International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 5(1): January-February 2015

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Review Article……!!!**

Received: 19-12-2014; Revised: 14-01-2015; Accepted: 15-01-2015

A STUDY OF POLES APART LOOM OF IMPLANTABLE DRUG DELIVERY SYSTEM AND ITS APPLIANCES

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Keywords:

Implants, Pumps reservoir, Polymer matrix, Biodegradable Polymer

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ABSTRACT

Effective drug concentration in the blood stream can be maintained for long periods by methods such as continuous intravenous infusion or frequent injections. Permits patient to receive medication outside the hospital, with minimal medical surveillance. Implantation therapy is also characterized by a lower incidence of infection related complications in comparison to an indwelling catheter based infusion system. Allowing a reduction or complete elimination, of patient involved dosing, compliance is increased. Implants are available which deliver drugs by zero order controlled release kinetics. Externally programmable pumps can facilitate intermittent release. Drug is delivered with minimal interference by biological and metabolic barriers. There is flexibility in the choice of materials; method of manufacture, degree of drug loading, drug release rate etc[1].The first is the use of implanted electrically driven pumps which can be refilled by simple injection of the drug through a septum into the pump reservoir. The second approach is the use of erodible implants. Here, the requirements are for a system that will be safe and whose erosion rate can be sufficiently well controlled to give a reproducible and precise drug-release rate over the entire lifetime of the implant. Various types of implants are used now a day which are useful for the replacement like dental implants, vision and hearing purpose like cochlear and brain implants etc.[2]

1. INTRODUCTION[3, 4]

Lafarge pioneered the concept of implantable therapeutics system for long term & continuous drug administration in 1861 with the development of subcutaneously implantable drug pellet. Solid pellet containing crystalline hormone were prepared to mimic the steady and continuous secretion of hormones from the gland. Implantable drug delivery systems are designed to transmit drugs and fluids into the bloodstream without the repeated insertion of needles. These systems are particularly well suited to the drug delivery requirements of insulin, steroids, chemotherapeutics, antibiotics, analgesics, total parenteral nutrition, and heparin. Implantable drug delivery systems are placed completely under the skin usually in a convenient but inconspicuous location. The patient is aware of only a small bump under the skin. Because the device is completely subcutaneous, with no opening in the skin, there is little chance of infection or interference with daily activities.

While it is possible to surgically implant and remove drug-concentrating devices or polymeric matrices, the requirement for such intervention could have a significant negative impact on the acceptability of a product candidate. Two approaches to this problem seem possible. The first is the use of implanted electrically driven pumps which can be refilled by simple injection of the drug through a septum into the pump reservoir. An advantage of such pumps is that the pumping rate can be regulated by microprocessor control (it can be reliably programmed and altered via radio signals). The major disadvantages are the large size of the devices and the need for surgical implantation with the possibility of infection. The second approach is the use of erodible implants. Here, the requirements are for a system that will be safe and whose erosion rate can be sufficiently well controlled to give a reproducible and precise drug-release rate over the entire lifetime of the implant.

OBJECTIVE TO DEVELOPMENT OF IMPLANTABLE DRUG DELIVERY SYSTEM[3]

A. Diffusion controlled system

1. Membrane permeation –controlled system

In this implantable controlled release drug delivery device the drug reservoir is encapsulated within a capsule shaped or spherical compartment that is totally enclosed by a rate controlling polymeric membrane. The drug reservoir can be either drug solid particles or dispersions of drug solid particles in a liquid or a solid type dispersing medium. The polymeric membrane can be fabricated from a homogenous or heterogeneous nonporous polymeric material or a micro porous membrane. The encapsulation of drug reservoir inside the polymeric membrane can be accomplished by molding capsulation, microecapsulation, or other techniques.

An example of this type of implantable drug delivery device is the Norplant subdermal implant consist of levonorgestrel.

Fig 1. Norplant subdermal implants

2. Matrix diffusion controlled system

In this, the drug reservoir is formed by homogeneous dispersion of drug solid particle throughout a lipophillic or hydrophilic polymer matrix. The dispersion of drug solid particle in the polymer matrix can be accomplished by blending drug solid with a viscous liquid polymer or a semi solid polymer at room temperature, followed by cross linking of polymer chains. This drug polymer dispersion is then extruded to form drug delivery device of various shapes and sizes.

An example of this type of implantable drug delivery device is the Compudose implant for estradiol manufactured by Elanco's .

Fig 2. Compudose implants

It can also be fabricated by dissolving the drug solid and/or the polymer in a common organic solvent followed by coacervation and solvent evaporation at an elevated temperature and/ or under a vacuum to form microsphere.

B. Activation controlled systems

Several implantable pumps for the sustained release of drug have been developed utilizing activated system to mechanically push the medication into body at a controlled rate. Among many such systems the following category of products have received much attention and some of them have also undergone commercialization.

TYPES OF IMPLANTS ON THE BASIS OF POLYMERS[3]

A. Non-Degradable Polymeric Implants[1,4]

One of the methods of steroid release involves the use of a nondegradable polymer, silastic. The polymer is shaped into capsules or rods, which are implanted subdermally. The advantages of these devices are that their effectiveness does not depend on patient compliance, the duration of action is longer, and the effects can be terminated by removing the implant. The usefulness of such implants, however, may be limited by the occurrence of menstrual abnormalities and systemic side effects. A primary disadvantage with their use is the need for medical personnel to implant and remove them. Additional concerns are the possibility of the implants migrating, thus making retrieval difficult.

Two main types-

1. Reservoir devices, in which drug is surrounded by a rate controlling polymer membrane.
2. Matrix devices, in which the drug is distributed throughout the polymer matrix.

1. Reservoir type non-degradable polymeric implants-

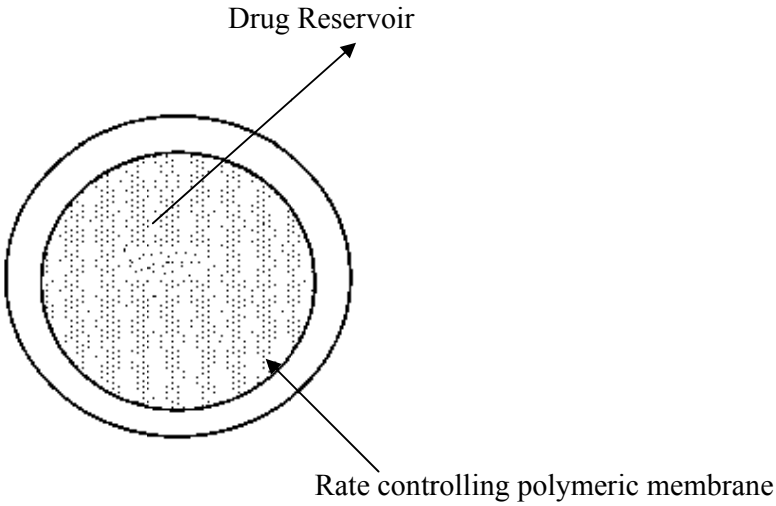


Fig 3. Reservoir type polymeric implants

2. Martix type non-degradable polymeric implants-

Summary of drug release properties of reservoir, matrix non-degradable implant devices

System	Release Mechanism	Release Properties	Release Kinetics
Reservoir	Diffusion through a polymeric membrane(which can be compact or microporous)	Constant drug release with time	Zero order release $M \alpha t$
Matrix	Diffusion through a polymeric matrix	Drug release decreases with time	Square root of time release $M \alpha t^{1/2}$

3. Reservoir/matrix hybrid-type polymeric implants-

Such systems are designed to improve the "M α $t^{1/2}$" release kinetics of matrix system, so that release approximates the zero-order release rate of a reservoir device.

Examples of these types of systems are

- ✓ Syncro-Mate-C subdermal implant
- ✓ Implanon

Limitations of Non-degradable polymeric implants-

- ✓ The implants must be surgically removed after they are depleted of drug.
- ✓ Water soluble or highly ionized drugs and macromolecules, such as peptides and proteins, have negligible diffusivities through dense hydrophobic membranes.
- ✓ It is difficult to achieve versatile release rates.

B. Biodegradable Polymeric Implants[1,4]:-

Biodegradable polymers are the most recent developments in contraceptive drug delivery systems. They appear to be an excellent contraceptive strategy since they can provide a programmed rate of release of steroids, thereby possibly eliminating menstrual abnormalities associated with constant steroid levels. Following implantation or injection, the devices can be used for three months and longer. The primary mechanisms of steroid release are erosion, diffusion, cleavage of covalent linkage, or a combination of these processes. The most investigated polymer materials are poly(lactic acid), poly(glycolic acid), and poly-(e-caprolactone). The steroids used are primarily norethisterone and levonorgestrel.

The degradation can take place via-

- ✓ Bioerosion – the gradual dissolution of polymer matrix
- ✓ Biodegradation – degradation of the polymer structure caused by chemical or enzymatic processes.

Synthetic polymers used in the fabrication of biodegradable implants are-

Water soluble polymers	Biodegradable polymers
Poly(acrylic acid)	Poly(hydroxybutyrate)
Poly(ethylene glycol)	Poly(lactide-co-glycolide)
Poly(vinylpyrrolidone)	Polyanhydrides

Polymer degradation is classified into two patterns-

- ✓ Bulk erosion
- ✓ Surface erosion

In bulk erosion the entire area of polymer matrix is subject to chemical or enzymatic reactions, thus erosion occurs homogeneously throughout the entire matrix.

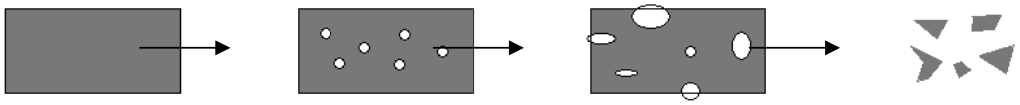


Fig 4 Bulk erosion

In surface erosion, polymer degradation is limited to the surface of an implant exposed to a reaction medium. Erosion therefore starts at exposed surface, works downwards, layer by layer.

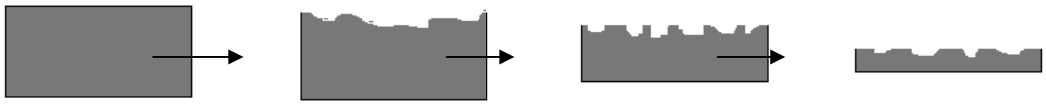


Fig 5. Surface erosion

TYPES OF IMPLANTS ON THE BASIS OF SITE

A. Breast Implants[5,6,7]

Breast implants have been used for about four decades for both reconstructive and aesthetic purposes. In 1963, the quality of the artificial implants was revolutionized by the introduction of the silicone gel-filled implant. There are two main types of breast implants. One is filled with silicone gel and the other is filled with saline (sterile salt water); both of these implants have an outer silicone shell. Prior to 1991 both types of implants were approved by the FDA, but in April of 1992 silicone filled implants were restricted by the FDA to patients with needs of reconstruction, replacement of deformities, and replacement of ruptured silicone-gel filled implants that were used for augmentation. Saline filled implants are currently approved by the FDA for women 18 years old or older desiring breast augmentation and for reconstruction in women of all ages.

Types of breast implants:-

1) Saline implants

2) Silicone gel implants

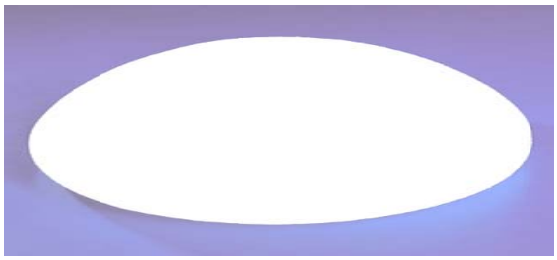


Fig 6. silicone gel-filled implant.

B. Cochlear Implant[8]:-

Cochlear implants are electronic devices which are implanted in the cochlea and designed to provide useful hearing and improved communication ability to individuals who have profound hearing losses and are unable to achieve speech understanding with hearing aids. They do not restore hearing to "normal." Cochlear implants are designed to bypass cochlear hair cells that are non-functional and provide direct stimulation to the auditory nerve.

A cochlear implant consists of several components. All implants have microphones, external speech processors, signal-transfer hardware, transmitters, receivers, and electrodes. Each plays an important part in converting sound to an electrical stimulus. The microphone simply receives and transduces sound into an electrical representation.

Every Cochlear Implant is comprised of the following:

1. electrode array(s)
2. microphone
3. signal processor
4. signal coupler (transmitter and receiver)

Two different models are shown:

A: behind the ear processor

B: body processor

A – Behind the Ear Processor

Fig 8 Cochlear implants A

B – Body Processor

Fig 9 Cochlear implants B

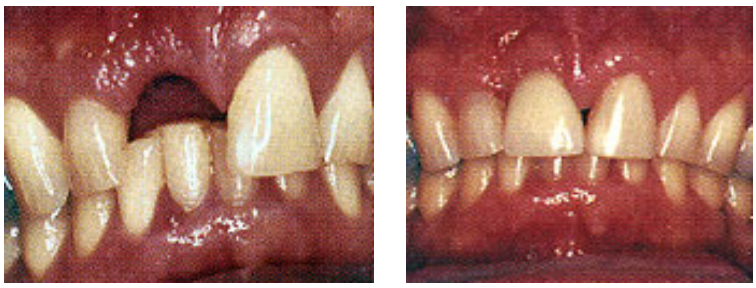
C. Dental implants[9,10]:-

A dental implant is an artificial tooth root that a trained dentist places into jaw to hold a replacement tooth or bridge. Dental implants are an ideal option for people in good general oral health who have lost a tooth or teeth due to periodontal disease, an injury, or some other reason. Dental implants and their crowns help restore the ability to chew the food. Dental implants are generally made from metal or a combination of metals as shown in the figure below.

Fig 10. Dental Implants

What Dental Implants Can Do?

- Replace one or more teeth without affecting bordering teeth.
- Support a bridge and eliminate the need for a removable partial denture.
- Provide support for a denture, making it more secure and comfortable.



Before dental implant After dental implant

Fig 11. Dental implants

D. Intraocular implants[11]:-

Ocular implantable drug delivery systems are to be specifically designed and adapted to the targeted tissue or cell type, the physico-chemical properties of the active compound to be used and to the desired kinetic of intraocular release. Non-biodegradable implants offered in the early 70s the advantages of long-lasting release and reduced host response. Nowadays, new eroding polymers ensuring sustained release and limited induced-inflammation have been designed. The erosion rate and spontaneous degradation of these polymers can be modulated to allow for the desired intraocular kinetics of drug release to take place. Non-degradable polymers used are –

- ✓ Polyvinyl alcohol (PVA)–ethylene vinyl acetate(EVA)
- ✓ PCF (polysulfone capillary fiber)

Biodegradable polymers can be used to form solid or injectable implants or they can be used to encapsulate particular systems as nano and microparticles. Particulate systems can be injected through thin needles and have different behavior and distribution in the ocular media associated with their size and composition. Polymers can be devised as viscous or semi-solid materials which can be localized within the eye and used as a slow release intraocular "implant" after a simple injection. Finally, thermo or light sensitive polymers can be used and appropriately delivered as needed by localized application of heat or various light lengths. Biodegradable polymers used are –

- ✓ Poly lactic acid (PLA), poly glycolic acid (PGA), and poly lactic-co-glycolic acid (PLGA)
- ✓ Polycaprolactones (PCL)
- ✓ Polyanhydrides

Therapeutic applications of ocular implants

1. Implantation in the anterior segment of the eye –

a) Sub-conjunctival implantation at the site of a filtering surgery –

The main therapeutic application in the anterior segment of the eye has been the slow delivery of agents to control certain stages of the wound healing response for the prevention of glaucoma filtering surgery failure.

b) Intracameral implantation to prevent corneal graft rejection or post-operative inflammation

c) Intracameral implantation for the treatment of uveitis

2. Implantation in the posterior segment of the eye -

a) Intravitreal implantation for the prevention of proliferative vitroretinopathy (PVR)

b) Intravitreal implantation to treat CMV retinitis

c) Intravitreal and intrascleral implants for the treatment or prevention of endophthalmitis

d) Intravitreal implantation to treat uveitis

E. Brain implants[12]:-

Brain implants, often referred to as neural implants, are technological devices that connect directly to a biological subject's brain - usually placed on the surface of the brain, or attached to the brain's cortex. A common purpose of modern brain implants and the focus of much current research is establishing a biomedical prosthesis circumventing areas in the brain, which became dysfunctional after a stroke or other head injuries. This includes sensory substitution, e.g. in vision. Brain implants electrically stimulate or block or record (or both record and stimulate

simultaneously) from single neurons or groups of neurons in the brain. The blocking technique is called intra-abdominal vagal blocking. This can only be done where the functional associations of these neurons are approximately known. Because of the complexity of neural processing and the lack of access to action potential related signals using neuroimaging techniques, the application of brain implants has been seriously limited until recent advances in neurophysiology and computer processing power.

Fig 12. Brain implants

9. Delivery of chemotherapeutic agents using implants[13-20]:-

Programmable drug administration device (DAD) makes it a useful device for chronotherapy. Chronotherapy is based on the fact that the efficacy of a drug can change when administered at different times during the circadian cycle.

The preferred objective is to deliver the chemotherapeutic agent when normal cells are least susceptible and when cancer cells are more susceptible. Chronic evaluation of these principles is difficult in large numbers of patients because of the complex, nonlinear dosing patterns required for rhythm-based chronotherapy.

The DAD, however, may be capable of implementing these protocols automatically and over an extended period of time. The DAD has been used clinically in several patients in three primary application areas:

- ✓ terminal cancer pain management,
- ✓ intractable spasticity management,
- ✓ cancer chemotherapy.

The use of the DAD in cancer chemotherapy illustrates the therapeutic effect of implanted programmable drug infusion. In one series of patients with carcinoma of the kidney, constant-rate intravenous infusion of floxuridine (FUDR) was compared with time-modified administration.

The time-modified schedule consisted of four dosage intervals: low-level administration in the early morning quadrant, a stepwise dosage increase from late morning into early afternoon (second quadrant), peak delivery rates from late afternoon into early evening, and a decrease in dosage to second quadrant levels in the final interval.

Recent advances in implants[21-23]:-

1. Veterinary application

COMPUDOSE is a polymeric controlled-release device for the delivery of estradiol to improve both growth rate and feed efficiency in beef cattle. The product is composed of a nonmedicated silicone rubber core coated with a thin layer of medicated silicone rubber containing estradiol COMPUDOSE is implanted subcutaneously in the ear of beef cattle.

2. Peptide delivery

The development of inexpensive, biocompatible, subcutaneous implants for the controlled delivery of peptides has been undertaken. The release of peptides from Eudragit NE30D coated implants using an incubating medium was studied. In vivo, the implants containing LHRH have been used to induce ovulation and mating in anestrus sheep.

3. Insulin pump

The feasibility of incorporating insulin into an osmotic pump whose pumping rate is dependent on blood glucose has been evaluated. Such a pump could contain insulin in virtually any liquid or semisolid form, and its release rate would be independent of the formulation. The approach has been to develop a semipermeable membrane whose aqueous permeability increases with blood glucose concentration. The membrane consists of two layers: the first layer contains immobilized glucose oxidase, which convert glucose to gluconic acid, thereby lowering the local pH, while the second layer consists of a cross-linked, hydrophobic, polybasic hydrogel. This hydrogel absorbs little water at physiologic pH, but becomes quite hydrated as pH is lowered.

11. Future prospects[24]:-

Among implants, ambulatory drug delivery technology represents one of the fastest growing areas in the health care market. Vascular access ports are particularly important because of their compatibility with current economic trends aimed at reducing the length of hospital stays and moving adaptable therapies to more profitable settings in the hospital, such as the outpatient surgery unit, outpatient clinic, or home health department. Perhaps the most promising market segment for ambulatory long-term infusion therapy is chemotherapy. This segment alone is projected to increase at a rate of 30 to 40% annually during the next decade. In addition, other relatively new markets for these devices, such as long-term antibiotic therapy, total parenteral

nutrition, and pain management, will expand greatly as infusion therapy is moved to ambulatory settings, such as the outpatient clinic, the home, and the physician's office. In the near future, pediatric and epidural venous access systems will undoubtedly be introduced, and additional products serving the dual lumen market will probably be developed. But the most interesting opportunities for growth lie in the area of dedicated port and pump systems. It would be highly desirable to combine an insulin- delivery device with a totally implanted glucose sensor, thereby achieving the development of a completely "closed-loop" implantable artificial beta cell.

CONCLUSION

Implantable drug delivery systems are placed completely under the skin usually in a convenient but inconspicuous location. Because the device is completely subcutaneous, with no opening in the skin, there is little chance of infection or interference with daily activities. It is possible to surgically implant and remove drug-concentrating devices or polymeric matrices, the requirement for such intervention could have a significant negative impact on the acceptability of a product candidate. Two approaches to this problem seem possible. The first is the use of implanted electrically driven pumps which can be refilled by simple injection of the drug through a septum into the pump reservoir. The second approach is the use of erodible implants. Here, the requirements are for a system that will be safe and whose erosion rate can be sufficiently well controlled to give a reproducible and precise drug-release rate over the entire lifetime of the implant. Various types of implants are used now a days which are useful for the replacement like dental implants, vision and hearing purpose like cochlear and brain implants and also for the purpose of delivery of potent drugs like hormones, steroids, insulin etc. They are also used in chemotherapy.

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