AN OVERVIEW ON IMPLANTABLE DRUG DELIVERY SYSTEM

ABSTRACT

Drug delivery systems that can sustain pharmacologically effective therapeutic drug levels for long periods of time while also permitting "dosing-on-demand" would be immensely useful in modern medicine. Physicians can choose from a variety of precision delivery options, such as local or systemic circulation, while still ensuring appropriate dose over the duration of treatment with implantable drug delivery systems. These systems have several advantages, including focused local medication delivery at a steady and predetermined pace, which reduces the amount of drug required and potential side effects while boosting therapeutic efficacy. These systems are especially useful for conditions including cardiovascular disease, tuberculosis, diabetes, cancer, and chronic pain management, to mention a few, that require long-term medication or face issues with patient compliance. This chapter begins with an overview of several implantable drug delivery devices, ranging from biomaterial-based to electromechanical. Design techniques to optimal drug delivery are also discussed, including ways for tailoring drug release patterns and the process of release kinetics. Following that, potential therapeutic applications and biocompatibility problems will be briefly reviewed. These systems' performance and related applications differ. The performance, functioning principle, fabrication procedures, and dimensional constraints of each technology are highlighted. We look at the current research on implanted drug delivery systems, with an emphasis on application and chip performance, as well as a comparison of passive and active delivery systems. Finally, this article sums up with an overview of implantable drug delivery systems' future prospects, particularly in terms of

Keywords:- Implantable drug delivery systems, biomaterial, release kinetics, biocompatibility

1. INTRODUCTION OF IMPLANTABLE DRUG DELIVERY SYSTEM

Implants are medical devices that are put inside or on the surface of the body, usually under the skin at a discreet but handy location. Implants help organs and tissues by delivering medication,

monitoring physiological functioning, and providing support. Insulin, hormones, chemotherapeutics, antibiotics, analgesics, heparin, and other drugs and fluids are some of the drugs and fluids that can be delivered through implants. Implants are small sterile solid masses created by compression, moulding, or extrusion from highly pure medication. Implants are sterile drug delivery devices for subcutaneous implantation can deliver the medication at a controlled rate over a prolonged period of time.

Drug absorption is a subject which is attracting increasing interest in the areas pharmaceutical sciences. The technique of solid drug pellet implantation has particular importance in livestock and poultry fields, in the area of cancer research where carcinogens or potential ones are studied, in theoretical studies involved in solid drug absorption, in endocrinological work, in studies concerned with metabolism and fate of drugs, and in many more areas where prolonged "continuous infusion" of drug is required[1].

Pharmaceuticals have primarily consisted of simple, fast acting chemical compounds that are dispensed orally or as injectables. During last three decades, however, formulations that control the rate and period of the drug delivery and target specific area of the body for treatment have become increasingly common and complex.

Drugs may be administered through many routes by variety of dosage form. However maintaining constant in vivo therapeutic concentration for an extended period of time has been problematic[2]. Peaks and troughs in drug concentration are often observed when the drug is administered either intermittently via the intravenous route or upon oral administration. High drug concentration may cause toxicity, whereas low drug concentration may be sub-therapeutic.

The best approach to eliminate the peaks and troughs during drug therapy is by continuous intravenous infusion. However this requires constant monitoring, and can be performed by health-care professionals[2].

To alleviate the kind of problem, number of drug delivery system such as oral controlled release dosage forms, transdermal, injectables and Implantable drug delivery systems, have been investigated and commercialized. It is well established that dosage form design can modify drug action. A new, more far reaching and positive expression of this principle is taking shape as dosage form design advances to control the rate of drug release from its delivery system and this may contribute to the therapeutic value of drug.

One means of administering drugs that are, more site selective given less often require smaller dosages, is through Implantable Drug Delivery Systems (IDDS).

According to USP XX[3], (The United States Pharmacopoeia, XX,1980) the implants were defined as "The pellets consisted of pure drug with no added excipients and were defined as small, rod-shaped or ovoid-shaped, sterile tablets consisting of highly purified drug usually compressed without excipients, intended for subcutaneous implantation in body tissue". The simplest Implantable device in current usage is administered subcutaneously and depends solely on upon extremely slow dissolution of heavily compressed drug to provide a very extended period of drug release.

With rapid advances in implantation therapy and excipients to control the release pattern, the USP XXII has redefined the implants as "Small, rod-shaped or ovoid shaped, sterile tablets or pellets consisting of highly purified drugs compressed with recognized excipients and can be implanted in body at sites other than subcutaneous"[4].

Table 1. Advantages and Disadvantages

Advantages[2,5,6,7,8]	**Disadvantages**[2,5,6,7,8]
1) Delivery of medication is long-term and under strict control.	1) Invasive procedure: Large implants necessitate surgery.
2) Improved patient compliance due to reduced dose frequency	2) Discontinuation: Therapy is difficult to stop.
3) There is a possibility of intermittent release and local administration.	3) Biocompatibility i.e. the hosts and implant reaction.
4) Prevents first-pass metabolism and drug degradation in the GI tract.	4) Inflammatory reaction and Implants infection in the body
5) By lowering the required dosage drug side effects are can be reduced.	5) Device failure and implant dislocation are also risking.
6) Increased drug bioavailability and stability.	6) Cost: A drawback from a business standpoint

1.2 Ideal properties of Implantable Drug Delivery System[8]

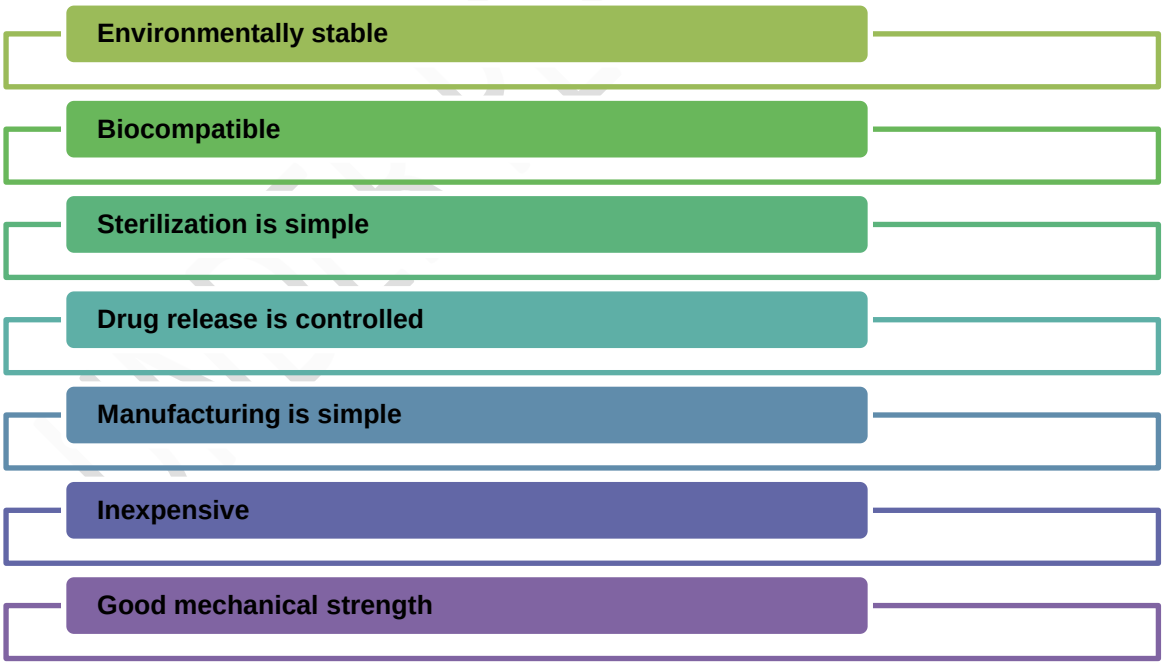


Fig. 1. Ideal properties of implantable drug delivery system

2. CLASSIFICATION AND APPROACHES OF IDDS[6,7,8,9,24]

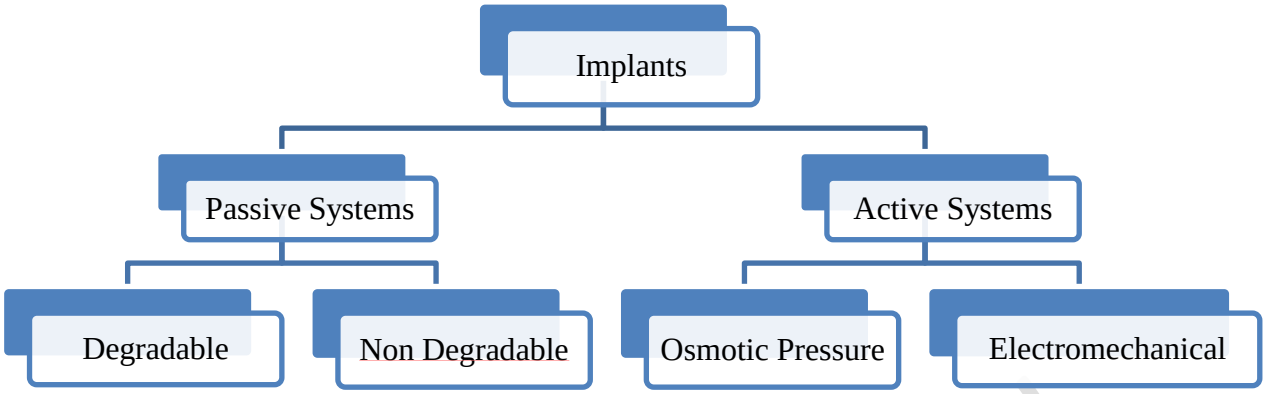
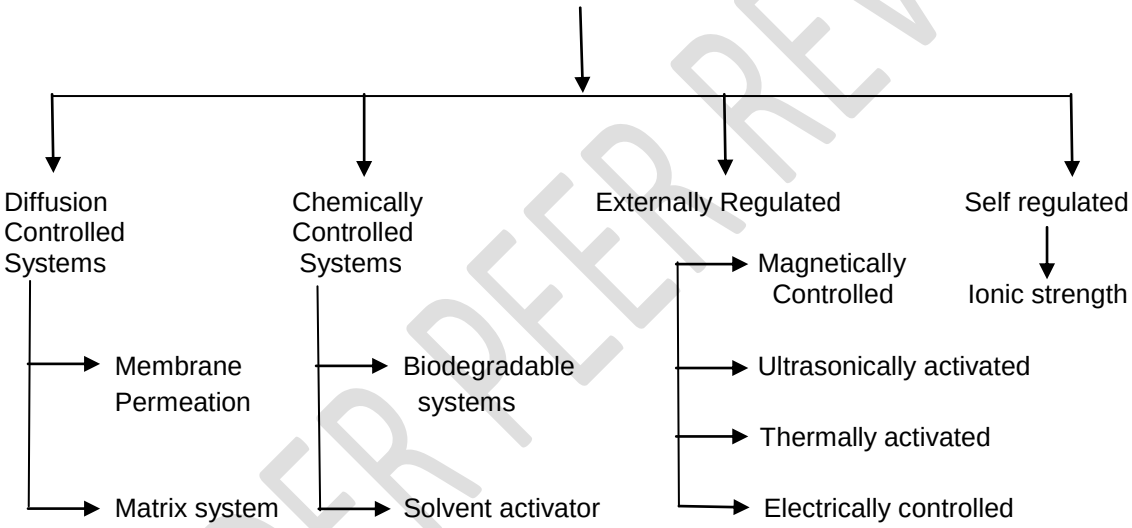


Fig. 2. Classification of Implantable drug delivery system

Fig 3. Approaches and drug release from Implantable drug delivery system[6,7,8,9]



Types of ICDDS:

There are two major classes of ICRDDSs. The first major class consists of polymeric ICRDDSs which utilize different types of polymers and polymer membranes to control the release of drugs to biological systems. The second major class consists of mechanical pump-type ICRDDSs which utilise an infusion pump-type action to control the release of drug.

2.1. Polymeric ICDDS

Many different types of polymeric systems[10] are available for controlling the release of drugs in various types of drug delivery systems according to their mechanisms of controlled release as follows:

2.1.1 Diffusion Controlled Systems

Reservoir System: in which a core of drug is surrounded by a polymer membrane which controls the rate of release of the drug to the biological environment[11]. The important feature of these systems is that diffusion through the polymer membrane is the rate limiting step **Figure 4**.

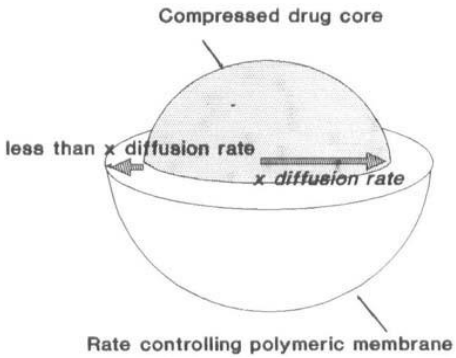


Fig. 4. Reservoir Polymeric drug delivery system

a) Biodegradable polymeric fibre system: The problems of non-biodegradability of reservoir type systems were overcome by biodegradable hollow polymer fibres (approximately 700 - 800 microns outside diameter and 445 - 600 microns internal diameter) to control the release of hormones **(Figure 5)**.

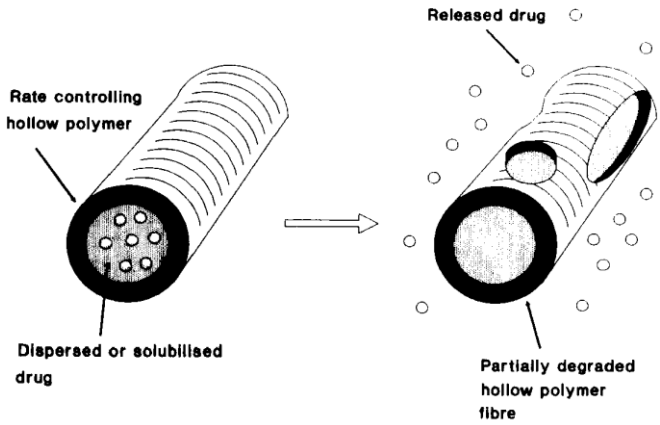


Fig. 5. Reservoir hollow biodegradable polymeric fibre drug delivery system

b) Matrix Systems: In this the active drug is uniformly distributed throughout a solid nonbioerodible polymer. Again, as in reservoir systems, drug diffusion through the polymer matrix is the rate limiting step **(Figure 6)**.

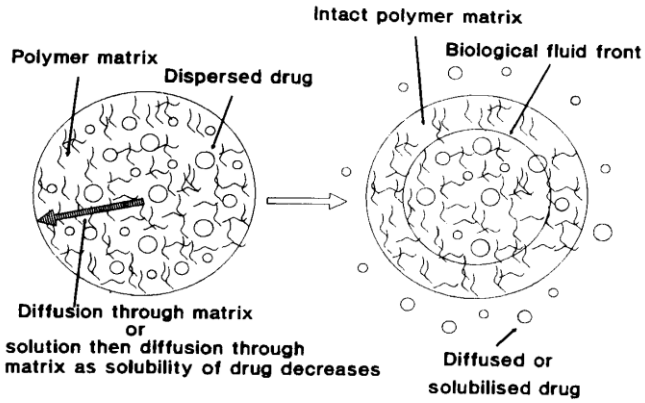


Fig. 6. Matrix polymeric drug delivery system

2.1.2. Chemically Controlled Systems

a) Bioerodible Systems: This system include drug dispersion in a polymer which is slowly biologically eroded at a controlled rate. Like matrix systems, the drug is evenly dispersed throughout the polymer and is manufactured in essentially the same manner. However, unlike matrix systems, which depend on solution-diffusion type mechanisms for controlled release, bioerodible systems release according to the rate of polymer bioerosion. It should be noted however, that in practice some diffusion of the drug from the polymer matrix does occur. The major advantage of bioerodible systems is that the bioerodible polymer is eventually absorbed by the body. This then alleviates the need for surgical removal resulting in a more positive attitude of patients towards therapy.

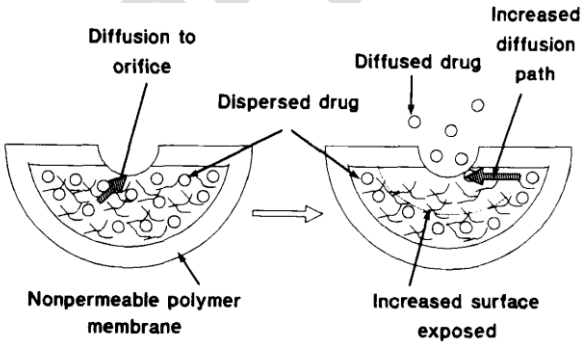


Fig. 7. Hemisphere polymeric drug delivery system

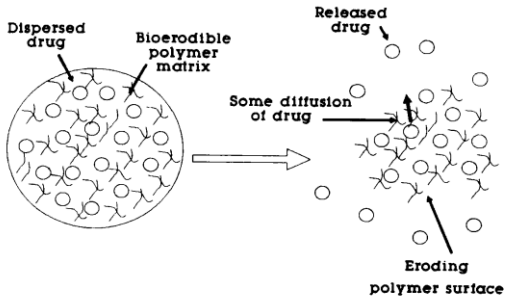


Fig. 8. Bioerodible polymeric drug delivery system

2.1.3. Swelling Control Systems

These prepared systems having drug dissolved or dispersed within a polymer matrix and is not able to diffuse through that matrix. Environmental biological fluid is then imbibed into the matrix at a controlled rate, causing it to swell and release the drug entrapped in that part of the polymer''. Thus, the release rate is determined by the rate of diffusion of biological fluid into the polymer **(Figure 9)**.

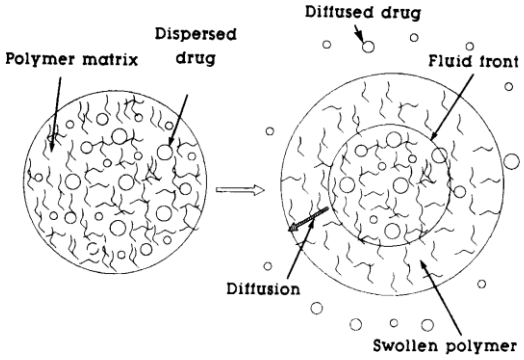


Fig. 9. swelling controlled polymeric drug delivery system

2.1.4. Magnetically Controlled Systems

The system having drug and small magnetic beads are uniformly dispersed within a polymer. Upon exposure to aqueous medium, drug is released in a fashion typical of diffusion controlled matrix systems. However, upon exposure to an oscillating external magnetic field, drug is released at a much higher rate. This is probably due to the compression of the polymer due to the movement of the dispersed magnets[12] **(Figure 10)**.

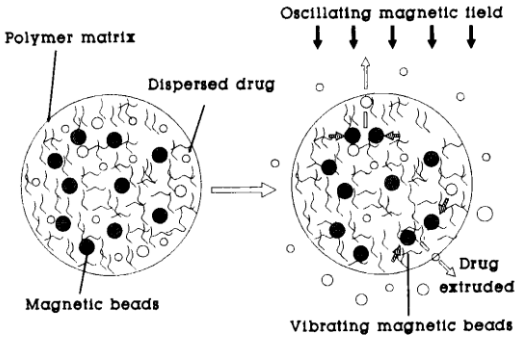


Fig. 10. magnetically controlled polymeric drug delivery system

2.2. Mechanical IDDSS

The second major type of IDDS is the mechanical IDDSs which release drug via mechanical pump type mechanisms. Some of the various types of mechanical IDDSs that have been clinically investigated are discussed below.

2.2.1 Infusion Pumps

One of the first completely implantable mechanical controlled release drug delivery systems to be developed and that is commercially available, is the Infusaid (Infusaid Corp., Sharon MA) infusion pump[13].

2.2.2 Peristaltic Pumps

Peristaltic pumps are mainly rotary solenoid-driven type pump[14]. Laser-welded titanium chambers are used to receive the pump, electronics, and battery. It is essential that the chambers are coated with silicone polymers for reinforced biocompatibility.

2.2.3 Osmotic Pumps

Several dosage forms have been developed that use an osmotic pressure differential to drive the release of drug from a reservoir at a controlled rate **(Figure 11).**

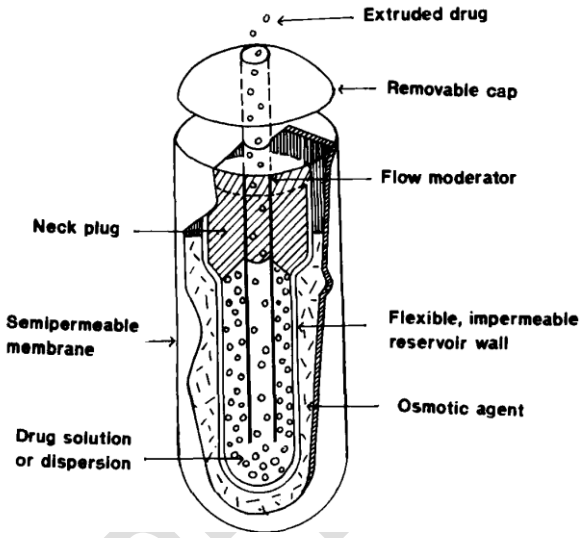


Fig. 11. Alzet[R] mini-osmotic pump

2.2.4 Controlled Release Micropumps

Controlled release micropumps utilise diffusion across a rate controlling membrane to appropriate basal delivery, while a rapidly oscillating piston acting on a compressible disc of foam increases the delivery. Without an external power source, the concentration difference between the drug reservoir and the delivery site is sufficient to cause diffusion of the drug to the delivery site; this is basal delivery. Increased delivery is achieved without valves by repeated compression of the foam disc by a coated mild steel piston. The driving piston is located within a solenoid and compression of the foam disc results when a current is applied to the solenoid coil.

3. DRUG RELEASE FROM IMPLANTABLE DRUG DELIVERY SYSTEM[15,16]

The most successful methods for delivering drugs in a linear process, where the drug dosage released is proportional to the square root of the release period, are osmotic pumping and diffusion.

Swelling control, solvent penetration into the matrix of the drug device is typically significantly slower than drug diffusion, resulting in a decreased release rate. The solubility and diffusion coefficient of the drug in the polymer, the drug load, and the polymer's in vivo degradation rate all influence drug release kinetics in systems mediated by osmotic pressure, swelling, and passive diffusion.

3.1 Drug release from Nondegradable Polymeric Matrices

Reservoir Systems: Drug is released at a constant rate, do not depend on concentration gradient. The thickness and permeability of the rate-controlling polymer membrane regulate this, and zero-order release kinetics may be achieved.

Matrix Systems: drug release via Fickian diffusion; solute movement is mediated by diffusion lengths and the degree of swelling and is directly directed by the concentration gradient.

Non-erodible, diffusion-controlled drug delivery systems are most effective for medicines having a molecular weight of 1000 DA or less.

3.2 Drug release from Biodegradable Polymeric Matrices

Diffusion, degradation, or a combination of the two governs medication release from biodegradable polymeric systems. When a drug's diffusion rate is less than a polymer carrier's degradation or erosion rate, a degradation regulated mechanism occurs. The medicine is released at the same time that the polymer degrades. Surface degrading and bulk degrading approaches can be used to control drug release based on the degradation-controlled mechanism.

Surface degradation: Drug release is affected by the surface to volume ratio and the geometry of implants, and degradation is limited to the device's outer surface.

Bulk degradation: The degradation is homogeneous throughout the material in a bulk degrading polymer.

4. POLYMERS FOR IDDS[16,17,18,19,20]

4.1 Biodegradable polymers[21]

1) Synthetic Polymers
2) Natural Polymers

4.2 Non biodegradable polymers[21]

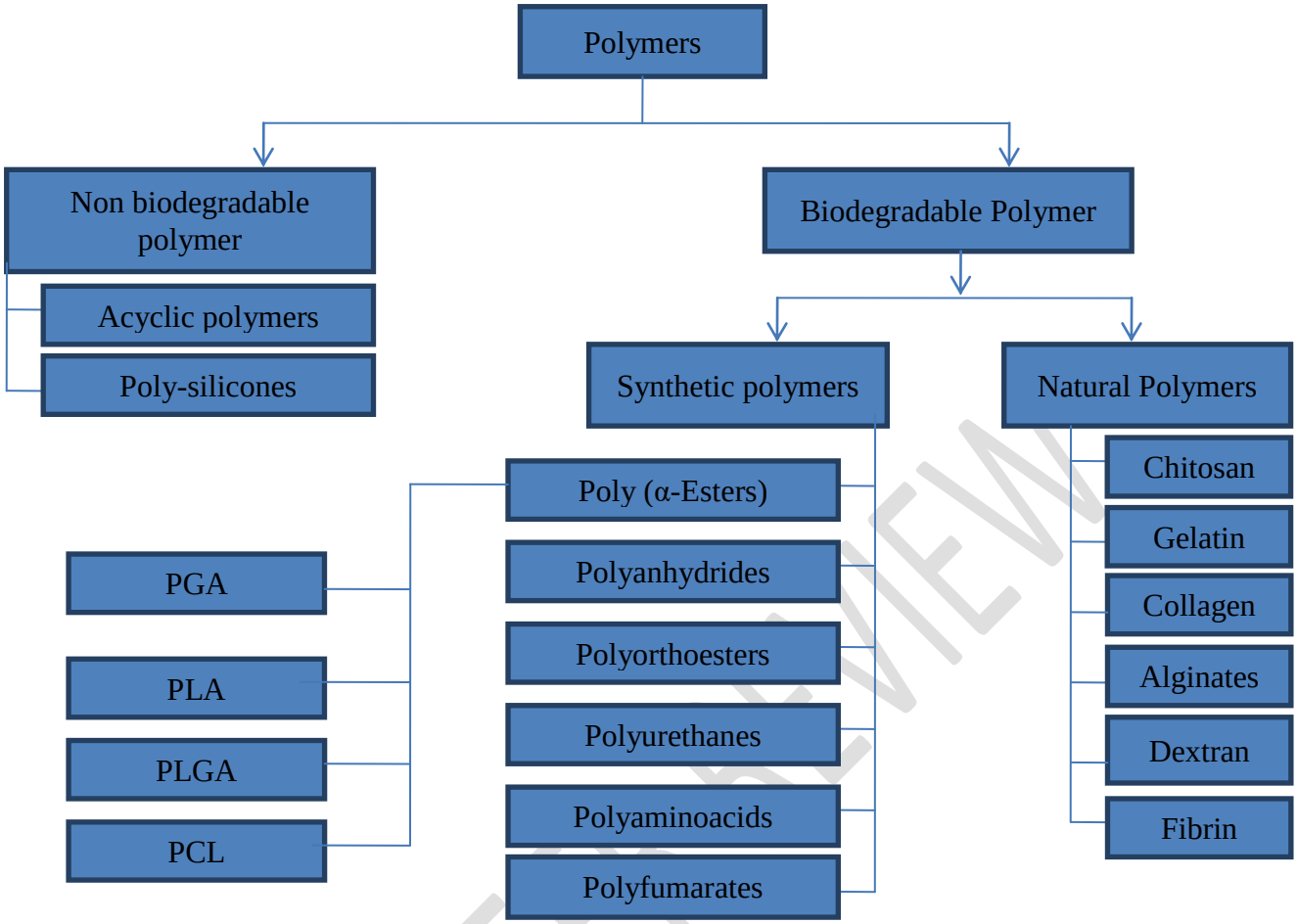


Fig. 12. Polymers generally used in implantable drug delivery system

5. METHODS FOR IMPLANT MANUFACTURE [2,6,7,8]

5.1. Compression Method

It's employed in the production of implants that contain heat or solvent-sensitive components like proteins or peptides. It has a more rapid release profile than other manufacturing procedures. Additional treatments, such as covering the implant, may be required to extend drug release. The irregular surface of a compressed implant, which has many pores and channels, might cause irregular release.

1) **Solvent Casting: -**The polymer is first dissolved in a suitable solvent, after which it is cast into a mould and the solvent is evaporated. Films or laminar implants are frequently the product of this approach. This approach has the problem of requiring significant volumes of organic solvent, which might affect drug stability and toxicity, as well as raise environmental concerns.
2) **Hot Melt Extrusion**: - Melting, mixing, and forcing a polymer through a small opening called a die process. The thermoplastic polymers utilised must be aliphatic poly (esters) such as PLA, PGA, and PLGA. It has the advantage of not requiring any solvents, but it can cause thermolabile medicines to degrade. Melt extrusion is used to make products like Zoladex®, Depot Profact®, and Implanon®. Extrusion can be done in a continuous process, allowing for great throughput.
3) **Injection Moulding**: -Injection moulding can be used to make implants out of thermoplastic

polymers like PLGA or PLA. The polymers were heated before being put into a mould and allowed to harden. The polymers' molecular weights have decreased as a result of the high heat used. Implants made by extrusion degraded faster than those made by injection moulding.

4) **3D Printing**: -Dental implants, prosthetics, and orthopaedic implants are all made with it. It's a low-cost, repeatable, and extremely customizable approach. 3D printing was utilised to create the biodegradable implant structure, which would then be filled with the drug, with drug release controlled by the implant structure's degradation or a rate-controlling membrane covering orifices in the implant.

6. TECHNIQUES OF IMPLANTING

Subcutaneous tissue is essentially a sheet of areolar tissue lying directly underneath skin. It is rich in fat, but poor in nerve network and haemoperfusion. Therefore, the subcutaneous tissue is an ideal location for implantation and prolonged drug administration because of its ready access to implantation, slow drug absorption, and low drug reactivity to the insertion of foreign materials[17].

Implantable Drug Delivery are implanted in vivo by means of various techniques, depending on whether they are in the form of microspherical beads, pellets or capsules, or miniatured devices.

Microspherical beads in the particle size range of 600 micron are normally suspended in an inert liquid vehicle and injected via 16 gauge or larger needles at a subcutaneous site nearest to the target site. The advantage of microsphere is that in most cases a local anaesthetic is not required and the implantation procedure is rather simple.

Pellet or capsule forms of IDDSs are placed subcutaneously by means of a small incision in the skin. Before implantation, the skin nearest the intended target site of the implant is covered with iodine or other suitable antiseptic solution, and the area anaesthetized using a local anaesthetic. A transverse operational incision normally not longer than 1.5cm long is then made. The pellet or capsule is placed under the skin and moved away from the incision. The incision is then stitched and covered with iodine or other suitable collodion.

Mechanical or pump type IDDSs can either be implanted under local or general anaesthetic depending on their size. In general they are not normally larger than 5cm in diameter and can be implanted under local anaesthetic[6].

7. STERILIZATION TECHNIQUES AND ASEPTIC PROCESS FOR BIODEGRADABLE DRUG DELIVERY SYSTEMS

Sterilization is a process to remove or destroy all microorganisms in or on an object or preparation, and to assure that it is free of infectious hazards[22]. Aseptic process is the procedure that is used to exclude microorganisms in the manufacturing process. Injectable or implantable drug delivery systems are required to be free of infectious hazards before they are used to deliver drugs into the body.

Terminal sterilization and aseptic processing are the two major methods to ensure the sterility of these drug delivery systems. Drug delivery systems prepared with biodegradable polymers cannot be sterilized by steam sterilization, since biodegradable polymers are hydrolytically unstable in presence of moisture and heat. For example, at least one material property of poly (L-lactide) was changed by seven different steam sterilization techniques[23]. The commonly used techniques for terminal sterilization are 60-Co g-irradiation and exposure to ethylene oxide gas.

If the biodegradable polymer is soluble in organic solvents used to prepare drug delivery systems or devices, it is also possible to sterilize the polymer solution in a clean environment using the filtration technique. Aseptic processing is the last alternative, if filtration and terminal sterilization are not feasible[9].

8. IN VITRO RELEASE METHOD FOR IMPLANTS

As such there is no official method to carry out the in-vitro release test for implants and implantable drug delivery systems. Below are some of the methods reported in various research journals to carry out the in vitro release test by different investigators.

8.1. The Rotating Flask Technique[25,26,27]

Several investigators have used this technique. In this method the implant is placed inside a screw-capped flask-containing buffer at physiological pH and ionic strength. This flask is placed in a water bath at 37^{o}C, oscillating at a low speed to provide mild agitation. Periodically, samples are removed from the flask and the buffer is replenished. The samples are analyzed for the cumulative amount of the drug. A major disadvantage of this technique is that for poorly soluble drugs frequent replenishing of entire medium is necessary in order to maintain sink condition. Another disadvantage is that with chemically unstable drugs, significant drug activity can be lost before sampling. Modification of this technique includes the incorporation of surfactants, alcohol in the dissolution medium to increase the solubility of poorly soluble drugs and shortening the in vitro duration of drug release.

8.2. Flow through cell[28]

This system provides an alternative advantage to the shaking-flask technique, while minimizing the above-mentioned disadvantages. In this system the implant is placed in a flow cell maintained at 37^{o}C. The dissolution medium is gently perfused through the flow cell and the perfusate is collected by a fraction collector for subsequent analysis or passed through on-line detectors for immediate analysis of drug content. Hollenback have successfully utilized the above concept for determining the release rate from polyanhydride implants containing 1,3-bis(2-chlorethyl)-1-nitrosourea (BCNU), a water unstable drug. An added advantage is the extensive characterization of release profiles and possibilities for complete automation of the release studies.

8.3 Vial method[29,30,31,32]

This method has been also used by several investigators. The in vitro drug release studies are performed in 10 or 14 ml screw capped glass vials. In this the implants are placed into vials and immersed with phosphate buffer containing antibacterial agent and also surfactant if recommended. Samples are incubated at 37^{o}C for definite period without agitation and are only shaken for 5 minutes at sampling time. At defined time points, 8.0 or 10.0 ml of the release medium is withdrawn and replaced with fresh buffer. The removed medium is analyzed for amount of drug released by the respective analytical method.

Intrinsic Dissolution Studies[33]**:** The measurement of intrinsic dissolution is a tool in the functionality and characterization of bulk drug substances and excipients.The intrinsic dissolution rate is defined as the dissolution rate of pure drug substance under the condition of constant surface area. The dissolution rate and bioavailibity of a drug substance are influenced by its solid state properties: crystallinity, amorphism, polymorphism, hydration, salvation, particle size and particle surface area. The measured intrinsic dissolution rate is dependent on these solid state properties. The dissolution rate is also influenced by extrinsic factors, such as hydrodynamics (e.g., test apparatus, and disk rotation speed or fluid flow) and test conditions (e.g., temperature, fluid viscosity, pH, and buffer strength in the case of ionizable compounds). By exposing the surface area of a material to an appropriate dissolution medium while maintaining constant temperature, stirring rate, and pH, the intrinsic dissolution rate can be determined. Typically the intrinsic dissolution rate can be expressed in terms of mg per minute per cm^{2}.

Appratus-A typical apparatus consist of a punch and die fabricated out of hardened steel. The base of die has three threaded holes for the attachment of surface plate made of polished steel, providing mirror smooth base for compacted pellet. The die has a 0.1cm to 1.0-cm cavity into which is a placed measured amount of the material whose intrinsic dissolution rate is to be determined. The punch is then inserted in the die cavity and the weighed material is compressed with a benchhop tablet press. A compacted pellet is formed in the cavity with a single face of defined area exposed on the bottom of the die. The bottom of the cavity is threaded so that at least 50% to 75% of the compacted pellet can dissolved without falling out of the die. The top of the die has the threaded shoulder that allows it to be attaché to the holder. The holder is mounted on laboratory stirring device and the entire die, with the compacted pellet still in place, is immersed in the dissolution medium and rotated by stirring device.

Table 2: In vitro-release methods at a glance

Method	Intrinsic Dissolution Method[33]	Vial Method[29,30,31,32]	R.F. Method[25,26,27]
Quantity of phosphate buffer	900ml	10.0ml (at pH 7.4)	100.0ml (at pH 7.4)
		10.0ml (at pH 6.0)	100.0ml (at pH 6.0)
Agitation speed	50 R.P.M.	Shaken 5 min. at	25 R.P.M.

		sampling	
Temperature	$37^{o}C \pm 0.5\ ^{o}C$	$37^{o}C \pm 0.5\ ^{o}C$	$37^{o}C \pm 5\ ^{o}C$

9. APPLICATIONS OF IDDS[34]

1) Chemotherapeutical Implants
2) Contraceptive Implants
3) Neuropsychological Implants
4) Pain killers loaded Implants
5) Ocular Implants
6) Cardiovascular Implants
7) Orthopaedic Implants
8) Dental Implants

Table 3: Examples of Implantable drug delivery devices used in the area of Health[35]

Examples of Implantable drug delivery devices used in the area of Women's Health.				
Product Name.	**Implant Type.**	**Material.**	**Drug Delivered.**	**Indication.**
Norplant/ Jadelle®	Sub-cutaneous.	Silicone.	Levonorgesterel.	Contraception.
Estring®	Intra- vaginal.	Silicone.	Estradiol.	Menopausal Symptom.
Nuvaring®	Intra- vaginal.	PEVA	Etonogestrel, Ethinyl Estradiol.	Contraception.
Implanon®/ Nexaplanon®	Sub-cutaneous.	PEVA	Etonogestrel.	Contraception.
Examples of Implantable drug delivery devices used for Anticancer Therapy				
Zoladex®	Sub-cutaneous.	PLGA	Goserelin.	Prostate Cancer.
Prostap® SR	Sub-cutaneous.	PLGA	Leuprolide.	Prostate Cancer.
Glidal® Wafers	Intra-tumoural.	Silicone.	Carmustine (bcnu)	Primary Malignant Glioma.
Oncogel®	Intra-tumoural.	PLGA-PEG-PLGA	Paclitaxel.	Oesophageal Cancer.
Vantas®	Sub-cutaneous.	Methacrylate based	Histrelin.	Prostate Cancer.

		hydrogel.		
GemRIS®	Intra- vesical.	ND.	Gemcitabine.	Non-muscle Invasive Bladder Cancer.
Examples of Implantable drug delivery devices used to treat Ocular Diseases				
Ocusert®.	Intra- Ocular.	PEVA	Pilocarpine, Alginic acid.	Open Angle Glaucoma
REtisert.®	Intra- Ocular.	MCC, PVA, Magnesium Stearate	Fluocinolone.	Non-infectious Uvetis.
Vitrasert®.	Intra- Ocular.	PVA/PEVA	Ganciclovir.	CMV retinitis in AIDS patients.
Examples of Implantable drug delivery devices for Pain Management, Infectitious disease and CNS Disorders:-				
ND Axxia Pharma-ceuticals	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.
ND	ND	PLGA	Isoniazid.	TB
ND	ND	PLGA	Isoniazid, Pyrazinamide.	TB
Med-Launch®	Sub-cutaneous.	PLGA	Risperidone.	Schizophernia.
Nd	Sub-cutaneous	PU	Risperidone.	Schizophernia.
Risperdal Consta®	Intra-muscular.	PLGA	Risperidone.	Schizophernia.

10. CONCLUSION

New drug candidate development is costly and time-consuming. It has been sought to improve the safety-efficacy ratio of "old" medications using various strategies such as individualising drug therapy, dose titration, and therapeutic drug monitoring. Other strategies that have been aggressively studied include delivering drugs at a controlled rate, gradual delivery, and targeted delivery. As a means of

improved pharmacological therapy, IDDSs have had some clinical and commercial success. However, it is vital to optimise performance qualities such as long-term biocompatibility and drug release kinetics. However, as shown above, a variety of commercial methods can achieve near-ideal zero-order release. Drug delivery systems that can be implanted: An overview of in vivo kinetic profiles over long periods of time. For chronically ill patients, IDDSs present a viable, cost-effective, and clinically acceptable alternative method of sustained medication administration.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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