



A REVIEW ON: RECENT MODERN IN IMPLANTABLE DRUG DELIVERY SYSTEM

Khurde S. S.¹, Nagoba S. N.*¹ and Thonte S. S.¹

Channabasweshwar Pharmacy College, Latur, Maharashtra, India.

***Corresponding Author: Dr. Nagoba S. N.**

Channabasweshwar Pharmacy College, Latur, Maharashtra, India.

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ABSTRACT

Implant is an object or material inserted into the body for prosthetic, therapeutic, diagnostic or experimental purposes. Implants are one of the dosage forms used to achieve effective concentration for long time. Implant dosage forms are useful for patients having difficulty in taking drugs orally, and it allows the avoidance of frequent dosage by sustained supply. Types of implants are in-situ forming implant and solid implants. The rate of release of drugs from the implant is based on various mechanism i.e. diffusion controlled, chemically controlled, osmotically controlled, magnetically controlled. Compression, solvent association method, injection-molding, hot-melt extrusion these are the various process techniques have been used to prepared implant drug delivery system. Examples of implantable drug delivery devices are Norplant, compudose, Synchro mate, Alzet osmotic pump, GLIADEL wafer implant, DURIN implants etc.

KEYWORDS: Implants, insitu forming implant solid implants, compudose, Alzet osmotic pump, injection-molding etc.

INTRODUCTION

Implant is a small object inserted in to body especially by the surgery. An implant is a medical device manufactured to replace a missing biological structure, support a damaged biological structure, or enhance an existing biological structure. Medical implants are man-made devices, in contrast to a transplant, which is a transplanted biomedical tissue. The primary objective of any implant system is to have firm fixation to the bone and this could be influenced by biomechanical as well as biomaterial selection. Today implants are made either of commercially pure titanium (cpTi) or titanium alloys. In addition to its biocompatibility, titanium was also initially believed to be inert, nontoxic and non allergenic. An increasing number of people who suffer some form of tooth loss are choosing to replace their teeth with dental implants. A threaded implant design made of pure titanium that showed direct contact with bone. This phenomenon was called **osseointegration**, defined by the American Academy of Implant Dentistry as “the firm, direct and lasting biological attachment of a metallic implant to vital bone with no intervening connective tissue”. Different materials, such as platinum, silver, steel, cobalt alloys, titanium and alloys, acrylic, carbon, alumina, tantalum, niobium, zirconium and calcium phosphate compounds have been used as dental implant material.^[1,2,3,4]

The implantable therapeutic systems are mainly approached for the

Long term, continuous drug administration, and controlled release of drug.

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.^[5,6]

Nowadays, numbers of drugs have been used for the implantable drug delivery systems. Such as:

- Progestin + estradiol, megestrol, norgestrel for the purpose of Contraception.
- Cyclophosphamide, merchloro ethamide for the purpose of Cancer.
- Pilocarpine for the Glaucoma.

Non-degradable and biodegradable implant systems

Non-degradable systems

There are several types of non degradable implantable drug delivery systems available on the market place today, but the non degradable 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 non degradable membrane whose thickness and permeability properties can control the diffusion of the drug into the body. Matrix systems are also commonly used as non degradable implants. These systems consist of uniformly distributed drug throughout a solid non biodegradable polymer.^[7,8]

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.^[9,10,11]

Two different types of biodegradable delivery systems are currently available:

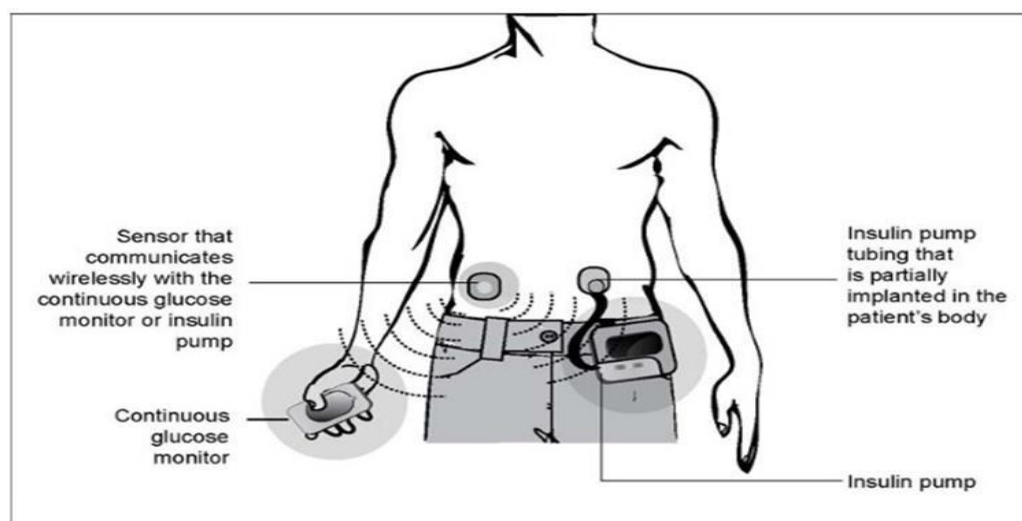
The first type,

A reservoir system is similar in structure to the non degradable reservoir type. The mechanism of drug release from both systems is quite similar. However, these bioerodible Systems, in contrast, contain an exterior polymeric membrane that degrades at a slower rate than the expected rate of drug diffusion through the membrane. Therefore, the membrane remains intact while the drug is released completely. Eventually, the exterior polymeric membrane is degraded, in vivo, and, ultimately, eliminated.

The second type, of **bioerodible system** consists of drug dispersed in a polymer, monolithic type, which is slowly eroded, in vivo, by biological processes at a controlled rate. The most popular biodegradable polymers currently being investigated include polyglycolic acid, polylactic acid, polyglycolic lactic acid, polyaspartic acid and polycaprolactone.^[12]

Implantable pump systems

Many different drugs require external control of delivery rate and volume. Such control cannot be obtained when using biodegradable or non degradable delivery systems with the exception of the magnetic type delivery systems. Pump systems have been used to provide the control needed in these situations. Recently, due to the availability of advanced micro technology, it has been possible to create pump systems small enough to implant, subcutaneously, for drug delivery. This allows the patient to maintain the control of drug release without the need for an external pump system. In recent advances, insulin implantable pump systems have been invented and used for the control of type-1 diabetes. Pump systems differ from other implantable systems due to their mechanism of drug delivery. Pump systems release drugs through a pressure difference generated gradient that results in the bulk flow of a drug at controllable rates. To date, five different types of implantable pump systems have been tested including infusion pumps, peristaltic pumps, osmotic pumps, positive displacement pumps and controlled release micro pumps.^[13,14]



Implantable rods

Implantable rods are prepared with the help of different type of biodegradable and non biodegradable polymers.

The implantable rod releases the drug in a controlled manner.^[15]



Recent advances in Implantable drug delivery system **DURIN™ TECHNOLOGY**

The Durin™ biodegradable implant technology is used for parenteral drug delivery for periods of weeks to six months or more. The technology is based on the use of biodegradable polyester excipients, which have a proven record of safety and effectiveness in approved drug delivery and medical device products.^[16]

Features

1. It contains Superior delivery kinetics.
2. It is Flexible.
3. It acts as a Superior drug loading and stability.
4. It is fully biodegradable.
5. It is safe in human use.

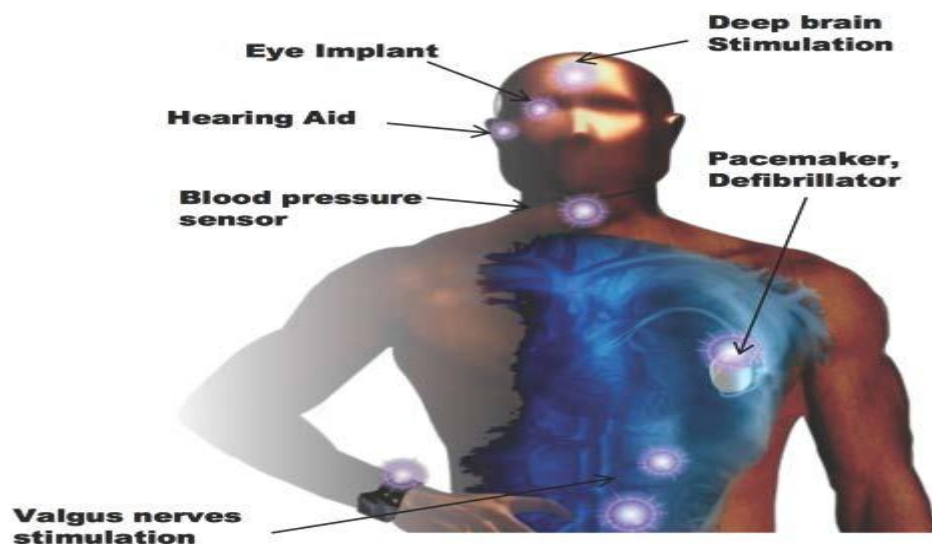
6. It is Cost effective.

ATRIGEL DRUG DELIVERY TECHNOLOGY

Atrigel system is a proprietary delivery system that can be used for both parenteral and site-specific drug delivery. It consists of biodegradable polymers dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using standard needles and syringes, it solidifies upon contact with aqueous body fluids to form a solid implant. Atrix Laboratories has continued to develop the technology and to extend its use to a large number of both drug delivery and medical device applications. Atrigel system and its relatively pain-free subcutaneous injection into the body provide significant advantages over both solid implants and micro particles.^[17]

ALZAMER DEPOT™ TECHNOLOGY

The Alzamer Depot™ technology was designed to offer sustained delivery of therapeutic agents, including proteins, peptides, other biomolecules and small molecular weight compounds, for up to a month with minimal initial drug burst and bioerosion of the dosage form.^[18]



Application in implant drug delivery **Sensory and neurological**

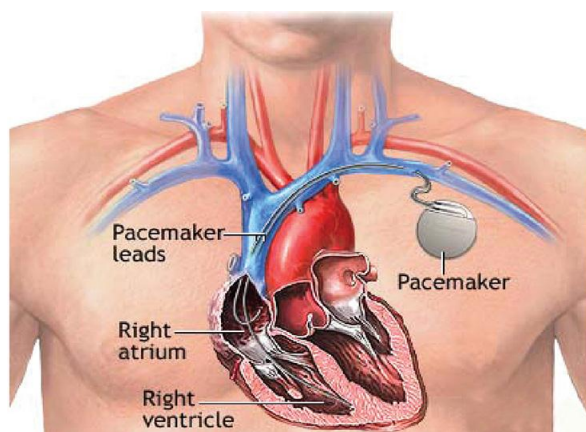
Sensory and neurological implants are used for disorders affecting the major senses and the brain, as well as other neurological disorders. They are predominately used in the treatment of conditions such as cataract, glaucoma, and other visual impairments; otosclerosis and other hearing loss issues, as well as middle ear diseases such as otitis media; and neurological diseases such as epilepsy, Parkinson's disease, and treatment resistant depression.

Examples include the intraocular lens, intrastromal corneal ring segment, cochlear implant and neuro stimulator.^[19]

Cardiovascular

Cardiovascular medical devices are implanted in cases where the heart, its valves and the rest of the circulatory system is in disorder. They are used to treat conditions such as heart failure, cardiac arrhythmia, ventricular tachycardia, valvular heart disease, angina pectoris and atherosclerosis.

Examples include the artificial heart, artificial heart valve, cardiac pacemaker, and coronary stent.^[20]



Orthopedic

Orthopedic implants help alleviate issues with the bones and joints of the body. They're used to treat bone fractures, osteoarthritis, scoliosis, spinal stenosis and chronic pain.

Examples include a wide variety of pins, rods, screws, and plates used to anchor fractured bones while they heal.

Metallic glasses based on magnesium with zinc and calcium addition are tested as the potential metallic biomaterials for biodegradable medical implants.^[21]



Contraception

Contraceptive implants are primarily used to prevent unintended pregnancy and treat conditions such as non-pathological forms of menorrhagia.

Examples include copper and hormone based intrauterine devices.^[22]

Cosmetic

Cosmetic implants often prosthetics attempt to bring some portion of the body back to an acceptable aesthetic norm. They are used as a follow-up to mastectomy due to breast cancer, for correcting some forms of disfigurement and modifying aspects of the body (as in buttock augmentation and chin augmentation).

Examples include the breast implant, nose prosthesis, ocular prosthesis, and injectable filler.^[23,24]

Other organs and systems

Other types of organ dysfunction can occur in the systems of the body, including the gastrointestinal, respiratory, and urological systems. Implants are used in those and other locations to treat conditions such as gastro esophageal reflux disease, gastro paresis, respiratory failure, sleep apnea, urinary and fecal incontinence and erectile dysfunction. Examples include the LINX, implantable gastric stimulator, diaphragmatic/phrenic nerve stimulator, neuro stimulator, surgical mesh, and penile prosthesis.^[25]

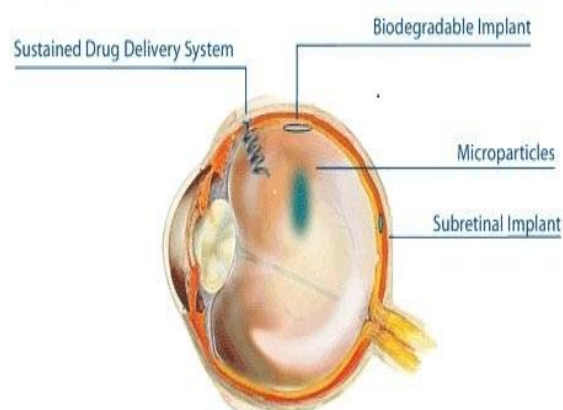
Implantable Ocular Drug Delivery

Implantable drug delivery systems in ocular diseases/disorder should be attributed to many factors which include

- (1) Implantation would bypass the blood-retina barrier to enhance intraocular bioavailability;
- (2) Sustained drug release will reduce the need for daily dosing which could improve patient adherence to treatment;
- (3) Prolonged drug release will alleviate/ minimized effects associated with repeated injection or systemic drug administration; and
- (4) Effective drug delivery will avoid drug wastage while maximizing the efficacy of treatment.

Examples for biodegradable ocular drug delivery:

- 1) Lacrisert
- 2) SurodexTM
- 3) Ozurdex



Dental

With technological advancement, dental treatments involving dental implants have gained increased acceptance by patients. Among the latest technology in dental imaging is Cone Beam Computed Tomography (CBCT) which uses 3D images from different planes like axial, coronal and sagittal views. It provides a stream of data which helps a dental surgeon to reconstruct images when needed, while exposing patients to less amount of radiation. Indications of Dental Implant Therapy have

expanded with change in implant shapes, sizes, materials, coatings and technological advances, like guided tissue regeneration, immediate loading concepts. Research aiming at improving the design of implant's surface treatment like increasing bone to implant contact ratio with plasma sprayed surface, Ion-sputtering coating, Anodized surface, Sand-blasted and acid etched, Hydroxyapatite coating and biochemical surface, aids in controlling the tissue implant interface with molecules delivered directly to the interest.



In the dental implant placement, imaging is the key to successful case planning. The Latest technology in dental imaging is Cone Beam Computed Tomography CBCT which implements revolutionary 3D Images with axial, coronal, and sagittal views and a stream of useful data that the doctor can reconstruct as in the form of images when needed, while delivering substantially less amounts of radiation to the patient. Recent Advances in Computed Tomography are.^[26,27]

Implantable devices for cancer therapy

Currently the main route of administration for cancer drugs is by the intravenous route, which has limited effectiveness, since only a minimal amount of the systemic blood flow reaches the tumour. Therefore, only a fraction of the total dose actually reaches the site of action. The remainder of the dose is distributed throughout healthy organs and tissues, leading to a variety of undesirable side effects. Many chemotherapeutic drugs have a very rapid plasma clearance, leading to short tumor exposure times. This leads to the use of higher doses of these chemotherapeutic drugs in order to achieve the required therapeutic level at the tumor site, which further increases their side effects. To overcome some of these problems chemotherapeutic drugs have been formulated into targeted drug delivery systems such as liposome and PLGA nanoparticles. A biodegradable implant(s) containing a chemotherapeutic drug placed within or around the tumor would allow for local delivery of these chemotherapeutic drugs, maximizing drug delivery to the tumor while reducing systemic exposure and limiting damage to the surrounding normal tissue. Furthermore, use of targeted drug delivery systems would allow for the local delivery of a targeted dosage form, further improving efficacy and reducing side effects. Some cancers and tumors are seen as inoperable due to their

size and location (brain, liver and lungs etc.). Studies have shown that the use of a drug releasing implant can reduce the size of tumors and allow surgical removal to be an option.^[28,29,30]

CONCLUSION

A number of implantable drug delivery devices have recently developed for human or veterinary uses with one or more of requirements in mind. Implantable drug delivery system have been developed that aim to achieve continuous administration of systemically active drugs for long-term regulation of physiological process. Implant delivery technologies are being utilized for many therapeutics applications such as dental, ophthalmic, parental, cardiovascular, contraception etc. Implanted drug delivery technologies have ability to reduce the frequency of patient driven dosing and to deliver the compound in targeted manner.

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