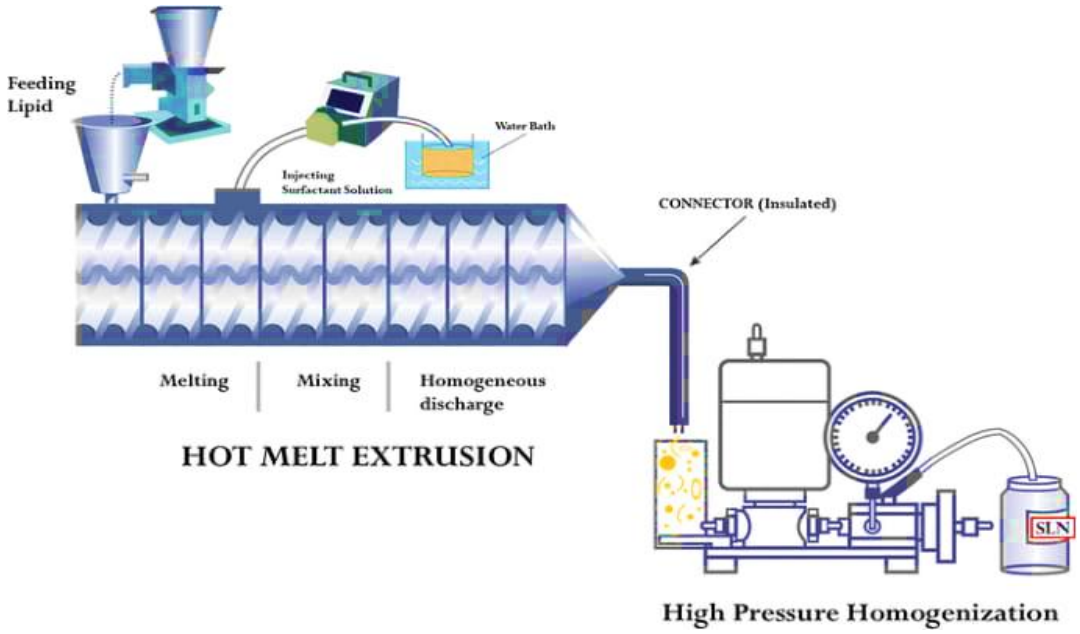


Figure 4: Hot melt extrusion for manufacturing of Implants.[9]

4.2. Solvent Casting

The chemical is first mixed in a suitable solvent in the solvent casting process. The resultant mixture is then formed into a mould, and the solvent is eliminated by evaporation. Typically, implants made using this technology result in films or layered implants. One disadvantage of this approach is the requirement for large volumes of organic solvent, which might impact medication safety and toxicity and raise environmental concerns.[32]

4.3. Compression

One benefit of using compression as a manufacturing process is that it does not require the use of heat or solvents, which makes it an excellent choice for implants made of materials like proteins or peptides that are sensitive to heat or solvents. However, compared to implants made using other manufacturing processes, implants made using this technology frequently exhibit a quicker release profile. As a result, it could be necessary to use additional treatments, including coating the implant, to prolong drug release.[33] Additionally, implants made via compression had a surface that was irregular and had a lot of holes and channels, which might cause an uneven release from the implant made this manner.[34]

4.4. Injection Moulding

Injection moulding is a method used to create implants out of thermoplastic polymers like PLA or PLGA. After being heated, the polymer is injected into a particular mould and let to harden. A drop in the molecular weight of the polymers is observed because of the high heat applied. Rothen-Weinhold et al. examined the effects of extrusion vs injection moulding on the characteristics of PLA polymeric matrix degradation. Both methods were shown to lower the molecular weight and polydispersity, although injection moulding produced a more noticeable drop. Consequently, implants made by extrusion deteriorated more quickly than implants made by injection moulding.[35]

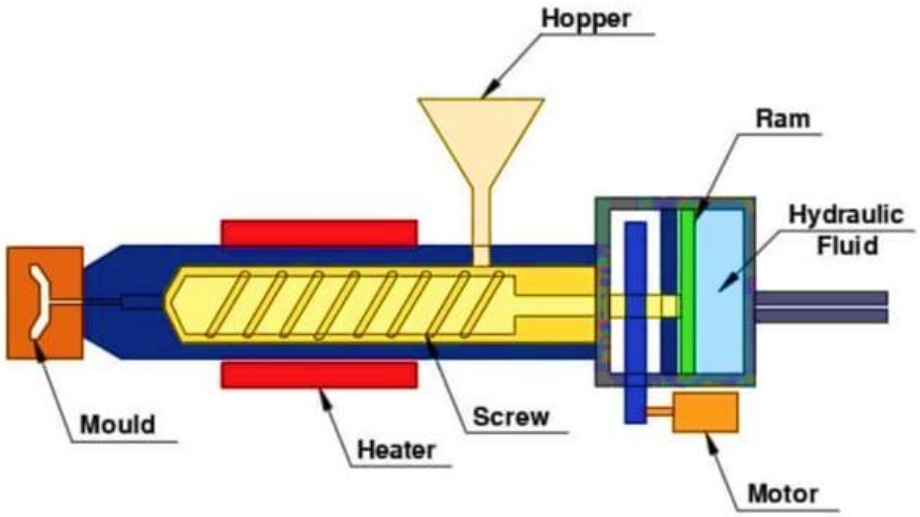


Figure 5: Injection Molding for Implants.[36]

4.5. 3D Printing

It is a cost-effective, reliable, and adaptable process that may be helpful in the future, particularly for the rapid production of standard units for research needs. Although it is not produced in large quantities, its applicability advanced in 2015 when the FDA authorised a particular substance. This method is mostly utilised to create implants and prostheses for usage in orthopaedics and dentistry.[37]

5. THERAPEUTIC APPLICATIONS

Implantable drug delivery system is finding increasing applications in the areas of Ocular implants, dental Implant, Cancer therapy, Infectious diseases, Contraceptive Implants, Pain management.

5.1. Ocular Implants

Prolonged ocular administration using a variety of implanted methods has been tested. These consist of silicone implanted devices, membrane-controlled devices, and implantable infusion systems.[38] The Ocusert device, which contains pilocarpine and alginic acid in a drug reservoir enclosed by an ethylene-vinyl acetate membrane that regulates release rate, is an illustration of a membrane-controlled system. The Ocusert system's release kinetics for pilocarpine administration at 20 or 40µg/h demonstrate an initial burst release, which is followed by a near-zero-order release over a week. Adults' device performance seems to be adequate, controlling intraocular pressure with little adverse effects.[39]

Table 2: Examples of Implantable drug delivery devices used to treat Ocular Diseases.[40]

Product Name	Implant Type	Material	Drug Delivered	Indication
Ocusert®	Intraocular	PEVA	Pilocarpine, Alginic acid	Open Angle Glaucoma
REtisert®	Intraocular	Microcrystalline cellulose (MCC), PVA, Magnesium Stearate	Fluocinolone	Non-infectious Uvetis
Vitrasert®	Intraocular	PVA/PEVA	Ganciclovir	Cytomegalo Virus retinitis in AIDS patients.

5.2. Dental Implants

Polymeric implants have been studied for a variety of dental uses, including as the local, sustained delivery of antibiotics and fluoride antibacterial agents. To provide fluoride with a prolonged release, stannous fluoride was included into several dental cements. To be a rate limiting factor in drug release, another was distributed in the hydroxyethyl methacrylate and methyl methacrylate copolymer hydrogel covered with an outer layer of the same copolymers in a different ratio. The device was affixed to the buccal surface of the maxillary first molar and was meant to release 0.5 mg of fluoride every day for 30 days. It was approximately 8 mm long and contained 42 mg of fluoride in its core.[41,42]

5.3. Cancer therapy

The main obstacle in the treatment of cancer is the development of drug delivery systems that can safely and efficiently administer chemotherapy medications without causing adverse effects. Consequently, IDDSs have significant promise for improving the efficiency and safety of the delivery of chemotherapeutic medications. There have been attempts to enable therapy with a drug delivery device for several cancers, including bladder, prostate, and brain.[43]

Table 3: Examples of Implantable drug delivery devices used for Anticancer Therapy.[40]

Product Name	Implant Type	Material	Drug Delivered	Indication
Zoladex®	Subcutaneous	PLGA	Goserelin	Prostate Cancer
Prostap® SR	Subcutaneous	PLGA	Leuprolide	Prostate cancer
Glidal® Wafers	Intra-tumoral	Silicone	Carmustine	Primary Malignant Glioma
Oncogel®	Intra-tumoral	PLGA-PEG-PLGA	Paclitaxel	Oesophageal Cancer
Vantas®	Subcutaneous	Methacrylate based hydrogel	Histrelin	Prostate Cancer
GemRIS®	Intravesical	Not disclosed	Gemcitabine	Non-muscle Invasive Bladder Cancer

5.4.Infectious diseases (Tuberculosis)

Long-term therapy and medication side effects are major issues in the treatment of tuberculosis (TB). These factors can negatively impact a patient's lifestyle, lead to noncompliance, treatment failure, and the emergence of drug-resistant strains. To produce more efficient and obedient medication delivery for tuberculosis, implantable drug delivery devices are utilised.[44] According to pre-clinical research, after implantation in rabbits, a single Isoniazid in PLGA copolymer implant may guarantee sustained levels of free Isoniazid for up to eight weeks.[45]

5.5.Contraceptive Implants

The FDA has approved the sale of Norplant, a subdermal implant designed to deliver levonorgestrel over an extended period. Six silicone membrane capsules, each containing around 36 mg of levonorgestrel, make up the device. Through a trocar with a single trocar entry site, the capsules are subcutaneously inserted on the inside of the upper arm or forearm in a fan-shaped arrangement. Other polymer-based contraceptive systems under investigation include progestasert, an intrauterine drug-releasing device made of ethylene vinyl acetate copolymer that lasts for a year, and suspensions of injectable microspheres or rods made of biodegradable polymers. Vaginal rings made of silicon rubber are typically used for three to 76 months, with a removal period of one week each month to allow for menstruation.[46]

5.6. Pain management

Because it requires repeated dosages, can be fatal or cause morbidity from overdose, and has a high risk of addiction to oral and parenteral drugs, chronic pain is an especially difficult illness condition to treat.

Table 4: Examples of Implantable drug delivery devices for Pain Management and CNS disorders.[40]

Product Name	Implant Type	Material	Drug Delivered	Indication
LiRIS®	Intravesical	Silicone	Lidocaine	Interstitial Cystitis /Bladder Pain Syndrome
Probuphine®	Subcutaneous	PEVA	Buprenorphine	Opioid abuse
Med-Launch®	Subcutaneous	PLGA	Risperidone	Schizophrenia
Risperdal Consta®	Intra-muscular	PLGA	Risperidone	Schizophrenia

CONCLUSION

In conclusion, implantable drug delivery devices offer a promising solution for targeted and controlled drug delivery in various therapeutic applications. The manufacturing methods discussed in this paper provide insights into the diverse techniques used to create these devices, while the examples of therapeutic applications showcase the versatility and potential impact of implantable drug delivery systems in healthcare. Understanding the mechanisms of drug release from these systems is crucial for optimizing their efficacy and safety. Despite the advantages they offer in terms of patient compliance and treatment efficiency, it is important to address the limitations associated with implantable drug delivery devices, such as the potential for adverse reactions and the invasive nature of surgical implantation. Further research and development in this field can lead to advancements that enhance the effectiveness and accessibility of implantable drug delivery systems for improved patient outcomes.

REFERENCES

1. Alexey FZ, Alesia BK, Karen MK, Anatoly SK, Anna G. Implantable Drug Delivery Systems and Foreign Body Reaction: Traversing the Current Clinical Landscape. Bioengineering, 2021; 8: 205.
2. Eric CP. Implanatble drug delivery devices. Drug Delivery Devices and Therapeutic Systems, 2021; 129-156.
3. Anoop KM and Jonathan PL. Implantable drug delivery systems: An overview. Nanostructures for the Engineering of cells, Tissues and Organs, 23 Feb 2018; 473-511.
4. Ian MJ, Sarah LK, Maurice DT, Christopher MC. Implantable drug delivery system. Engineering drug delivery system, 24 Jan 2020; 111-146.

5. Soeb HU, Dharmendra SK, Rajat YD, Yusuf KH. Implantable Drug Delivery System: An Overview. IJPPR Human Journals, March 2021; 20(4): 116-132.
6. Santosh PD, Sonal SH, Vikas B WB. Review on: Implantable drug delivery system. IJRTI, 2022; 7(11): 380-390.
7. Dr. Meenakshi GP. Implantable drug delivery system. Novel drug delivery system.
8. Rajgor N, Patel M, Bhaskar VH. Implantable Drug Delivery Systems: An Overview. Systematic Reviews in Pharmacy, July-December 2011; 2(2): 91-95
9. Soha AM, Shahidulla SM, Aasia ST, Fatima NM. Implantable Drug Delivery System: An Innovative Approach. Journal of Drug Delivery and Therapeutics, 2023; 13(5): 98-105.
10. Dasara TH, Implantable drug delivery system, 26 April 2020, https://www.slideshare.net /DasaraThanmayi/implant-drug-delivery-system
11. Colaris, M.J.L, de Boer, M, van der HL, R.R, Cohen TR. Two hundreds cases of ASIA syndrome following silicone implants: A comparative study of 30 years and a review of current literature. Immunol. Res, 2017; 65: 120–128.
12. V. Prasad SH. Non-Degradable Biocompatible Polymers in Medicine: Past, Present and Future. Current Pharmaceutical Biotechnology, 2003; 4: 331-337.
13. Sarah A. Stewart, Juan Domínguez-RB, Ryan F. Donnelly, Eneko LR. Implantable Polymeric Drug Delivery Devices: Classification, Manufacture, Materials, and Clinical Applications. Polymers, 12 December 2018; 10: 1379.
14. Concept of diffusion: drug release from polymer matrices (Part 1) and MCQs for GPAT, NIPER, Pharmacist and drug inspector exam. 13 August 2021.
15. Claes L, Ignatius A. Development of new, biodegradable implants. Chirurg, 2002; 73: 990–99.
16. Xiaopeng WN, Tianning CH, Zhanxiao YN, Wanjun WN. Study on structural optimum design of implantable drug delivery micro system. Simulation modelling practice and theory, Jan 2007; 15(2): 47-56.
17. Cao L, Mentell S, Polla D. Design and simulation of an implantable medical drug delivery system using microelectromechanical systems technology. Sensors & Actuators A: Physical, 31 October 2001; 94(1-2): 117-25.
18. Renard E. Implantable closed-loop glucose-sensing and insulin delivery: The future for insulin pump therapy. Current Opinion in Pharmacology, 1 December 2002; 2(6): 708-16.
19. Alekha K. Dash, Greggrey C. Cudworth. Therapeutic Applications of Implantable Drug Delivery Systems. Journal of Pharmacological and Toxicological Methods, 13 July 1998; 40: 1-12.

20. Jayendrakumar PT, Shalin PR, Shwetaben PT. Comprehensive review on Osmotic drug delivery system. world Journal of pharmaceutical research, 2021; 10(5): 523-550.
21. Richard Rauck MD, Timothy Deer MD, Steven Rosen MD, Gurpreet Padda MD, John Ba rsa MD. Long term follow up of a novel Implantable programmable infusion pump. Neuromodulation: Technology at the neural interface, April 2013; 16(2): 163-167.
22. Ankita MA, Neha MH, Piyush GH. Approaches to the development of Implantable Therapeutic System. Biomaterials and Bio-nanotechnology, 2019: 191-224.
23. Danckwerts M, Fassihi A. Implantable controlled release drug delivery systems: a review. drug development and industrial pharmacy, 1991; 17(11): 1465-1502.
24. Wang Y, Gu, B. & Burgess, D.J. Microspheres Prepared with PLGA Blends for Delivery of Dexamethasone for Implantable Medical Devices. Pharmaceutical Research, 2014; 31: 373–381.
25. DeXia LI, Gang GU, RangRang FN, Jian LI, Xin DE. PLA/F68/Dexamethasone implants prepared by hot-melt extrusion for controlled release of anti-inflammatory drug to implantable medical devices: I. Preparation. characterization and hydrolytic degradation study, international journal of pharmaceutics, 30 January 2013; 441(1-3): 365-372.
26. Harilall SR, Choonara E. Y, Lomas Kumar TM, Charu TY. Development and in vivo evaluation of an implantable nano-enabled multipolymeric scaffold for the management of AIDS dementia complex (ADC). International Journal of pharmaceutics, 30 December 2015; 496(2): 863-877.
27. Danyuo Y, Obayemi J.D, Dozie-Nwachukwu S, Ani C.J, Odusanya O.S. Prodigiosin release from an implantable biomedical device: kinetics of localised cancer drug release, Materials science and engineering, 1 September 2014; 42: 734-745.
28. Michael A. WH, Devin J. S, Kerri R. BL, Morgan V. FD. The impact of monomer sequence and stereochemistry in the swelling and erosion of biodegradable poly (lactic-co-glycolic acid) material. Biomaterials, February 2017; 117: 66-76.
29. Hill A, Geisler S, Meyring M, Hecht S, Weigandt M. In vitro-in vivo evaluation of nanosuspension release from subcutaneously implantable osmotic pumps. International Journal of pharmaceutics, 15 July 2013; 451(1-2): 57-66.
30. Zaher A, Li S, Wolf K T, Pirmoradi F N, Yassine O. Osmotically driven drug delivery through remote- controlled magnetic nanocomposite membrane. Biomicrofluidics, 29 Sept 2015; 29(5): 054113.
31. Breitenbach J., Melt extrusion: from process to drug delivery technology. European journal of pharmaceutics and bio pharmaceutics, 2002; 54(2): 107- 117.

32. Hirenkumar K. MK, Steven J. SI. Poly Lactic-co-Glycolic Acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers, 26 August 2011; 3(3): 1377-1397.
33. Gemachu DI, Literature Review Implantable Drug Delivery System and Drug Delivery Device, 16 November 2020.
34. Fialho, S.L; da Silva CU. A. Manufacturing Techniques of Biodegradable Implants Intended for Intraocular Application. Drug Delivery, 2005; 12(2): 109–116.
35. Rothen-WE, Besseghir K, Vuaridel E, Sublet E, Oudry N. Injection-molding versus extrusion as manufacturing technique for the preparation of biodegradable implants. European journal of pharmaceutics and biopharmaceutics, 1 September 1999; 48(2): 113-121.
36. Matal Injection Molding: Advantages, disadvantages. https://www.iqsdirectory.com /articles/metal-injection-molding.html
37. James NR, Rapti D. MD, Christine M.V, Mansoor A. KH, Khairuzzaman AK. A new chapter in pharmaceutical manufacturing: 3D- printed drug products. Advanced Drug delivery reviews, 1 January 2017; 108: 39-50.
38. Jaleh BR, Ayuob AG, Marziyeh FA, Yadollah OM. Advanced drug delivery and targeting technologies for the ocular disease. Bioimpacts, 2016; 6(1): 49-67.
39. Deivasigamani KR, Mithun BH, Vijay Prakash PN, Nandhakumar JO. The concept of ocular inserts as drug delivery systems: An overview. Asian Journal of pharmaceutics, 2008; 2: 192-200.
40. Sandip FU, Sunil R. BV, Bhushan P. GY, Jyotiram SW. An Overview on Implantable Drug Delivery System, Journal of Pharmaceutical Research International; 16 March 2022; 34(25A): 1-13.
41. Koka S. The Implant-Mucosal Interface and Its Role in the Long-Term Success of Endosseous Oral Implants: A Review of the Literature. Int J Prosthodontics; 1998; 11(5): 421-432.
42. Sennerby L, Roos J. Surgical determinants of clinical success of osseointegrated oral implants: a review of the literature. Int J Prosthodont, Sept – Oct 1998; 11(5): 408-20.
43. Alexandre A. BA, Shane BW, Carlos Ol, Estevão LI, Ana Rita C. DU. Drug-eluting biodegradable ureteral stent: New approach for urothelial tumors of upper urinary tract cancer. International Journal of Pharmaceutics, 20 November 2016; 513(1-2): 227-237.
44. Robin FE, Stefan KF, Volker ter ME, Alimuddin ZU. Drug-resistant tuberculosis in the european union: opportunities and challenges for control. Tuberculosis, May 2010; 90(3): 182-187.

45. Kailasam S, Daneluzzi D, Gangadharam P.R.J. Maintenance of therapeutically active levels of isoniazid for prolonged periods in rabbits after a single implant of biodegradable polymer. Tubercle and lung disease, October 1994; 75(5): 361-365.
46. Mohammad Zaki AJ, Satish K. PT, Dheeraj T. BV, Dinesh K. JA. Implantable Drug Delivery System: A Review. International Journal of PharmTech Research, 2012; 4(1): 280-292.