Implantable Controlled Drug Delivery Systems

WEEK 11

IMPLANTS

- Implants are long-acting dosage forms that provide continuous release of the drug substance often for periods of months to years.
- Implants are usually administered by means of
  - a surgical incision or by
  - a suitable special injector (e.g., trocar).

Implants are available in a variety of shapes, sizes and materials:

- pellets,
- resorbable microparticles,
- polymer implants (biodegradable or non-biodegradable),
- metal or metal/plastic implants (osmotic pumps and stents).

Advantages

- Localized delivery
- Improved patient compliance
- Minimized systemic side effects
- Lower dose
- Improved drug stability
- Suitability over direct administration
- Facile termination of drug delivery

Disdvantages

- Difficult implantation procedure (surgery-large implants)
- Complications of surgery (pain, infection)
- Local reactions
- Inadequate drug release

Therapeutic Applications of Implants

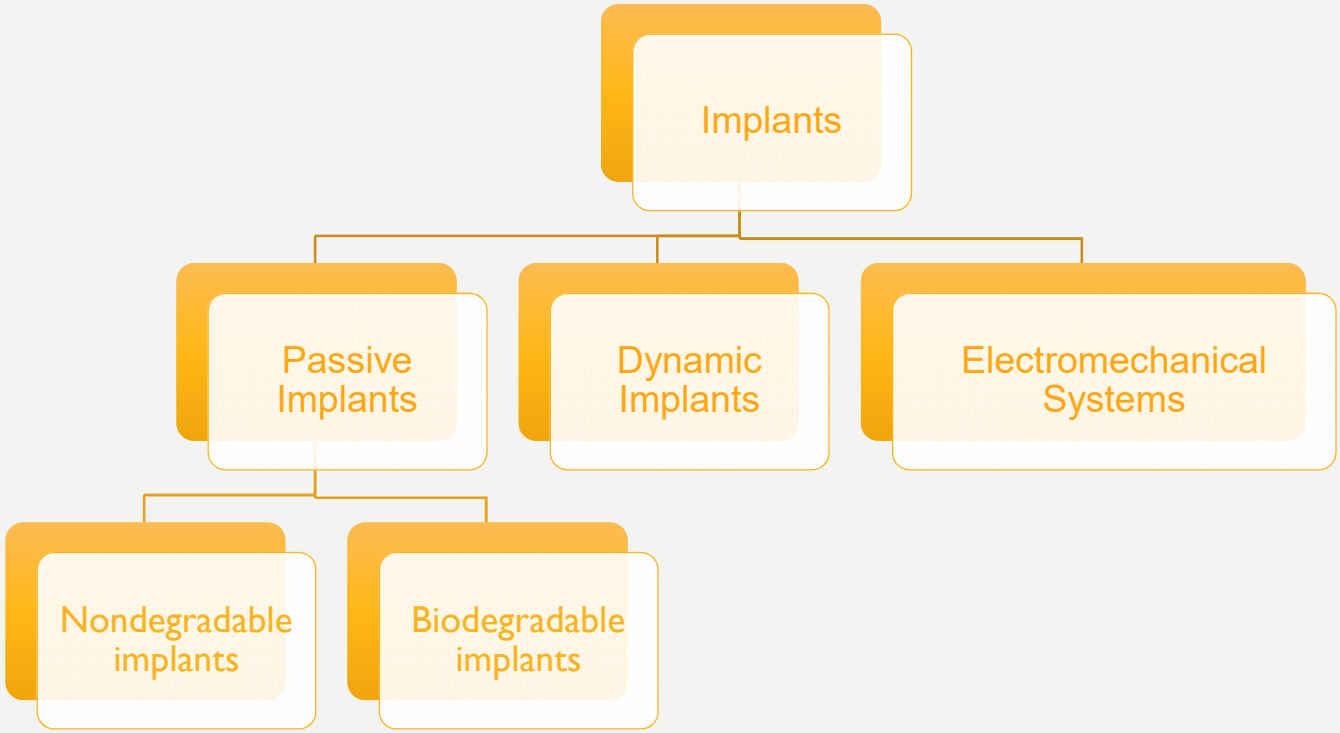
- Women's Health
- Chronic Diseases
- Infectious Diseases (Tuberculosis)
- Neurology and Central Nervous System Health

- Therapeutic effects of implants

- Systemic (SC,IM,IV)

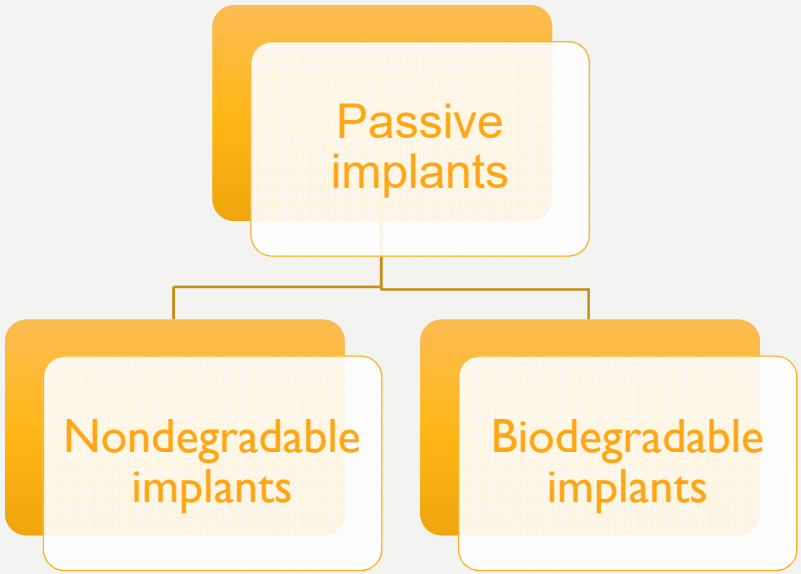
- Local therapeutic effects (intravaginal, intravascular, intraocular, intrathecal intracranial,peritoneal)

Classification of Implantable Drug Delivery Systems



Passive implants

Passive implants tend to be relatively simple, homogenous and singular devices, typically comprising the simple packaging of drugs in a biocompatible material or matrix. By definition, they do not contain any moving parts, and depend on a passive, diffusion-mediated phenomenon to modulate drug release.



Nondegradable implantable drug delivery systems

membrane-enclosed reservoirs and matrix-controlled system

Polymers include elastomers such as silicones and urethanes, acrylates and their copolymers, and copolymers vinylidenefluoride and polyethylene vinyl acetate (PEVA)

NORPLANT

- Contraceptive system
- six thin, flexible silicone capsules (silastic tubing)
- 36 mg of the hormone levonorgestrel
- SC implantation on the inside upper arm of female users,
- 5 years

IMPLANON

- Contraceptive system
- A single-rod implant (length 4 cm, width 2 mm)
- PEVA membrane
- 68 mg of etonogestrel
- SC implantation
- 3 years

DES- drug-eluting stent

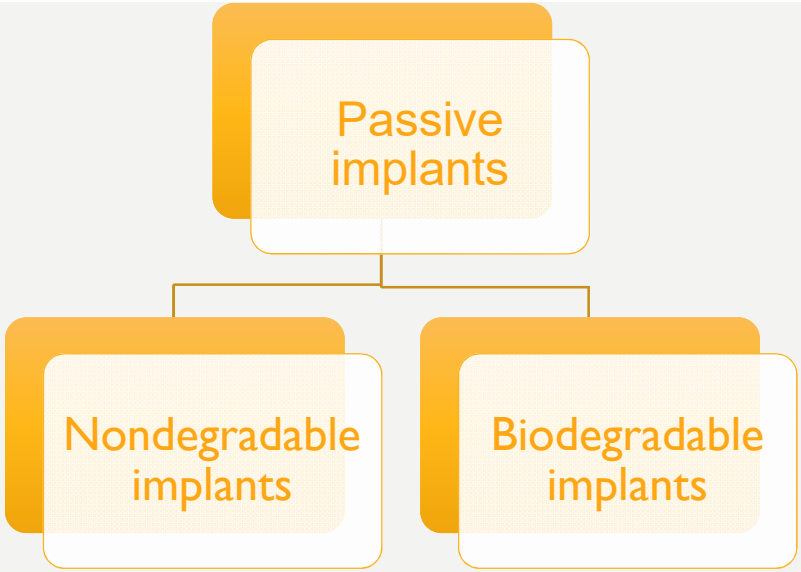
- treatment of vascular diseases
- reduce restenosis typically seen in bare-metal stents
- a three-component system, comprising a scaffold (or stent) for ensuring vascular luminal patency, a matrix or coating (polymer) to control drug release, and a drug to inhibit neointimal restenosis.
- Diffusion controlled drug release

Vitrasert

- Antiviral drug- ganciclovir
- cytomegalovirus (CMV) retinitis.
- compressed tablet of the drug coated with polyvinyl alcohol (PVA), then partially over-coated with PEVA, and finally affixed to a PVA suture stub.

Drawbacks:

- Need for extraction after depletion of the drug cargo
- Risk of infection and cosmetic defacement at the site of subcutaneous implantation



Biodegradable implantable drug delivery systems

biocompatible polymers used for fabricating these delivery systems are eventually broken down into safe metabolites and absorbed or excreted by the body

Polymers include poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(caprolactone) (PCL) or their block copolymer variants with other polymers

Gliadel wafer

- approved by the FDA in 1996
- of biodegradable polyanhydride disks (1.45 cm in diameter and 1.0 mm thick)

- chemotherapeutic drug, carmustine
- biodegradable polyanhydride copolymer

Zoladex

- goserelin acetate
- PLGA or PLA -drug is dispersed in the polymer matrix using hot-melt extrusion method
- prefilled syringe
- biodegradable polyanhydride copolymer
- continuously released over a period of 1 or 3 months

Profact Depot or Suprefact Depot

- buserelin acetate (gonadotropinreleasing hormone agonist)
- PLGA (75:25 molar ratio
- 2- and 3-month drug release

Passive implants

Dynamic implant systems harness a positive driving force to enable and control drug release. As a result, these are typically able to modulate drug doses and delivery rates much more precisely than passive systems. However, this comes at a higher cost, both in terms of complexity and actual device price.

- Implantable pump systems
- Osmotic pumps
- Propellant infusion pumps

• IMPLANTABLE PUMP SYSTEMS

External control of dosing is a requirement for many drugs, a feature that is difficult to obtain when using biodegradable or nondegradable delivery systems. Pump systems have been used to provide the higher precision and remote control needed in these situations. Additionally, they offer a number of advantages, such as evasion of the GI tract, avoidance of repeated injections, and improved release rates (faster than diffusion-limited systems).

Implantable pumps primarily utilize osmosis, propellant-driven fluids, or electromechanical drives to generate pressure gradients and enable controlled drug release.

Osmotic pumps

The design comprises a drug reservoir surrounded by a semipermeable membrane, which allows a steady inflow of surrounding fluids into the reservoir through osmosis. A steady efflux of the drug then ensues via the drug portal, an opening in the membrane, as a result of the hydrostatic pressure built on the drug reservoir. Nearly constant or zero-order drug release is maintained until complete depletion of the drug packaged in the reservoir

Viadur-DUROS Device

The system is under further development for the delivery of exenatide and has also been investigated for the delivery of other drugs, including interferon (OMEGA DUROS system), sufentanil (Chronogesic system), and other opioids.

Propellant infusion pumps

- The volume of drug that they can release limits the usage of osmotic pumps
- Propellant gas is used instead of an osmotic agent

Infusaid

- Device consists of a small titanium disc which is divided into two chambers by cylindrical titanium bellows that form a flexible but impermeable barrier between the compartments.
- The outer compartment contains Freon (chlorofluorocarbon propellant);
- The inner compartment contains the infusate and connects via a catheter to a vein or artery through a series of filters and flow-regulating resistant elements.
- The vapour pressure above the liquid propellant remains constant because of the relatively constant temperature of the body, and hence a constant pressure is exerted on the bellows, ensuring a constant rate of delivery of infusate into the bloodstream.
- utilized for insulin delivery, anticoagulant therapy, and cancer chemotherapy

Electromechanical Systems

While osmotic and propellant-driven constant pressure pumps work well for small volumes of medication, this may be a severe limitation for certain chronic diseases requiring daily infusion of medication, precluding their use over long timespans. In such cases, it may be necessary to consider larger implants, wherein the storage capacity of the pump may be replenished from time to time, while the pumping mechanisms stay implanted. By necessity, this implies the use of electrically powered mechanical pumps, typically with moving parts and advanced control systems

Synchromed

- a peristaltic pump implant
- external micro-electronic control of the delivery rate
- pain management using intrathecal delivery of opioids
- The pump consists of an outer titanium shell that encases the pump mechanism and controller, a reservoir holding the drug solution, and a battery.
- It can be conveniently refilled with a needle and syringe via a silicone rubber septum on the system.
- The system is typically implanted in the abdominal cavity.

Micro electromechanical systems (MEMS) technology enables the manufacture of small devices using microfabrication techniques, similar to that used to fabricate silicon-based computer chips. MEMS technology has been used to construct micro-reservoirs, micropumps, nano-porous membranes, nanoparticles, valves, sensors, micro-catheters, and other structures using biocompatible materials appropriate for drug administration.