International Journal of Research and Reviews in Pharmacy and Applied science

www.ijrrpas.com

A REVIEW ON PARENTRAL IMPLANTS

TEJASHREE A. GHADGE*,SAGAR D. CHAVARE, DR. AJIT KULKARNI, SHRUTI KAMBLE.

Department of Quality assurance techniques,

Satara College of Pharmacy,Satara. Maharashtra

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 insitu 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

DEFINATION OF PARENTERALS

Parenteral preparation is sterile preparation containing one or more active ingredients intended for administration by injection, infusion, or implantation into the body. Parenteral preparations may require the use of excipients such as solvents, substances to enhance solubility, suspending agents, and buffering agents, substances to make the preparation isotonic with blood, stabilizers or antimicrobial preservatives. The addition of excipients is kept to a minimum. There must be no incompatibility between any of the components of the dosage form. Water for injections is used as the vehicle for aqueous injections.

Parenteral controlled-release drug delivery systems-

Number of drug delivery systems has been developed over the years, parenteral drug delivery system being one of them. Parenteral drug delivery refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa. Conventional parenteral drug delivery systems, typically intravenous injection, occasionally cause a high plasma drug concentration, close to the minimum toxic concentration. Repetitive administration is sometimes required due to the short duration of action from traditional systems. To avoid the problems from conventional systems, parenteral controlled-release drug delivery systems are designed to achieve consistent, predictable or desired drug release profiles. They can be administered via a parenteral route either by subcutaneous injection, intramuscular injection, or injection to other specific sites such as intra-articulate injection. Suspensions, emulsions, liposomes, micro particles and implants are identified as parenteral controlled release drug delivery systems. The systems are useful and necessary when drug candidates have poor absorption by other routes of administration and short half-lives, such as when peptides and proteins are used. The advantages of parenteral controlled-release over conventional drug delivery systems are:

- To maintain a high drug concentration in the blood circulation or prolonging the duration of action.
- Improved drug pharmacokinetics.
- Enhancement of physical stability
- Reduction of side effects by maintaining a constant drug level via parenteral depot systems
- Increasing specificity and reducing systemic adverse effects for targeted drug delivery.
- An opportunity to control a precise drug release rate and
- Improvement of patient compliance by decreasing invasive administration and dosing frequencies.

Types of Parenteral Controlled Drug Delivery Systems:

• Surgical implants

• Microspheres

• Liposomes

• Injectable gel

Table1.1. Examples of parenteral controlled-release drug products (exceptional parenteralcontrolled-release based on biodegradable polymers)

Product	Drug	Company	Deliver technology
Ambisome	Amphotericin	Gilead	Liposome
DaunoXome	Daunorubicin	Gilead	Liposome
Doxil	Doxorubicin	Johnson and Johnson	Liposome
Implanon	Etonogesterol	Organon	Implant
Plenaxis	Abarelix	Praecis	Carboxymethylcellulosecomplex
Myocet	Doxorubicin	Elan	Lipid complex

PARENTERAL IMPLANTS

Implant is an object or material inserted or grafted into the body for prosthetic, therapeutic, diagnostic, or experimental purposes. Implants are one of the dosage forms used to achieve effective concentrations for a long time. Therefore the base materials for implants are required to be biocompatible. Biodegradable and non-biodegradable polymers are often utilized as a base material. Non biodegradable polymers have to be taken out surgically after completion of the drug release, resulting in pain and a burden on patients. On the other hand, as biodegradable polymers disappear spontaneously from the body during or after drug release, their implants are superior in lowering the burden on patients. In particular, poly-dl-lactic acid (PLA) and poly (dl- lactic acid-co-glycolic acid) copolymer (PLGA) are clinically available as biocompatible and biodegradable polymers, and have been examined extensively and widely. PLGA and PLA show a prolonged drug release for 1 and 3 months, respectively. Other biodegradable polymer like polyanhydride shows a longer drug release about 1 year. Non bio-degradable polymer includes poly vinyl acetate (PVA) etc. Various types of implants are available for the drug delivery system like for delivery into eye, heart, bone, cochlea etc.

Product	Drug	Company	Delivery technology	Polymeric carrier
Decapeptyl SR	Triptorelin	Ipsen	Microparticles	PLGA
Nutropin Depot	Somatropin	Genetech	Microparticles	PLGA
Risperdal Consta	Risperidone	Janssen	Microparticles	PLGA
Sandostatin LAR	Octreotide	Novaris	Microparticles	PLGA
Trelstar Depot	Triptorelin	Watson Pharma	Microparticles	PLGA
Trelstar LA	Triptorelin	Watson Pharma	Microparticles	PLGA
Vivitrol	Naltrexone	Cephalon	Microparticles	PLGA
Profact Depot	Buserelin	Sanofi-Aventis	Solid implant	PLGA
Zoladex	Goserelin	AstraZeneca	Solid implant	PLGA
Gliadel	Carmustine	MGI Pharma	Targeting solid implant	Polifeprosan 20
Atridox	Doxycycline	Tolmar	In situ implant	PLA
Atrisorb-D FreeFlow	Doxycycline	Tolmar	In situ implant	PLA
Eligard	Leuprolide	Sanofi-Aventis	In situ implant	PLGA
Lupron Depot	Leuprolide	Abbott	In situ microparticles	PLGA

Implants classified as-

1.Solid implants-

Solid implants typically exhibit biphasic release kinetics, with initial burst of drug is usually due to the release of drug deposited on the surface of the implant although zero order kinetics may be achieved by. E.g. Coating the implant drug impermeable material Overall drug release may be controlled by varying polymer

composition- an increase in the level of lactic acid in a polylactic acid co-glycolic acid copolymer retards drug release and increase in polymer molecular weight also retards drug release and prolongs drug effects.

2. In-Situformingimplants-

Biodegradable injectable *in situ* forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot systems. The controlled release of bioactive macromolecules via (semi-) solid *in situ* forming systems has a number of advantages, such as:

1. Ease of administration,
2. Less complicated fabrication,
3. Less stressful manufacturing conditions for sensitive drug molecules.

From a manufacturing point of view, *in situ* forming depot systems offer the advantage that they are relatively simple to manufacture from polymers adapted for this approach. Compared with microspheres, which have to be washed and isolated after preparation, operating expenses for the production of *in situ* forming applications are marginal, thus lowering investment and manufacturing costs.

Classification of injectable *in situ* forming implants-

In situ cross-linked polymer systems
In situ polymer precipitation
Thermally induced gelling systems

Polymeric controlled release systems-Polymeric release systems can be classified into reservoir and matrix systems (Fig. 1). In reservoir systems the drug forms a core surrounded by polymer that forms a diffusion barrier. The drug release is by dissolution into the polymer and then diffusion through the polymer wall. In polymeric matrix systems the drug is dispersed or dissolved in a polymer. The drug release can be diffusion, swelling, and/or erosion controlled. Compared to reservoir systems, matrix systems are easier to be manufactured because they are homogeneous in nature and they are also safer since a mechanical defect of the reservoir device rather than matrix device may cause dose dumping. However, if polymer matrix is non-degradable, the constant release profile is difficult to be achieved with matrix system.

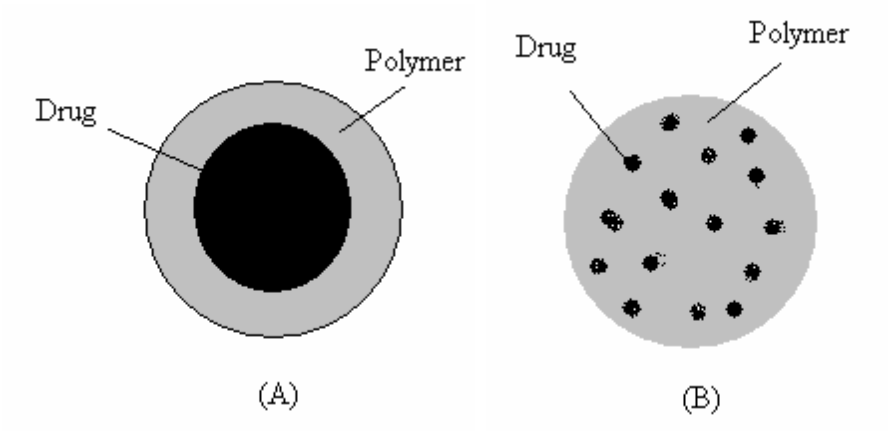

Fig.1. Polymeric delivery systems ;(A) Reservoir systems; (B) Matrix systems.

The first polymeric controlled release devices is a reservoir system based on nonbiodegradable polymer silicone rubber.

CONTROLLED DRUG DELIVERY BY DIFFUSION PROCESS

a) Polymer membrane permeation controlled drugdelivery device: In this implantable drug delivery device the drug reservoir is encapsulated by a rate controlling polymeric membrane. Different shapes and sizes of implantable drug delivery devices can be fabricated. An example of this type of implantable drug delivery device is the **Norplant**sub dermal implant. Norplant® is a well-known contraceptive implant approved by U.S. Food and Drug Administration (FDA) in 1990.

Fig.2 Norplant sub dermal implant.

b) Polymer matrix diffusion-controlled drug delivery devices: In this implantable controlled-release drug delivery devices the drug reservoir is formed by homogeneous dispersion of solid particle throughout the a lipophilicor hydrophilic polymer matrix .The dispersion ofdrug solid particle in the polymer matrix can be accomplished by blending drug solid with a viscous liquid polymer at room temperature followed by cross linking of polymer chains or by mixing drug solid with a melted polymer dispersion are then molded or excruded to form a drug delivery device of various shapes and sizes. An example of this type of implantable drug delivery device is the compudose implant.

Fig: 3 compudose implant.

c) Membrane-matrix hybrid-type Drug Delivery Devices: This type of implantable controlled release drug delivery devices is hybrid of the polymer membrane permeation controlled drug delivery system and polymer matrix diffusion controlled drug delivery system. It aims to take advantages of the constant drug release kinetics maintained by the membrane permeation-drug delivery system while minimizing the risk of dose dumping from the reservoir compartment of this type of drug delivery system. An example of type of implantable drug delivery device is **Norplant II**sub dermal implant.

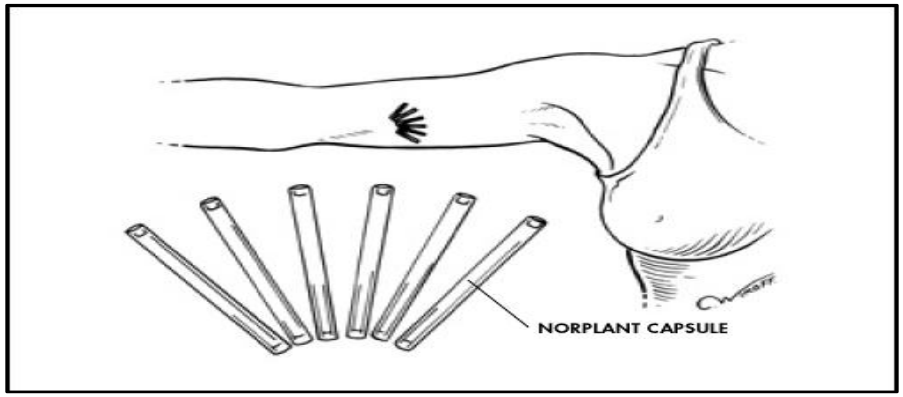

Fig: 4 Norplant II sub dermal implant

d) Micro reservoir partition-controlled drug delivery devices: in this implantable controlled drug delivery device the drug reservoir, which is a suspension of drug crystals in an aqueous solution of water-miscible polymers, forms a homogeneous dispersion of millions of discrete, unreachable, microscopic drug reservoir in a

polymer matrix. Different shapes and sizes of drug delivery system by molding or extrusion. Depending upon the physicochemical properties of drug and desired properties ofdrug rate release, the device can be further coated with a layer of biocompatible polymer to modify the mechanism and rate of drug release.An example of this type implantable drug delivery device is the **Synchro-Mate** implant. It contains drug**norgestomet**.

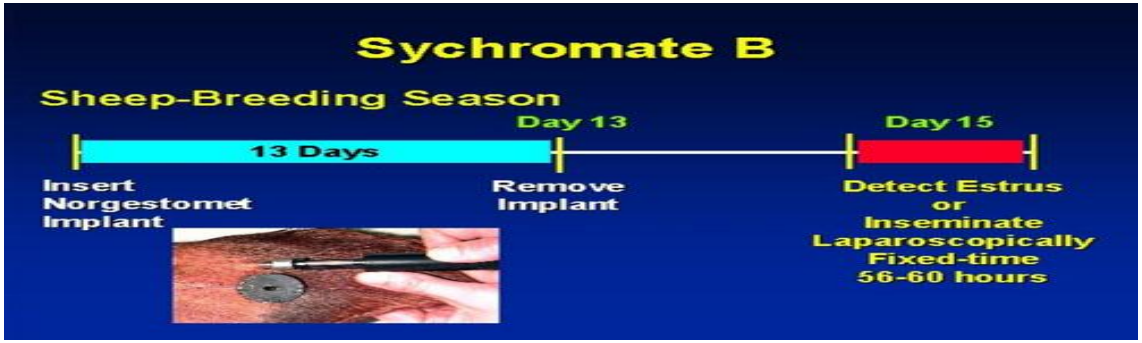

Fig: 5 Synchro-Mate implant.

2. Controlled drug delivery by activation process

A) Osmotic pressure-activated drug delivery device

In this implantable controlled-release drug delivery device osmotic pressure is used as the energy sourceto activate and modulate the delivery of drugs, thedrug reservoir, which is either a solution or asemisolid formulation.

Alzet osmotic pump

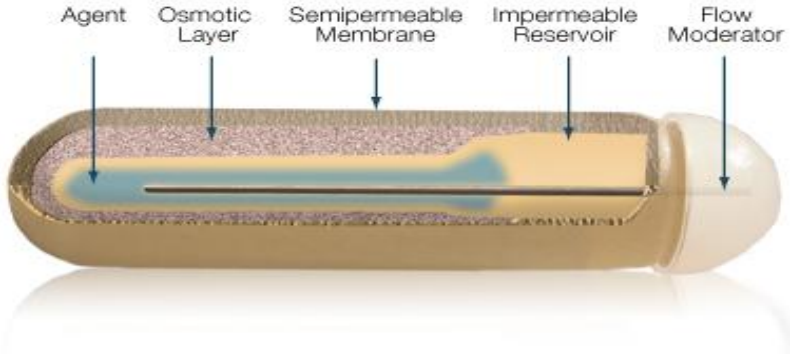

Fig: 6 subcutaneous implantable mini-osmotic pumps for administering β-adrenergic drugs.

The physical or chemical properties of a compound have no influence on the delivery rate of ALZETpumps. The delivery rate of ALZET pumps iscontrolled by the water permeability of the outermembrane. In short, water from the environmententers the pump through the semipermeablemembrane into the osmotic layer, which causescompression of the flexible, impermeable reservoir. The test solution is continuously released through the flow moderator. A flow modulator is a hollow tubewith an inner diameter of 500 microns. Solutions and even high molecular weight compounds can effectively flow through the flow moderator ofALZET pumps.

B) Vapor pressure activated drug delivery devices

In this implantable controlled release drug delivery device vapor pressure is used as the power source to activate the controlled delivery of drugs. The drug reservoir, which is a solution formulation, is contained inside an infusate chamber. By a freely movable bellows the infusate chamber is physically separated from the vapor pressure chamber, which contains the vaporizable fluid, such as fluorocarbon. The fluorocarbon vaporizes at body temperature and creates a vapor pressure that pushes the bellows to move upward and forces the drug solution in theinfusate chamber to deliver the drug.

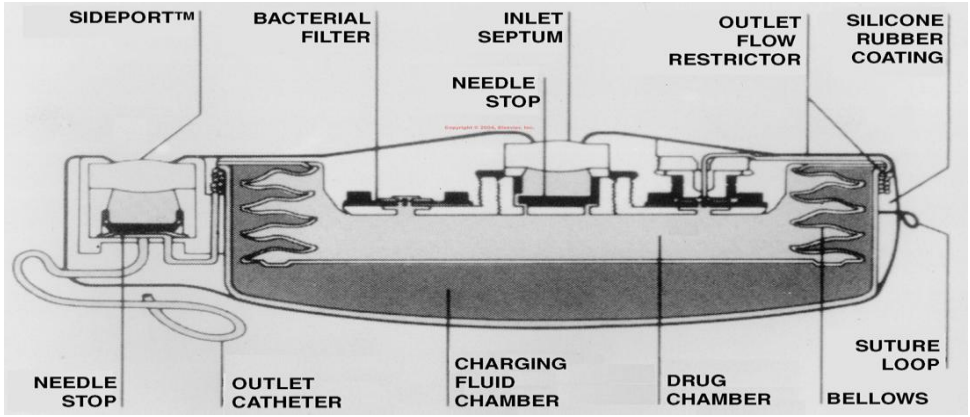

Fig: 7 Infusate chambers

A typical example of drugs that can be given by this type of infusion pump are morphine for patient suffering from intensive pain of terminal cancer, heparin for anticoagulation treatment and insulin for the treatment of diabetes.

Fig: Administration of Infusaid implant

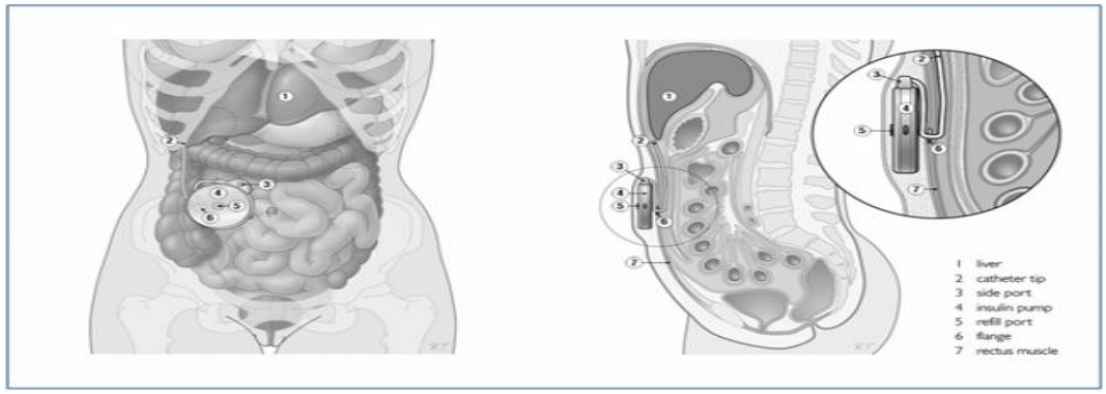

Fig: 8 Cross-sectional view of an implantable peristaltic pump showing all important components.

C) Magnetically activated drug delivery devices

In this implantable controlled release drug delivery device electromagnetic energy is used as the power source to control the rate of drug delivery. A magnetic wave triggering mechanism is incorporated into the drug delivery device, and drug can be triggered to release at varying rates depending upon the magnitude and the duration of electromagnetic energy applied. This sub dermallyimplantable, magnetically modulated hemispherical drug delivery device was fabricated by positioning a tiny donutshapedmagnet at the center of a medicated polymer matrix that contains a homogenous dispersion of a drug with polymer. The external surface of the hemispherical pellet is further coated with a pure polymer, such as ethylene vinyl acetate copolymer orsilicon elastomers, on all sides, expect one cavity atthe center of the flat surface, which is left uncoated topermit the drug molecules to be delivered through thecavity. Byapplying an external magnetic field the drugs areactivated by the electromagnetic energy to releasefrom the pellet at a much higher rate of delivery.

D) Hydration activated drug delivery devices

This type of implantable controlled release drug delivery device releases drug molecules uponactivation by hydration of the drug delivery device bytissue fluid at the implantation site. To achieve thisdrug delivery device is often fabricated from ahydrophilic polymer that becomes swollen uponhydration. Drug molecules are released by diffusingthrough the polymer matrix. The hydration activatedimplantable drug delivery device is exemplified by the development of the norgestomet releasing Hydro implant for estrus synchronization in heifers. Thiswas fabricated by polymerizing ethylene glycolmethacrylate (Hydron S) in an alcoholic solution that containsnorgestomet, a cross-linking agent (such asethylene dimethacrylate), and an oxidizing catalyst toform a cylindrical water swellable (but insoluble) Hydron implant.The Hydron Implant technology is based upon specialty blends of hydrogel polymers spun cast into small tubes measuring in the order of 1-inch in length and 1/8 inch in diameter.

E) Hydrolysis activated drug delivery devices

This type of implantable controlled release drug delivery device is activated to release drug moleculesupon the hydrolysis of the polymer base by tissuefluid at the implantation site. To achieve this drugdelivery device is fabricated by depressing a loadingdose of solid drug, in micronized form, homogeneously through a polymer matrix made from bioerodible or biodegradable polymer, which is thenmolded into a pellet or bead-shaped implant. Thecontrolled release of the embedded drug particles ismade possible by the combination of polymer erosionby hydrolysis and diffusion through the polymer matrix. The rate of drug release is determined by therate of biodegradation, polymer composition andmolecular weight, drug loading, and drug-polymerinteraction. The rate of drug release from this type of drugdelivery system is not constant and is highlydependent upon the erosion process of the polymermatrix.

IMPLANTS FOR EYE

Intravitreal injections can enhance ocular drug delivery, but the need for frequent retreatmentand potential injection-related side effects limit theutility of this technique. Sustained-release drugdelivery systems have been developed to overcomethese limitations; such systems can achieveprolonged therapeutic drug concentrations in oculartarget tissues while limiting systemic exposure andside effects and improving patient adherence totherapy. Topical drug therapy is the primary form oftreatment for front-of-the-eye diseases, such as ocularsurface diseases (e.g. conjunctivitis, dry eye), forelevated intraocular pressure, and for anterior uveitis.Anatomical and physiological barriers in the eye, including the corneal epithelium and conjunctivalclearance mechanisms, affords protection against theentry of xenobiotic. These barriers also greatly impede the entry of drugs to the posterior segment, making it difficult to achieve therapeutic drugconcentrations. Treatment of back-of-the-eyediseases such as diabetic retinopathy, neovascularage-related macular degeneration, and retinal venousocclusive disease is especially challenging withtopical therapy given the greater diffusional distance.Systemically administered drugs can be used fortreating front- and back-of-the-eye diseases.However, the accessibility of ocular tissues is greatlylimited by the blood-aqueous and blood-retinalbarriers. As a result, high systemic doses must beadministered, which increases drug exposure in non-ocular tissues and, consequently, the risk of adversesystemic side effects. Therefore Sustained-releaseintrascleral and Intravitreal drug implants and insertshave been developed for the treatment of oculardiseases.

EXAMPLES OF BIODEGRADABLE OCULAR DRUG DELIVERY SYSTEMS-

1) Lacrisert®

2) Surodex™

3) Ozurdex

NONBIODEGRADABLE OCULAR DRUG DELIVERY SYSTEMS

In nonbiodegradable reservoir-type devices, PVA, a permeable polymer, is typically used as a structuralelement, while the device's drug-restrictingmembrane is composed of EVA, a hydrophobicpolymer that is relatively impermeable to hydrophilicdrugs.

Examples of Non-biodegradable Ocular Drug Delivery Systems

- An Ethylene Vinyl Acetate and Poly(Vinyl) Alcohol Reservoir Device (Vitrasert)

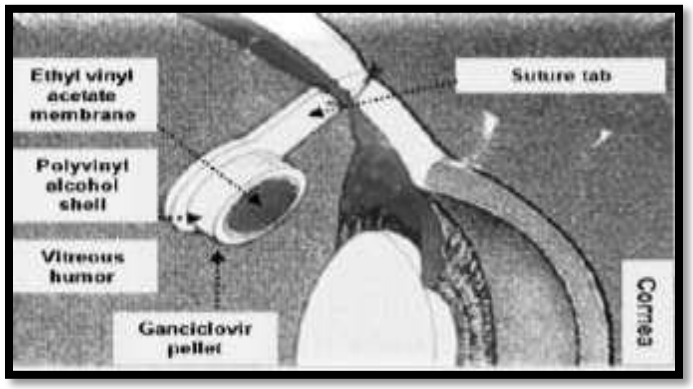

Fig: 9Vitrasert implant

- The Retisert and Medidur Devices-

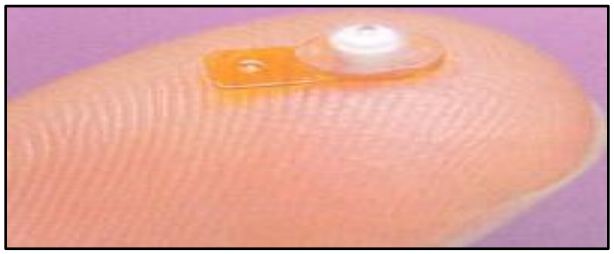

Fig: 10 Retisert and Medidure implant.

IMPLANTS FOR HEART-

Percutaneous trans luminal angioplasty (PTCA) is used in the treatment of Coronary Artery Disease. Over the past decade, extensive research has been performed addressing the design of stents, which are commonly used for PTCA. Endoluminal metallic endoprostheses (stents) have reduced procedural complications in PTCA like elastic recoil of the vessel wall, balloon-induced dissection, and reoccurrence of restenosis. To overcome the restenosis issue, stents for local delivery of severaldrugs were established. First generation drug elutingstents (1GDES) consist of a backbone stent (316 L stainless steel or Nitinol), a

polymer (biodegradable or non-degradable), and drugs such as Paclitaxel or Sirolimus. This 1 G-DES was designed to reduce in stent neointimal formation and to minimize the appearance of restenosis.

Example

CYPHER STENT-A stent is a permanent implant that remains in your artery. CYPHER® Stent is a small, expandable, slotted metal tube is inserted through a catheter into a coronary artery. There, it acts as a scaffold to help hold the artery open in order to improve blood flow to the heart and relieve the symptoms and dangers associated with artery blockage. The CYPHER® Stent is a drug-eluting stent. The metal of the stent has a soft, plastic coating that contains the anti-rejection-type medicine Sirolimus. Eighty percent (80%) of the Sirolimus is released during the first 30 days. The rest is released by the end of 90 days.

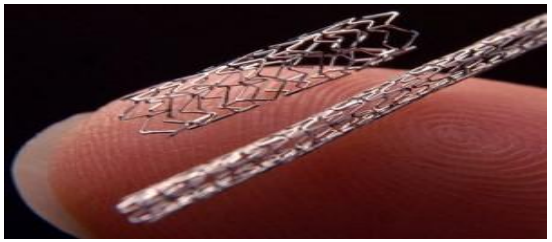

Fig: 11 CYPHER Stent implant.

TAXUS STENT-The TAXUS stent uses Translute™ Polymer, a proprietary polymer carrier technology, to control drug release. The durable Translute Polymer protects the drug and maintains coating integrity during preparation, delivery, and stent expansion. The polymer controls the release of paclitaxel, which may allow for consistent drug release and more uniform drug distribution.

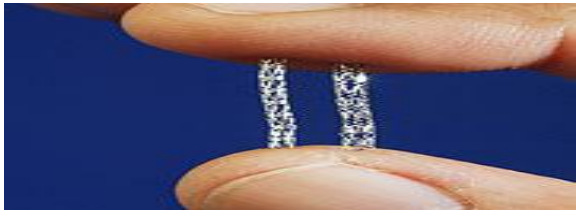

Fig: 12Taxes stent implant for heart.

METALLIC STENT

Fig: 13 Metallic stent implant.

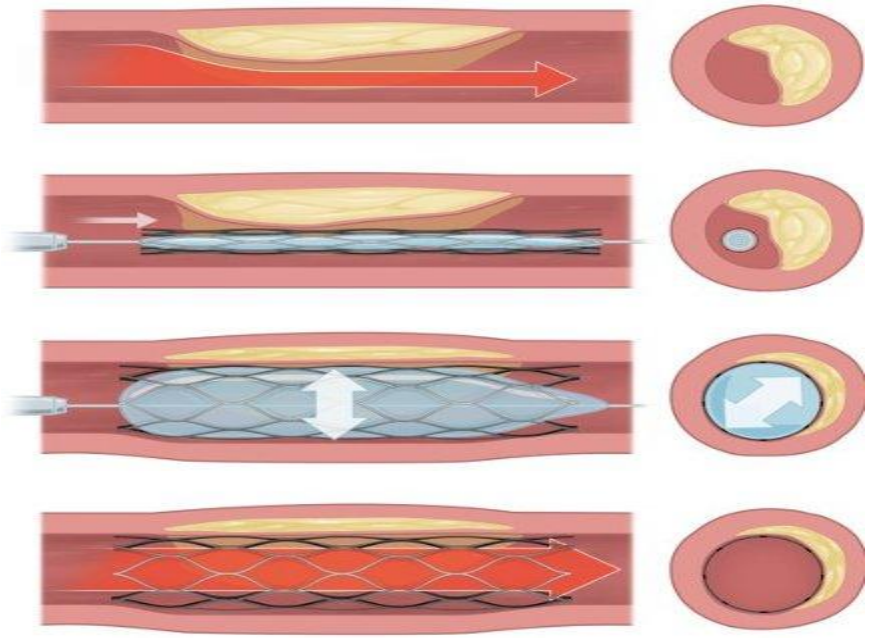

Fig: 14 Drug loaded stent inserted into coronary artery.

PROCESSES FOR PREPARING PLGA/PLA IMPLANTS-

The possible and available methods for fabricating implant drug delivery are as follows:

Compression

Compression is a possible method for a preparation of PLGA- or PLA-based implants. Thepreparation of implants by compression is the lack of heat and solvent. Itis a less stressful method in comparison with the other processes, for example injectionmolding and hot-melt extrusion. Therefore, it is a suitable method for drugs, proteins orpeptides, which are sensitive to moisture, solvent and heat. Threemechanisms are involved in the process of compression. Fragmentation occurs and powdersare fractured into smaller size. Subsequently, changes in shape of powders known asdeformation are usually observed. Powders are then moved closer to reduce porosity; andthus densification. The implants prepared by this method sometimes show a fast release with a short duration. Additional methods to suppress or prolong a drug release prepared by direct compression are necessary. Compressed heat and coating have been introduced. Heating and compression lead tohigh density of PLGA implants and the drug release is slower. Coating after compression isalso a useful method to slow the drug release due to an additional layer

Solvent associated methods

Biodegradable implants, particularly PLGA- or PLA- based implants can be prepared bymethods associated solvents. Solvent casting and solvent extrusion are included. For solventcasting, PLGA or PLA is first dissolved in an appropriate solvent that can dissolve thepolymers, for example dichloromethane and trichloromethane. The polymer solution is thencasting into a mold, which is usually a Teflon mold. The solvent is then evaporated at roomtemperature or a low temperature in order to control the evaporation rate. Finally, thebiodegradable film is vacuum-dried to remove the residual solvent. Biodegradable implants prepared by solventcasting always result into films or laminar implants. The implants can release a drug over aperiod of weeks to months. It also depends on the types of biodegradable polymers. Duration of action over several months is always demonstrated when using PLA as a carrier.Another solvent associated method is solvent extrusion. Firstly, a suitable volatile solvent isused to dissolve the biodegradable polymers. A high concentration of the polymer solution is required. The polymer solution is then extruded by force through a small orifice. The solventis allowed to evaporate and an extrudate is finally formed. For laboratory scale, a syringe anda silicone tube can be used in the process of solvent extrusion. A polymer solution is extrudedthrough a syringe connected to a silicone tube at the open end. The silicone tube helps a wetextrudate to form a required shape during solvent evaporation. An additional process is necessary when drug powders have to bedispersed in a high concentration of polymer solution. Micronization can solve this problem.The drug powders will be dispersed and suspended homogenously in the polymer solutionbefore extrusion. A drawback of the solvent associated methods is a presence of an organic solvent in the formula.

Injection-molding

Injection-molding was introduced to use as a pharmaceutical technique since 1964. It was previously a technique for plastic industries. A thermoplastic polymer is molten and injected into a specific mold. The molten polymer is solidified in the mold. A matrix tablet or implantis then achieved. The process is reproducibility and automatization. A tablet of an implant with desirable size and shape is easily obtained by injection-molding. Biodegradable polymers, particularly PLGA and PLA, can also be shaped in the form of an implant by injection-molding. Due to the exposure to heat of the process, a decrease in molecular weight of the biodegradable polymeris a problem of injection-molding when so high temperature is applied. A temperature rangeof 80 – 140°C by this method is suitable for the biodegradable polymer. Peptides, such as vapreotide, can beincorporated into PLA or PLGA by using injection-molding.

Ram extrusion

Ram extrusion is a process relating to force and high pressure. It is areciprocating (discontinuous) extruder. Heat is usually applied on thisprocess where a plunger presses on a soften polymer. PLGA- or PLAbasedimplants can be prepared by ram extrusion. Processing temperatures for extrusion ofPLGA and PLA polymers should be above their TG. The polymer is then softened enough tobe forced through a die. Since the processinvolving heat and pressure, a stability of an incorporating drug has to take in consideration. Dugs, which are unstable to heat and high pressure, cannot be prepared by this method without a process optimization. For therapeutic peptides and proteins, stability under a stresscondition as the high temperature and pressure in a ram extruder is an important issue. At thetemperature of 80°C, small amount of degradation or impurity have been found. An increasein the amount of impurity resulted from the ram extrusion at high temperature (above 120°C) for long extrusion time. Similarly, high temperatures and pressure effect on molecular weightof PLGA and PLA.

Hot-melt extrusion

Melt extrusion or hot-melt extrusion is briefly the process of melting, mixing, and forcing a mixer containing thermoplastic material through a small orifice called a die. Usually the process is performed under an elevated temperature. By this preparing method, PLGA- or PLA- based implants are basically a matrix system. The drug is disperseduniformly through put the implants. Depending upon type of melt-extruder, premixing is sometimes required to blend the polymer with the drug to obtain a homogeneous extrudate. The polymer carriers, which are PLGA or PLA for biodegradable implants, are molten and act as a thermal binder. To fabricate PLGA orPLA implants, an operating temperature above their TG has to be applied. By contrast, too high temperature is not allowed, because incorporating drugs can be thermallydegraded. Theoptimal extrusion temperature is in the range of 50-100°C. The difference in the temperature depends on drug loading, type and molecular weight of thebiodegradable polymer, and type of hot-melt extruders. Hot-melt extrusion for preparation of the biodegradable implants can considerate as an effective method. It is a continuous process and suitable for industrial productions A drug, peptide or protein, which is sensitive to organic solvents or water, can be incorporated into the biodegradable implants, for example degarelix. In comparison to the solvent associated methods and ram extrusion, degarelix was more stable the drug delivery system was prepared by hot-melt extrusion.

PRESENT AND FUTURE PROSPECTS

The implantable systems represent versatile devices especially well-suited for long term delivery of drugs. Steroidal contraceptive agents are delivered as subdermal implants for delivering agents at an optimum rate and concentration. Implantable infusion pumps are especially well suited for long term delivery of drugs in applications in which drug activity is enhanced by delivery directly into intravenous, intra-arterial, intrathecal, subdural, intra ventricular, intraperitoneal or other body location with the minimal risk of minimal infection and interference with the patient's life. This system provides a mean of accurately delivering therapeutic effect.

Implantable drug delivery devices with their use

DELIVERY SYSTEM	DRUG	USE
Reservoir type implantable system	Progestin+Estradiol	Contraceptive
	Megestrol	Contraceptive
	Norgestrel	Contraceptive
	Ibuprofen	Polyarthritis
	Naproxen	Polyarthritis
	Cyclophosphamide	Cancer
	Triethylene melamine	Cancer
	5-fluoro deoxyuridine	Cancer

REFERANCES

1. Jain N.K. "Advance in controlled and drug delivery" New Delhi CBS publishers & Distributers 2001 Pg. No.-204-26.
2. Brahmankar D.M., Jaiswal S.D. ―Bio pharmaceutics& pharmacokinetics, a treatise, 2nd Edition VallabhPrakashan 2009 pg.476-495.
3. Patel Ruchita, MogalRajendra, "Parenteral implants Drug delivery system –A Review" Pg. no.-194-203.
4. Milan Agrawal, Mahesh LImbachiya, " A review on Parenteral Controlled Drug Delivery system"International journal of pharmaceutical sciences & research (2012) vol.3 Pg.no. 3657-3669.
5. HimanshuK.Solanki *, JalaramH.Thakkar , GirishK.Jani, "Recent advances in implantable drug delivery" International Journal of Pharmaceutical Sciences Review and Research, Volume 4, October 2010; Article 028 Pg. no.168-177.
6. Hitesh Bari, "A Prolonged Release Parenteral Drug Delivery System – An overview", International Journal of Pharmaceutical Sciences Review and Research, Volume 3, Issue 1, July – August 2010; Article 001.Pg.no.1-11.
7. Karan Malik, Inderbir Singh, ManjuNagpal and SandeepArora, "Atrigel: A potential parenteral controlled drug delivery system", Pelagia Research Library
   Der Pharmacia Sinica, 2010, 1 (1): Pg.no. 74-81
8. WWW. Pharmatutor.org/ articles/Review-"Parenteral CDDS".