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IMPLANTABLE DRUG DELIVERY SYSTEM

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ABSTRACT

Drug delivery systems capable of offering the flexibility of maintaining pharmacologically effective therapeutic drug levels for extended periods of time while also allowing "dosing-on demand"would be considered extremely valuable tools in modern medicine. Implantable drug delivery systems offer physicians the choice of precision delivery, either locally or into systemic circulation, while guaranteeing optimal dosing over the course of treatment. The major advantages of these systems includes targeted local delivery of the drug at a constant and predetermined rate, thereby minimizing dose required and potential side effects, while improving therapeutic efficacy. These systems are particularly useful for diseases requiring long term therapy or facing challenges with patient compliance, such as cardiovascular disease, tuberculosis, diabetes, cancer, and chronic pain management to name a few. This chapter starts with a review of various types of implantable drug delivery systems from biomaterial-based to electro-mechanical systems. Further, design approaches to optimal drug delivery including methods to tailor drug release profiles and the mechanism of release kinetics are presented. Potential therapeutic applications and biocompatibility related issues are briefly discussed next. Finally, this chapter concludes with a summary of future perspectives of implantable drug delivery systems, particularly in their applicability to precision and personalized medicine.[1]

KEYWORDS: Implantable, drug delivery, design, manufacture.

INTRODUCTION

Orally administered drug must be protected against denaturation in the gastrointestinal tract and should be capable of absorption across the wall of the stomach or the intestine. After absorption and upon reaching the portal circulation, it must be resistant to hepatic enzymes. The rate of drug absorption and elimination should ensure the blood levels within the therapeutic range. Moreover, the amount of intact drug that reaches the site of action should be sufficiently large to obtain desired therapeutic effect but insufficient to cause untoward side effects. A controlled drug action may be achieved by either chemically modifying the drug moiety or by formulating it in a specific way to control its release. Oral controlled release dosage forms can provide efficacy for about 24 hours. The main drawback of oral dosage form is the long transit time of approximately 12hours through the gastrointestinal tract (GIT). If drug cannot be administered orally, a parenteral route of delivery is an alternative. Many proteins/peptides and other drugs, which are susceptible to the adverse conditions of GIT, are administered intravenously. Unfortunately, in intravenous drug administration, the duration of drug action is short for majority of therapeutically active agents and therefore frequent injections are required. The development of injectable controlled-release dosage forms is more likely to succeed commercially than alternative routes of delivery, assuming that these dosage forms provide the desired efficacy and safety. In case of topical drug administration, the percutaneous absorption of most drugs is limited due to physiological characteristics of the drugs and presence of highly impermeable stratum corneum. Implantable drug delivery devices are devoid of aforementioned limitations associated with oral, intravenous, topical drug administration vis-à-vis subcutaneously implantable drug delivery devices offer one unique advantage of a retrievable mechanism.

- Implants are drug delivery systems which provide controlled delivery of drug over a period of time at the site of implantation.
- Implants are small sterile solid masses consisting of a highly purified drug made by compression or molding or extrusion.
- Implants are intended for implantation in the body subcutaneous or intramuscular tissue by a minor surgical incision or injected through a large bore needle.

Types of Implantable Drug Delivery systems

1. Non biodegradable implants
2. Biodegradable implants[2]

1. NON BIODERADABLE IMPLANTS

- The drug is dispersed homogeneously, inside the polymeric matrix through which the drug diffuses slowly providing sustained release.
- As the outer membrane is non degradable 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.

2. BIODERADABLE IMPLANTS

- The inert polymers, used are eventually absorbed or excreted by the body.
- No need for surgical removal of the implant after the conclusion of therapy.

CLASSIFICATION OF IMPLANTABLE DRUG DELIVERY SYSTEMS

1. Rate programmed drug delivery
2. Activation modulating drug delivery
3. Feed back regulated process

1. RATE PROGRAMMED DRUG DELIVERY

- Polymer Membrane permeation controlled.
- Matrix diffusion.
- Membrane matrix hybrid type
- Microreservoir partition controlled drug delivery

2. ACTIVATION MODULATING DRUG DELIVERY

- Physical activation
- Osmotic pressure
- Vapor pressure
- Phonophoresis
- Hydration.
- Magnetically activated.
- Chemical activation Hydrolysis.

3. FEED BACK REGULATED PROCESS

- Bioerosion
- Bioresponsive

CLASSIFICATION BASED ON ROUTES OF ADMINISTRATION

✓ **Subcutaneous implants**: Beneath the skin, for prolonged drug administration.

✓ **Intra ocular implants/inserts**: In the eye compartment Ex:Ocusert

✓ **Intravaginal inserts:** Inserted in the vagina, specially hormonesEx: Intravaginal. Medroxy progesterone acetate

✓ **Intrauterine implants/inserts:** Inserted in the uterus specially contaceptives, Ex:Copper T.

1. RATE PROGRMMED DRUG DELIVERY SYSTEMSR

Release of drug molecules from the delivery systems has been pre- programmed at specific rate profiles. Diffusion of drug molecules into the medium is controlled.

B. Polymer Membrane permeation controlled drug delivery.
C. Matrix diffusion controlled drug delivery systems
D. Membrane matrix hybrid type
E. Microreservoir partition controlled drug delivery.[3]

A.POLYMER MEMBRANE PENETRATION CONTROLLED DRUG DELIVERY

- In this type, drug is totally or partially encapsulated within drug reservoir.
- Its drug release surface is covered by a rate-controlling polymeric membrane having a specific permeability.
- Drug reservoir may exist in solid, suspension or solution form.
- polymeric membrane can be fabricated from a nonporous (homogeneous or heterogeneous) polymeric material or a microporous (or semipermeable) membrane.
- The encapsulation of drug formulation inside the reservoir compartment is accomplished by injection molding, spray coating, capsulation, microencapsulation, or other techniques.

Different shapes and sizes of drug delivery systems can be fabricated.
Ex. Transderm-Nitro

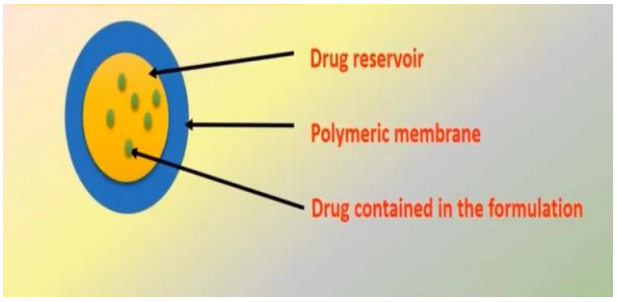

Fig. 1: Polymer membrane penetration controlled drug delivery.

It is designed for application on to intact skin for 24 hrs to provide a continuous transdermal infusion of nitroglycerin at dosage rate of 0.5 mg/cm/day for the treatment of angina pectoris.[4]

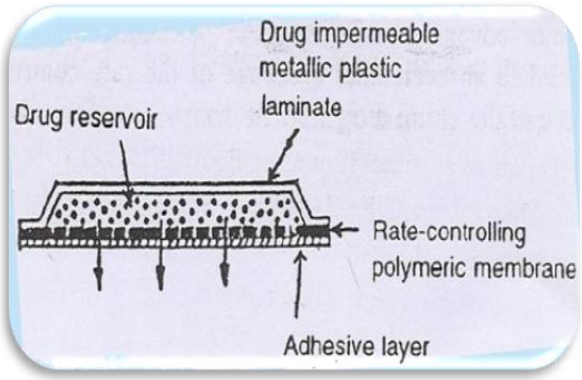

FIG. 2: Polymer membrane penetration controlled drug delivery.

B. MATRIX DIFFUSION CONTROLLED DRUG DELIVERY

- Drug reservoir is prepared by homogeneously dispersing drug particles at a rate controlling polymeric matrix fabricated from either a lipophilic or hydrophilic polymer.
- The drug dispersion in a polymer matrix is done by
- Blending finely divided drug particles with a liquid polymer or a viscous base followed by cross linking of the polymer chain
- Mixing the drug with a polymer at an elevated temperature
- Dissolving drug and polymer in a common solvent followed by solvent evaporation at elevated temperature or under vacuum.
- The resultant drug polymer dispersion is then molded or extruded to form a drug delivery devices of various shapes.

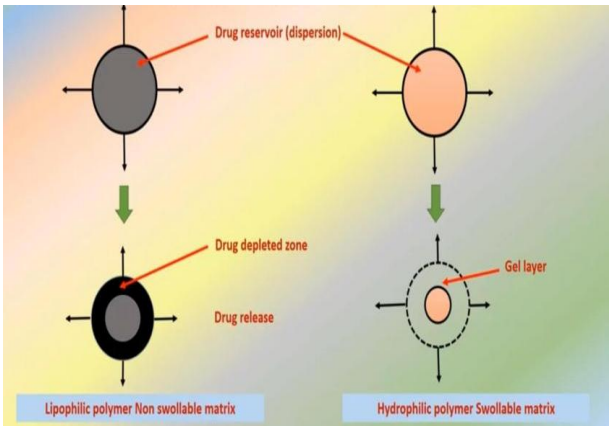

FIG. 3: Nitro-dur TDDS.

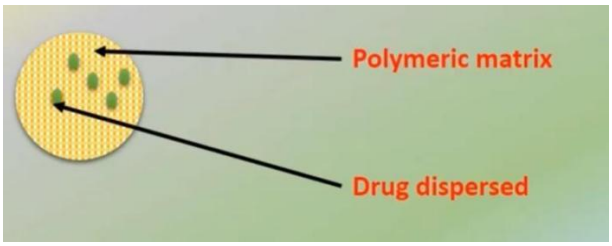

FIG. 4: Matrix diffusion controlled drug delivery.

C.MICRORESERVOIR PARTITION CONTROLLED DRUG DELIVERY

- In this type drug reservoir is fabricated by micro dispersion of aqueous suspension of a drug using a high energy dispersion technique in to a biocompatible polymer such as silicone elastomer to form a homogenous dispersion of many discrete, unreachable microscopic drug reservoir
- Depending on the physicochemical properties of the drug and the desired rate of drug release, the device can be further coated with polymer to modify mechanism and rate of release. Ex. Nitro-Dur

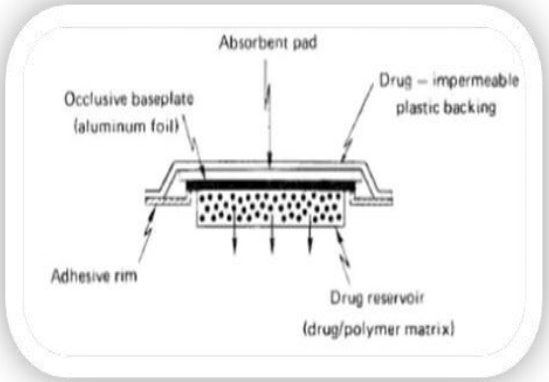

FIG. 5: Nitro-Dur.

- Nitro-Dur is a transdermal system contains nitroglycerin in acrylic based polymer adhesives with a resinous cross-linking agent to provide a continuous source of active ingredient for 24h.

MATRIX HYBRID TYPE DRUG DELIVERY SYSTEM

Membrane permeation controlled ⟷ Matrix diffusion controlled

- The aim is to take advantage of controlled release kinetic offered by Polymer membrane permeation-controlled drug delivery system and to avoid risk of dose dumping from reservoir compartment of this type of drug delivery system.[5]
- Drug reservoir is formed by dispersion of drug in to a polymer matrix which is further coated by a semi permeable polymeric membrane. Example is a Norplant II sub dermal system.

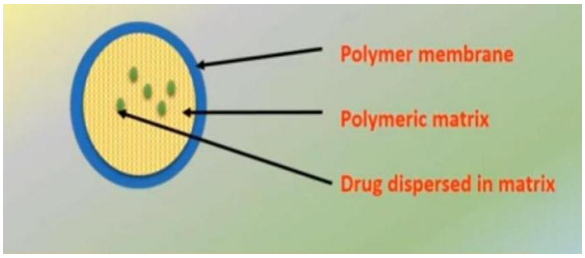

FIG. 6: Norplant 1.

Six silastic (silicon rubber) capsules containing 35 mg
Five year effectiveness.
Norplant 2:
Two solid silicon rod 44 mm x 2 mm size
Rods are inserted beneath the skin of forearm/upper arm
70 mg of LNG release 30 to 35 mcg daily
Effective contraception for three years.

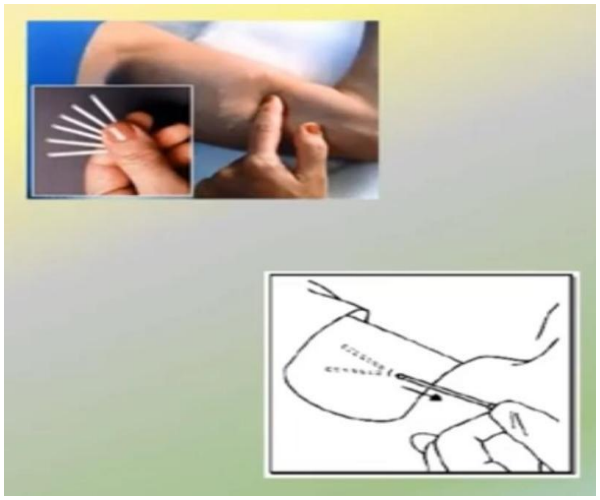

FIG. 7: Norplant 1, Norplant 2.

D.ACTIVATION MODULATED DRUG DELIVERY SYSTEM

The release of drug molecules from the delivery system is activated by some physical, chemical or biochemical process facilitated by an external energy supplier and the rate of release is then regulated by the processes applied or input of energy.[6]

A. Hydration activated drug delivery system.
B. Osmotic pressure activated drug delivery device.
C. Vapor pressure activated drug delivery system.
D. Hydrolysis activated drug delivery device.
E. Magnetically activated drug delivery device.

A.HYDRATION ACTIVATED DRUG DELIVERY SYSTEM

✓ This system depends on the hydration induced swelling process by tissue fluid at implantable site to activate drug release.

✓ In this system drug reservoir is dispersed in to swellable polymer matrix fabricated from hydrophilic polymer that become swollen upon hydration.

✓ Drug is released from microscopic water filled pore channels in to the polymer matrix

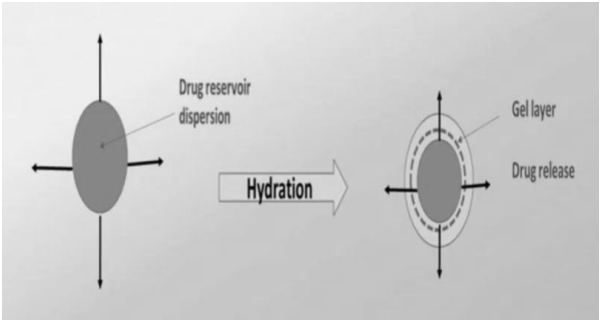

FIG. 8: Hydration Activated Drug Delivery System.

Release rate of drug is controlled by swelling of the polymer matrix.

Ex: Norgestomet releasing HYDRON implant.

B.OSMOTIC PRESSURE ACTIVATED DRUG DELIVERY SYSTEM

- In this type of controlled drug delivery system the release of the drug takes place due to osmotic pressure.
- Drug reservoir which can be either a solid or a suspension is contained in a semipermiable housing.
- The release is activated through a specially formed orifice and rate of release is modulated by controlling the osmotic gradient.
- Thus release rate is dependent on water permeability of membrane, solubility of osmogen, effective surface area of semipermeable housing as well as osmotic gradient.
- In this type of DDS, the drug in solution is released through a specialized laser drilled delivery orifice at a constant rate under a controlled gradient of osmotic pressure.
- External component: Rigid semipermeable housing made up of substituted cellulosic polymers containing an osmotically active salt.
- Internal compartment: Drug reservoir enclosed by a flexible partition layer and osmotic agent impermeable polyester bag.[7]

Ex: Alzet Osmotic Pump.

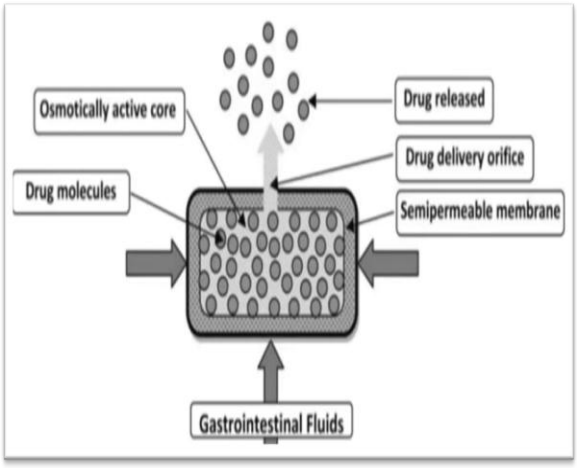

FIG. 9: Alzet Osmotic Pump.

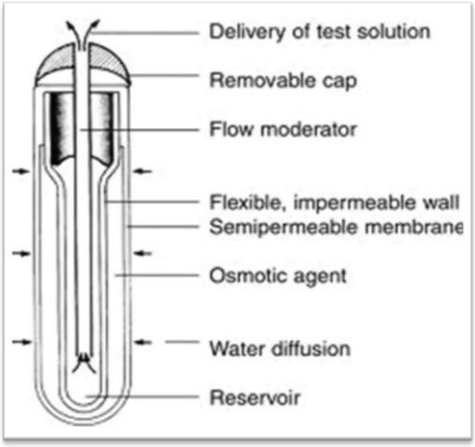

FIG. 10: Osmotic Pressure Activated Drug Delivery System.

C.VAPOR PRESSURE ACTIVATED DRUG DELIVERY SYSTEM

- In this system, the drug reservoir in a solution formulation, is contained inside an infusate chamber.
- It is physically separated from the vapor pressure chamber by a freely movable bellows.
- The vapor chamber contains a vaporizable fluid, such as a fluorocarbon which vaporizes at body temperature and creates a vapor pressure.
- Under the vapor pressure created, the bellows move upward and forces the drug solution in the infusate chamber to release, through a series of flow regulators and the delivery cannula into the blood circulation at a constant flow rate.[8]

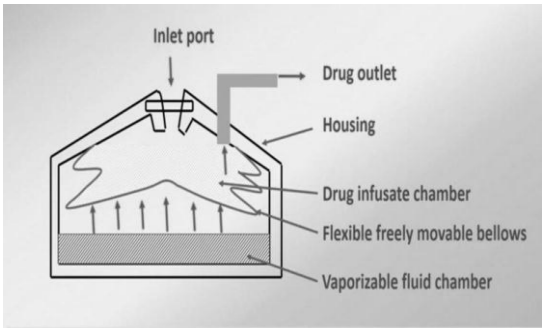

FIG. 11: Infusaid, implantable infusion pump for constant infusion of heparin in anticoagulation treatment.

D.HYDROLYSIS ACTIVATED DRUG DELIVERY SYSTEM

- These systems are prepared from a bio-erodible or bio-degradable polymer such as polylactide or glycolic)polymer, /Poly(anhydride) poly(lactide-glycolide), Co(lactic Poly (orthoester) Copolymer.
- Release of drug is activated by hydrolysis of a bioerodable polymer by the cell fluid at the implantation site.
- This system is made by dispersing loading dose of a drug with a biodegradable polymer, which is then molded in to pellet or a bead shaped implant.

Ex: ZOLADEX system, LHRH(goserelin) releasing biodegradable sub dermal implant.[11]

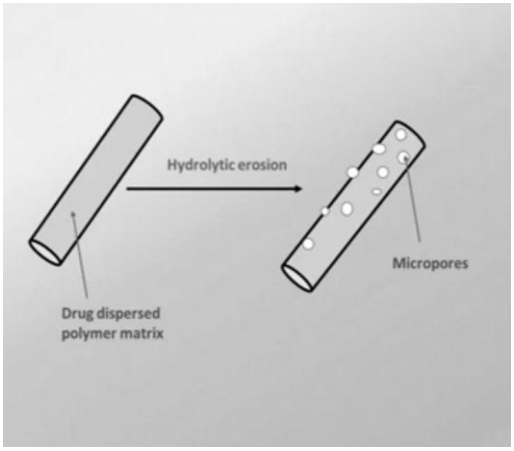

FIG. 12: Hydrolysis Activated Drug Delivery System.

E.MAGNETICALLY ACTIVATED DRUG DELIVERY SYSTEM

A magnetic wave triggered mechanism is incorporated in to drug delivery device and drug can be triggered to be released at varying rate depending on the magnitude and duration of the electromagnetic energy applied.[10]

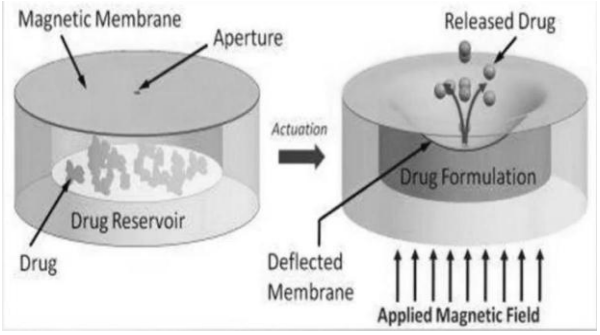

FIG. 13: Magnetically activated drug delivery system.

FEEDBACK REGULATED DRUG DELIVERY SYSTEMS

- The release of drug molecules is activated by a triggering system, such as a biochemical substance in the body, through some feedback mechanisms.
- The rate of drug release is regulated by the concentration of the triggering agent detected by a sensor built in the system.

✓ Bioresponsive Drug Delivery.
✓ Bioerosion regulated drug delivery system.[9]

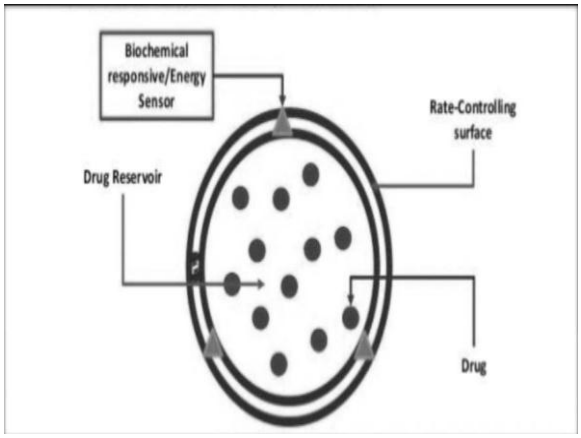

FIG. 14: Feedback regulated drug delivery systems.

CONCLUSION

Recently Implantable drug delivery is one ofthe technology sectors that often overlooked in the development of new drug delivery by the formulation, research and development in many pharmaceuticals. Implanted drug delivery technologies have ability to reduce the frequency of patient driven dosing and to deliver the compound in targeted manner. Many product utilizing implant delivery technologies are being utilized for many therapeutics applications such as, dental, ophthalmic, oncological disease. As with any implanted material, issues of biocompatibilityneed to be investigated, such as the formation of afibrous capsule

around the implant and, in the case oferosion-based devices, the possible toxicity orimmunogenicity of the by-products of polymer degradation. Additionally, convenient methods of triggering drug delivery from the externally controlled delivery systems need to be developed in order for them to be of practical use. These issues, coupled with the potential therapeutic benefits of pulsatile dosing regimens, should ensure that the current high level of interest in this area will extend well into the future and result in significant advances in the field of controlled drug delivery.

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