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UPDATED REVIEW ON IMPLANTABLE DRUG DELIVERY SYSTEM

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ABSTRACT

It's a real need to develop drug delivery system that could maintain a specific site of action. Therefore, drug delivery system were developed to optimize the therapeutic properties of drug products and render then more safe effective and reliable as compared to many other drug delivery systems Implantable pumps and implants for variable rate delivery are at crude stage of development. Implantable devices allow the site specific drug administration where the drug is needed most for example implants include in the treatment of brain tumors or prostate cancer Implantable devices allow for sustained release by the therapeutic agent. The major advantages of this system contain targeted local delivery of drug at constant rate, lesser amount of drug is required to treat the disease condition minimization of probable side effect and better efficacy treatment due to development of implantable drug delivery devices it's possible to administer unstable drugs once a week to once a year that in the past required to take at frequent daily dosing.

Keywords: Implantable Drug Delivery, Modulated Drug Delivery, Implants, Drug Delivery Systems, Implantable Pumps, Recent Technologies.

INTRODUCTION:

New methods in the domain of drug delivery are taking place at a much faster pace in contrast to last two decades the experts predict that in the upcoming years, the drugs will be more specific in their pharmacodynamic action and more site selectivity of drug involves preventing the drug molecules from coming across the many biological the barrier that drugs molecule has to face before reaching the active receptor site some of the barriers include binding to the plasma proteins, transports across GIT membrane removal via the lymphatic system first pass hepatic effects and transports across the blood-brain barrier. All of these biological barriers prevent large

amounts of drug molecules (sometimes 100%) from reaching their target site of action to overcome various biological barriers the implantable drug delivery devices should be preferred to be used . Implantable drug delivery devices are free from such limitations associated with oral intra-venous. Topical drug administration subcutaneous implant-able drug delivery devices offer one unique advantage of redeemable mechanisms therefore the implants are the advanced drug delivery system that are inserted completely under the skin through a minor surgical incision or injected through a large bore needle the System delivers drugs and fluids into the bloodstream without repeated insertion of the needle. An implantable drug delivery system has the potential to reduce the frequency of patient-driven dosing and also to deliver the therapeutic command in a targeted manner presently this system is being utilized for many therapeutic applications such as contraception treatments of cancer dental disease etc. also Large number of companies are involved in the development of this system which is evident by the increased number of implants available in the market .(1)

Despite of progression and innovations in the novel administration of drugs, the regulation of the constant uniform plasma therapeutic index of drugs is still a big concern. The potential harm of using periodic oral or IV drug administration comprises of elevated concentration of medication (peaks) which contribute to adverse effects or inadequate concentration of medication (troughs) which can lead to failure of therapy. The old way to overcome the issue of the variable concentrations of medication includes a constant intravenous infusion rate dependent on the medication's pharmacokinetic profile. To minimize these unwanted outcomes, there is a need for a modern approach to achieving an optimized rate of drug discharge.

Implantable drug delivery systems have potential superiority in regional administration with better pharmacologic outcomes at minimum doses. Due to this, they lower possible toxicities thereby improving the likelihood of medication adherence. This kind of administration enables convenient delivery of medications that are ordinarily incompatible with being taken by oral way, escapes presystemic elimination as well as enzymatic destruction in the abdomen, thus, remarkably enhancing bioavailability.(2)

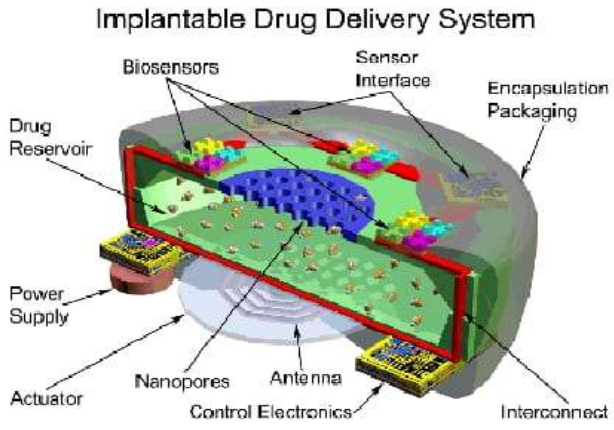

Figure 1: Illustration of an implantable drug device

Implantable drug delivery systems

Under the skin, implantable drug delivery systems are positioned to release medications into the bloodstream without the need for additional needle insertions. A sterile medication delivery system for a subcutaneous

implantation that includes a rod-shaped inner matrix with an elongated body and two ends is capabledelivering the medications over time at a predetermined rate.(3)

Typically, implantation is carried out via surgical techniques, needles, or special implantation devices in subcutaneous or intramuscular tissue. Due to their high fat content, which promotes sluggish drug absorption, limited innervation, good hemoperfusion, and low innervation, subcutaneous. tissue or intramuscular tissue are the perfect sites for the implantation of drug depot devices.Many medication classes are very interested in IDDSs, especially those that cannot be administered orally, have unpredictable gas trointestinal absorption, or benefit from site-specific dosage. Steroids, chemotherapy, antibiotics, and analgesics are a few examples. as well as birth control methods, as well as biologics like heparin or insulin. In order to improve patient compliance by reducing the frequency of drug administration throughout the course of treatment, rate-controlled drug release, environmental stability, biocompatibility, ease of sterilization, ease of manufacture &relatively low cost, mechanical strength, and lack of surgical procedure are all requirements for implantable drug delivery.(4)

Ideal properties of implantable drug delivery systems:

• Environmentally stable.

• Bioabsorbable.

• Sterile.

• Biostable.

• Improve patient compliance by reducing the frequency of drug administration over the whole amount of treatment.

• unleash the drug in a rate-controlled manner that ends up in increased effectiveness and reduction in facet effects.

• without delay recoverable by medical personnel to terminate medication.

• simple to manufacture and comparatively cheap.

• Easy to sterilize.

• Rate controlled release of drug.

• Easy to manufacture and relatively inexpensive.

• Good mechanical strength.

• Free from surgical procedure.

• The dosing frequency should be reduced to increase patient compliance and the drug during the entire treatment period.(5)

• The implant should be easy to evolve and should not be expensive.

• The implant should be easily removable by medical personnel to discontinue treatment.

• The implant should release the drug in a zero-order manner or in a controlled manner that leads to effective treatment and reduced

side effects.

• The implant should be safe, stable, and effective and should have enough mechanical strength.

• The implant should be easy to administer and would not require any special procedure for application.

• The implant should be free from any potential problems.

• Release the drug in a rate-controlled manner that leads to enhanced effectiveness and reduction in side effects.

• Readily retrievable by medical personnel to terminate medication.

• Free from surgical procedure.

• Minimum surface area, smooth texture.

• readily implantable and retrievable.

• provide cost-effective therapy.

• Nontoxic and non-carcinogenic.

The implantable therapeutic systems are mainly approached for

• long term,

• continuous drug administration, and

• controlled release[6]

Advantages Of Implantable Drug Delivery System

The implantable drug delivery system has the following disadvantages

Invasive: To implant certain cases major surgery is required which results in the formation of

scar at the site of implantation and also causes an uncomfortable feeling. Also, well-trained personnel is required for implanting the device.

Termination: Non-biodegradable polymeric implants need to be surgically removed from the body at the end of the treatment.

Danger of Device Failure: If the device fails to operate during the treatment due to any reason, the device should be surgically removed from the patient body.

Limited to Potent Drugs: In order to minimize patients' discomfort the size of the implant is usually kept small. Therefore most implants have limited loading capacity and are only suitable for potent medicament.[1]

Disadvantages

- **Invasive:** The patient must undergo either a major or minor surgical procedure to insert the implants.
- **Termination:** Non-biodegradable polymeric implants may be removed from the body after the conclusion of treatment via a surgical procedure.
- **Risk of device malfunction:** If the device doesn't function well during therapy forsome the reason, surgical steps should be done to remove it from the patient's body.
- **Only use potent pharmaceuticals:** Because the device is very small to lessen the discomfort of the patient, it is only possible to use very little amounts of potent drugs in this system.(4)

Foreign Body Reaction

According to the FDA's definition of implants, IDDS is presumed to have ongoing interaction with the bodily fluids and surrounding tissues. All implantable materials
and devices must satisfy the biocompatibility requirements, by the most recent safety
regulations, to be considered for clinical approval. A foreign body reaction (FBR) is the local immune response that develops as a result of the interactions between the implant and the surrounding tissues. FBR is a general protective mechanism that
creates a fibrotic capsule to isolate the unidentified poorly biodegradable material from the surrounding tissues and the body as a whole.(4)

The Benefits Of Implantable Drug Delivery Are:

1)**Convenience:** Effecting drug concentrations within the blood will be maintained for long periods by ways like continuous blood vessel infusion or frequent injections. However, underneath these regimens patients square measure typically needed to remain in hospital throughout administration for continuous medical observation. In distinction, implantation medical aid permits patients to receive medication outside the hospital setting with stripped medical police investigation. Implantation treatment is also characterized by a lower occurrence of infection-associated problems in comparison to an indwelling catheter-based infusion system.

2)**Compliance:** By permitting a discount, or complete elimination, of patient-involved dosing compliance is redoubled vastly. Someone will forget to require a pill, however drug delivery from AN implant is essentially freelance of patient input. Some implantable systems involve periodical filling despite this issue the patient has less involvement in delivering the desired medication By allowing a reduction, or complete elimination, of ok patient-involved dosing compliance is increased hugely. Patients can forget to take a medicine, but drug delivery from an implant is not dependent on patient input.

3)**Potential for controlled release:** Implants square measure offered that deliver medicine by zero-order controlled unleash dynamics. Zero order controlled unleash offers the benefits of:

a) the peaks (risk of toxicity) and troughs (risk of ineffectiveness) of standard therapy;

b) Reducing the dosing frequency;

c)Increasing patient compliance.

4)**Potential for intermittent release:** Externally programmable pumps will facilitate intermittent unleash. Intermittent unleash will facilitate drug unleash in response to such factors as:

(a) time unit rhythms;

(b) unsteady metabolic needs;

(c) The pulsatile unleash of the many peptides and proteins.

5) **Potential for bio-responsive protein:** Bio-responsive release from implantable is an area of ongoing research.

6)**Improved drug delivery:** Using an implant system drugs are delivered regionally or to be circulation with stripped interference purchase biological or metabolic barriers. For instance, the drug moiety bypassed the duct and also the liver. By passing impact is especially of profit to medicine, that square measure either absorbed poorly or simply inactivated within the duct and/or the liver before general distribution. The drug is distributed locally or in systemic circulation with the least interference by metabolic or biological barriers.

7)**Flexibility:** Considerable flexibility is feasible with these systems, within the alternative of materials, ways of manufacture, degree of drug loading, drug unleash rate etc. Commercial AN implantable dose kind diversifies the merchandise portfolio of a given drug. In the choice of materials, methods of manufacture, degree of drug loading, drug release rate etc. considerable flexibility is possible.[6]

Non-degradable and biodegradable implant systems :

Non-degradable systems There are several types of nondegradable implantable drug delivery systems available on the marketplace today, but the nondegradable matrix system and reservoir systems are the two most common forms In the polymeric matrix system, the drug is dispersed homogeneously, inside the matrix material. Slow diffusion of the drug through the polymeric matrix material provides sustained release of the drug from the delivery system. The reservoir-type system, on the other hand, consists of a compact drug core surrounded by a permeable nondegradable membrane whose thickness and permeability properties can control the diffusion of the drug into the body.The release kinetics of the drug from this system suggest that if the concentration of the drug within the reservoir is in constant equilibrium with the inner surface of the enclosed membrane, the driving force for the diffusional release of the agent is constant and zero-order release kinetics of the drug from the delivery system is obtained. This type of system, however, has several disadvantages. The outer membrane of most of these systems is nondegradable. Therefore, after the drug has been released, minor surgery is necessary for the removal of the delivery system from the body. There is also a possibility that membrane rupture will potentially lead to “drug dumping” during therapy. Depending on the type of drug involved in the reservoir, “drug dumping” may result in untoward toxic side effects from drug plasma concentrations that exceed maximum safety levels. The possibility of “drug dumping” has made the reservoir system a less popular method of drug delivery.

Table 1: Drugs used for the implantable drug delivery system

Name of Drugs	Purpose
Progestin+estradiol,megestrol,norgestrel	Contraception
Ibuprofen,naproxen,phenylbutazone	Polyarthritis
Cyclophosphamide,merchloroethamide	Cancer
Deoxycortisone	Antihypertensive studies
Morphine	Narcotic addiction studies
Pilocarpine	Glaucoma

Biodegradable systems:

Biodegradable systems have gained much popularity over non-degradable delivery systems. The major advantages of biodegradable systems include the fact that the inert polymers, used for the fabrication of the delivery system, are eventually absorbed or excreted by the body. This alleviates the need for surgical removal of the implant after the conclusion of therapy thereby increasing patient acceptance and compliance. However, developing biodegradable systems is a more complicated task than formulating nondegradable systems. When fabricating new biodegradable systems, many variables must be taken into consideration. For instance, the degradation kinetics of the polymer, in vivo, must remain at a constant rate to maintain sustained release of the drug. Many factors can affect the rate of degradation of the polymer in the body. Alterations in body pH or temperature can cause a transient increase or decrease in the degradation rate of the system. The surface area of the delivery system also plays an important role in its degradation. As the system is eroded, the surface area of the implantable system decreases. Thus, the change in shape of the drug delivery system that will occur, in vivo, should be taken into account during the formulation design. To attain a more uniform and constant release, it is necessary to use geometrical shapes whose surface area does not change as a function of time during erosion. A flattened slab-type shape that has no edge erosion is the shape that approximates most closely a zero-order release kinetic profile. Some manufacturers have also designed systems that contain a bioerodable inert core coated with the active drug matrix to alleviate the change in surface area problems encountered during erosion. Another problem that occurs with biodegradable systems is the slow diffusion of the drug from the polymer matrix. Diffusion of the drug usually occurs at a slower rate than the bioerosion of the system and is dependent upon the chemical nature of the polymeric substance utilized in the formulation of the drug delivery system.

Formulation of implantable drug delivery systems:-

Implantable drug delivery systems are an important area of research and development in the field of medicine. These systems are designed to provide controlled and sustained release of drugs within the body, offering several advantages such as improved patient compliance and reduced side effects. The formulation of implantable drug delivery systems involves several key steps:

1. **Drug Selection:** The first step is to select the appropriate drug for the intended therapeutic purpose. Factors such as drug solubility, stability, and release kinetics must be considered.

2. **Polymer Selection:** Biocompatible and biodegradable polymers are commonly used to encapsulate the drug. Polymers like PLGA (poly(lactic-coglycolic acid)) are often chosen due to their versatility.

3. **Drug-Polymer Compatibility:** Ensuring compatibility between the drug and polymer is crucial to maintain drug stability and achieve controlled release.

4. **Formulation Design:** The drug and polymer are combined to create a formulation. This can be done using various techniques, such as solvent evaporation or hot melt extrusion, depending on the chosen materials.

5. **Controlled Release Mechanism:** Implantable systems can be designed for various release mechanisms, including diffusion-controlled, erosion-controlled, or osmotic-controlled. The choice depends on the desired release profile.

6. **Biocompatibility and Safety:** The formulation must be thoroughly tested for biocompatibility and safety to ensure it won't cause harm when implanted in the body.

7. **Implantation Site Selection:** Depending on the therapeutic target, the appropriate site for implantation must be chosen. For example, subcutaneous, intramuscular, or intraocular implantation may be considered.

8. **Release Kinetics Optimization:** The release rate of the drug must be carefully controlled to achieve therapeutic efficacy. This may involve adjusting the polymer composition or implant geometry.

9. **Quality Control and Manufacturing**: Stringent quality control measures are necessary during manufacturing to ensure consistency and safety of the implantable drug delivery systems.

10. **Regulatory Approval:** Implantable drug delivery systems must undergo rigorous testing and seek regulatory approval before they can be used in clinical settings.

11**. Clinical Trials**: Clinical trials are conducted to evaluate the safety and efficacy of the implantable system in humans.

12. **Post-Market Surveillance**: Continuous monitoring and evaluation of the system's performance and any potential adverse effects in real-world use. Research in this field is ongoing, and advancements in materials science, Nanotechnology, and biotechnology continue to drive innovation in the formulation and development of implantable drug delivery systems[9]

Current Therapeutic Applications:

1. Implantable drug delivery devices have the potential to be used for a wide variety of clinical applications in areas including, but not limited to: women’s health, oncology, ocular disease, pain management, infectious disease and central nervous system disorders.

2. Women’s health is one area where implantable drug delivery devices have had a large impact, particularly in their use for contraception.

3. In 1990, Norplant became the first implantable contraceptive device to be approved.

4. Implantable long-acting contraceptives are among the most effective forms of contraception, with an annual pregnancy rate of less than 1% for women using these methods

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Mechanism of implantable drug delivery systems:

Most implanted drug delivery systems are based on three basic delivery mechanisms.

- Swelling control.
- Osmotic pumping.

• Diffusion. In solvent-activated systems, a swelling or osmotic mechanism is involved.

Applications have been made in the areas of dentistry, immunization, anticoagulation, cancer, narcotic antagonists, and insulin delivery.(7)

Method of preparation of implantable drug delivery systems:-

Implantable drug delivery systems are designed to release drugs gradually over an extended period. Here are some common ways to prepare them.

1. Encapsulation: Drugs are encapsulated in biocompatible materials such as polymers and lipids. As the material breaks down over time, the active ingredients are released. Examples of this include microspheres and liposomes.

2. Reservoir systems: These consist of a drug reservoir surrounded by a semi-permeable membrane. The active ingredient diffuses through the membrane in a controlled manner. One example is an osmotic pump.

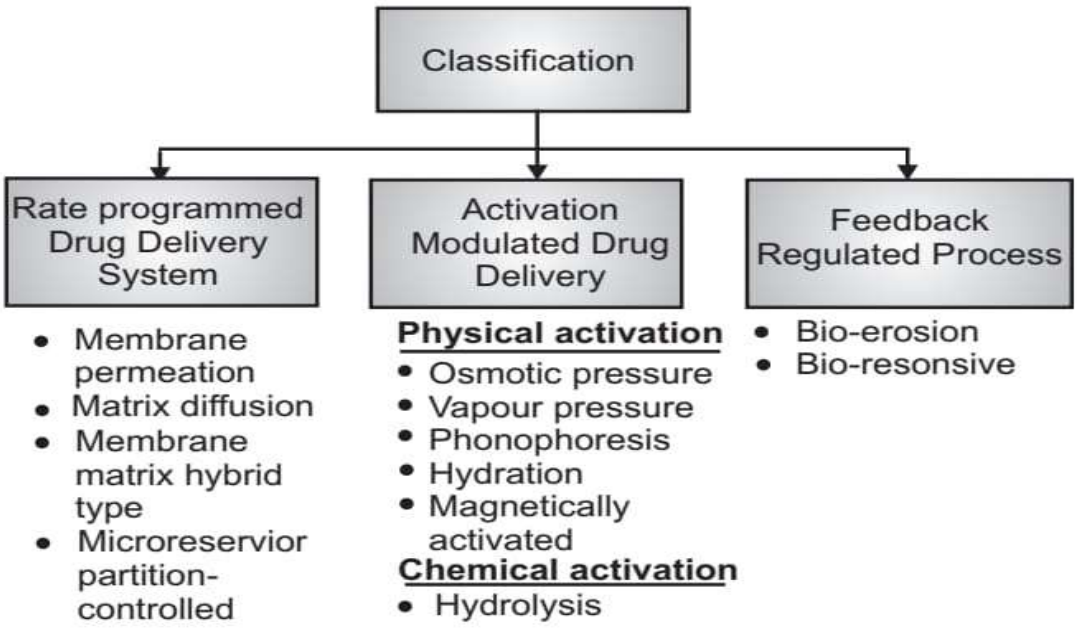
3. Biodegradable Implants: Biodegradable polymers are used to create implantable devices that gradually break down and release drugs. This eliminates the need for removal surgery.

4. Electrospinning: In this technique, a polymer solution is electrostatically spun to form nanofibers. Incorporation of drugs into these fibers allows for controlled release when the fibers dissolve.

5. Incorporation into devices: Drugs can be incorporated into medical devices such as stents and orthopedic implants that slowly release the drug locally over time

. **6. Injectable Depots:** Injectable implants, such as subcutaneous pellets, are surgically implanted and slowly release the drug as they dissolve or degrade.

7. Nanotechnology: Nanoparticles such as nano capsules and nanospheres can encapsulate drugs for controlled release. These particles can be manipulated to release drugs based on environmental factors or stimuli.(9)



BIOCOMPATIBILITY OF' IMPLANTS:

Many different types of materials have been used for implantable drug delivery systems, ranging from bioerodible collagen through to nonbiodegradable titanium metal. It is important that all materials used for implants being physically and chemically stable, but vitally important that the materials are biocompatible. Desirable criteria for implantable drug delivery biomaterials include:

1)The biomaterial must be inherently chemically inert in that it does not cause any biological effect or interact with other adjuvants in the formulation.

2) The biomaterial must not be physically or chemically (for mechanical ICRDDSs) modified by local tissues.

3) It must not cause any inflammatory or foreign body reaction in the body.

4) The biomaterial must not be carcinogenic. That criteria are includes the breakdown products from bioerodible polymers.

5) The biomaterial should not cause any allergic or hypersensitivity reactions.

6) It must be sterilizable without affecting any chemical, physical or mechanical properties.

7)Must be compatible with a wide range of & does not cause any thrombogenicity.

Therapeutic Applications Of IDDS:

Generally, IDDS involving the following important applications such as:

1)Women's health

2) Diabetes

3) Cancer

4) In Tuberculosis

5) Immunization

6) Ocular therapy

7) Cardiovascular system

8) Pain management.

1)Women's Health: In addition to subcutaneous implants, novel drug delivery forms such as intrauterine devices and intravaginal rings and are finding increasing applications in area of women health. Ex. Norplant was a popular 5- year non biodegradable implant.

2) Diabetes: Diabetes is a chronic disease sate where implantable systems have the potential to transform the current standard of both diagnosis and treatment.

3) Cancer: The major challenge in anticancer therapy is to develop IDDS's to deliver chemotherapeutic drugs safety and effectively without side effects.Ex. Zoladex.

4) In Tuberculosis: The fundamental problems in the treatment of TB long duration of therapy and side effects of drugs. Which can hamper patient lifestyle and induce patient non- compliance, treatment failure, and development of drug resistant strains.

5) Ocular therapy: Membrane controlled devices, implantable silicone devices, and implantable infusion systems have been evaluated to provide prolonged ocular delivery.

6)Associate in Nursing implantable drug delivery device would be ideal to create positive patient compliance and completion of the treatment. Poor patient compliance to tranquillizer treatment could also be a typical incidence and causes a high risk of relapse, treatment and completely different negative outcomes.

7)social unit of medical aid agents is that the most common route of administration. However, it generally involves delivery of the agents at their most tolerated dose which can cause severe side-effects like blood disease and cardiomyopathy [8]

Discussion :

The manufacturing of drug-eluting implants often includes complex processes and advanced machines. Implants need to be reliable, reproducible and adequately perform consistently over lengths of time, meaning they should be both durable and expected to release drug predictably. To meet these criteria, the fast-growing field of 3D printing has become perhaps the most important method in implant production nowadays.

CONCLUSION :

The market for polymeric implantable drug delivery devices is one that is growing. The advantages that this delivery route demonstrate over more conventional drug delivery methods, such as oral tablets, make it likely that it will continue to grow and that the number of implantable drug delivery devices on the market will increase. However, implantable drug delivery devices have a number of disadvantages including the invasive nature of this delivery method. The advantages that these devices can offer with respect to patient compliance, stability of drugs within these devices and removability if adverse reactions occur, outweigh these disadvantages that exist. Current therapeutic applications of implantable drug delivery devices are covered in this article. However, the use of implantable drug delivery devices has the potential to span far greater than these conditions mentioned. One such condition where these devices could have a major impact is in the treatment or prevention of human immunodeficiency disease (HIV). 3D printing offers an interesting prospect as an exciting new manufacturing method, one which provides a unique opportunity to produce complicated designs or personalised implantable devices. However, when compared to more traditional methods of implantable device manufacture, such as hotmelt extrusion or compression moulding, this manufacturing method comes with additional scale up and regulatory challenges. The FDA approval of the first 3D printed tablet in 2015 makes the reality of 3D printing as a pharmaceutical manufacturing method much more likely.

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