B Pharm 7th Semester
Novel Drug Delivery Systems
BP-704T Unit-2
Implantable Drug Delivery Systems

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Introduction

- **Implants are delivery systems that are inserted or grafted into the body for therapeutic, diagnostic, or experimental purposes.**
- Implants are designed to provide **continuous release** of drug into the bloodstream over long period of time without the repeated insertion of needles.
- Implants are placed under the skin and designed to release drugs into the bloodstream without the repeat insertion of needles.
- **Implants consist of drug and rate-controlling excipients.**

Introduction

- Implantable drug delivery system are very attractive for the classes of drugs that cannot be taken
- via the oral route due to
  - irregularly absorbed via the gastrointestinal tract
  - drugs that undergo first pass metabolism.
- Drugs that are give for prolong therapy like contraceptives.

Introduction

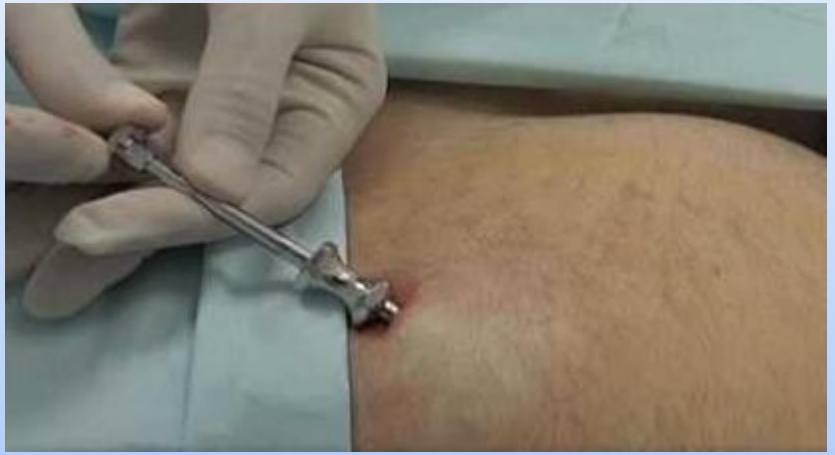
Subcutaneous and intramuscular tissue are ideal locations for implantation of drug-depot due to

- high fat content that facilitates slow drug absorption,
- minimal nerve supply,
- good hemoperfusion and
- low possibility of localized inflammation or
- low reactivity to the insertion of foreign materials

various other body regions have also successfully served as implantation sites, particularly for delivery to localized tissue such as intravaginal, rectal,intravascular, intraocular, intrathecal, intracranial, and peritoneal

Introduction

- Implant drug delivery systems can be used as delivery systems for either systemic or local therapeutic effects.
- Implants are administered by means of a suitable special injector or surgical incision.



Implants: Definition

- 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.
- A sterile drug delivery device for subcutaneous implantation having the ability to deliver drug at a controlled rate over a prolonged period of time, comprising a rod shaped polymeric inner matrix with an elongated body and two ends.

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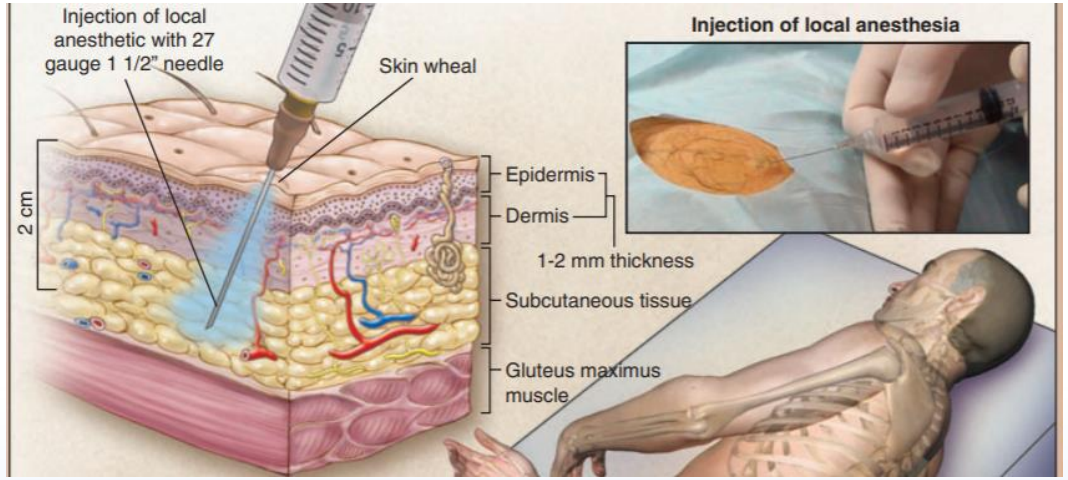

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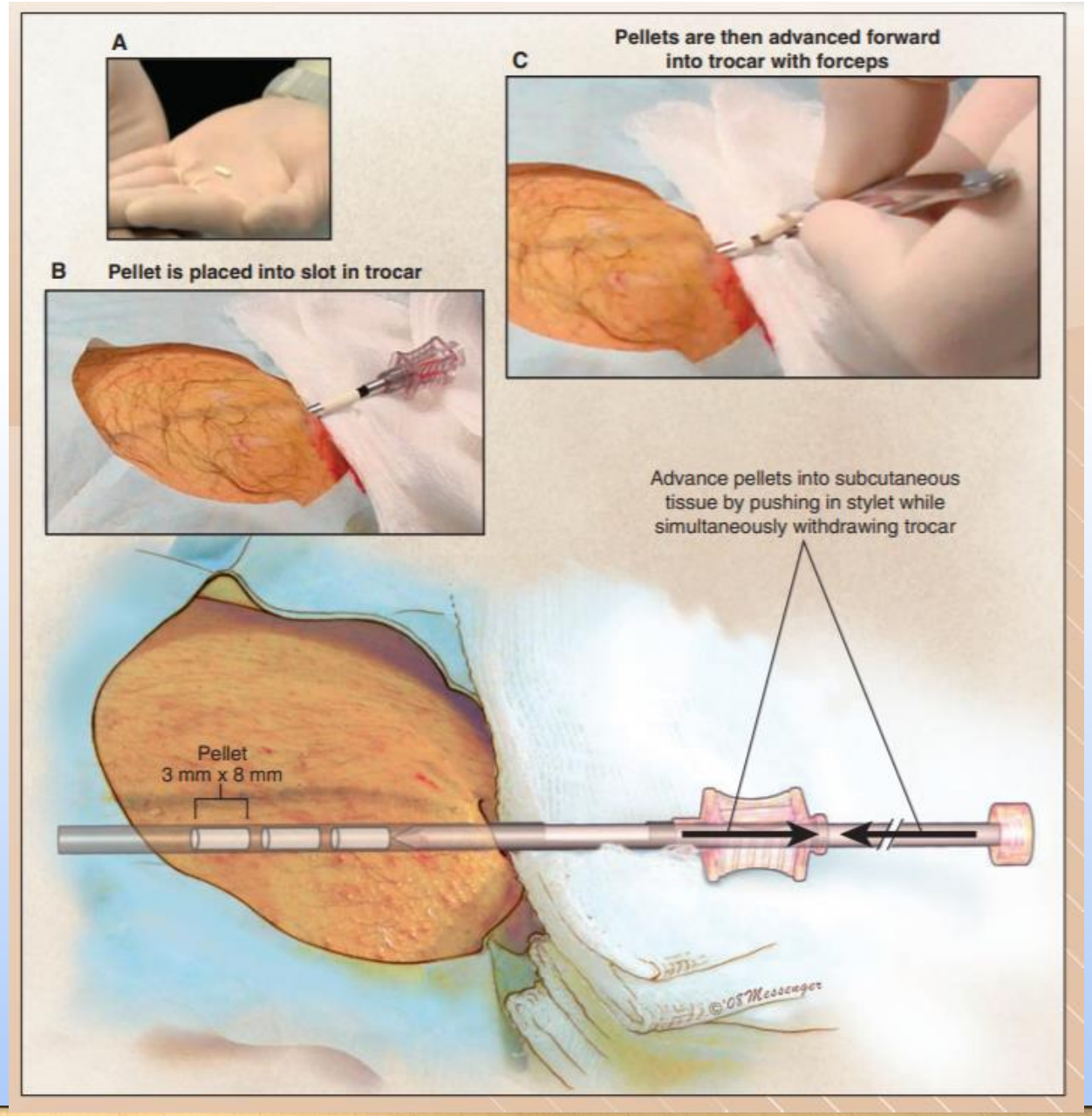

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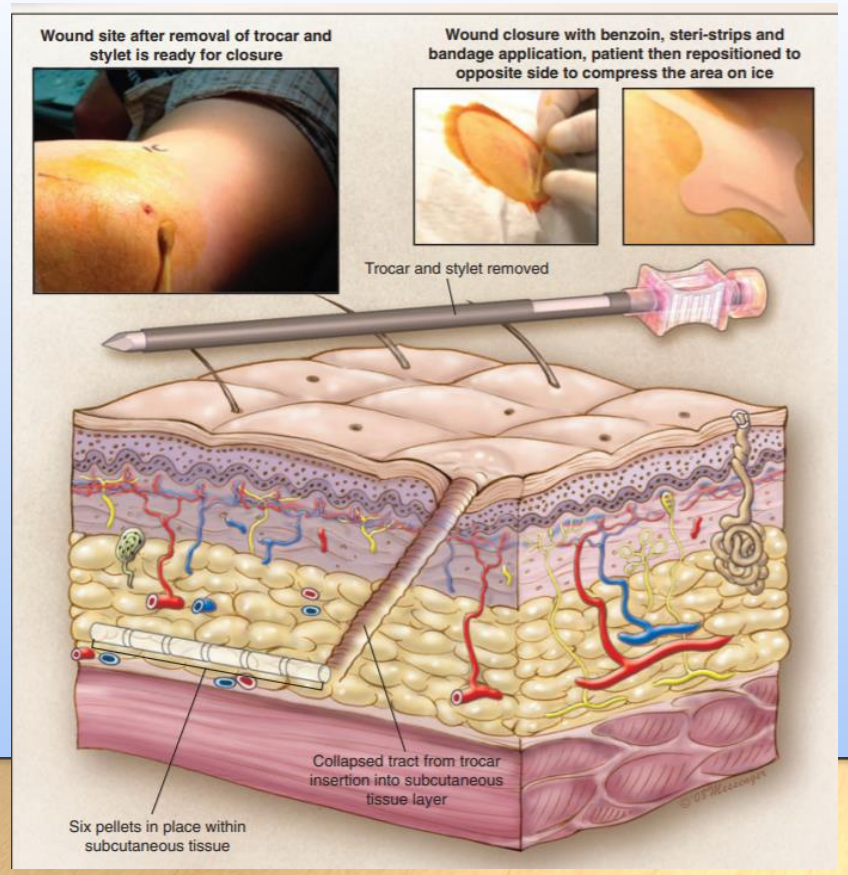

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Ideal properties of an implantable drug delivery system

- Environmentally stable
- Non toxic and non-carcinogenic
- Biocompatible
- Biostable.
- Easy to sterilize
- release drug in controlled rate
- Improve patient compliance by reducing the frequency of the administration

- Easy to manufacture & relatively inexpensive
- Good mechanical strength
- Free from surgical procedure.
- Minimum surface area, smooth texture.
- readily implantable and retrievable
- provide cost-effective therapy

Advantages

- Implantable drug delivery systems can provide controlled drug delivery for a long time period with unattended continuous delivery within the therapeutic window.
- Improved patient compliance and enhanced drug efficacy
- Avoids the highly variable peak and trough concentrations and minimized side effects
- Targeted drug delivery
- Bypasses first pass metabolism.

Advantages

- Localized implantation of site specific drugs can reduce dose required to ensure systemic bioavailability
- Improve the stability of drug by providing protection of drug against rapid degradation in the gastrointestinal and hepatobiliary system

Disadvantages

- Invasive: the patient has to face either a major or a minor surgical procedure
- Implantation procedure is difficult in the case of larger implants and it is painful.
- Termination: non-biodegradable polymeric implants after depletion of drug, they need to be removed by surgical method
- Inadequate release.
- The reaction between host and implant.
- sometimes they can cause infections, tissue damage or cosmetic disfigurement

Classification Of Implantable Drug Delivery Systems

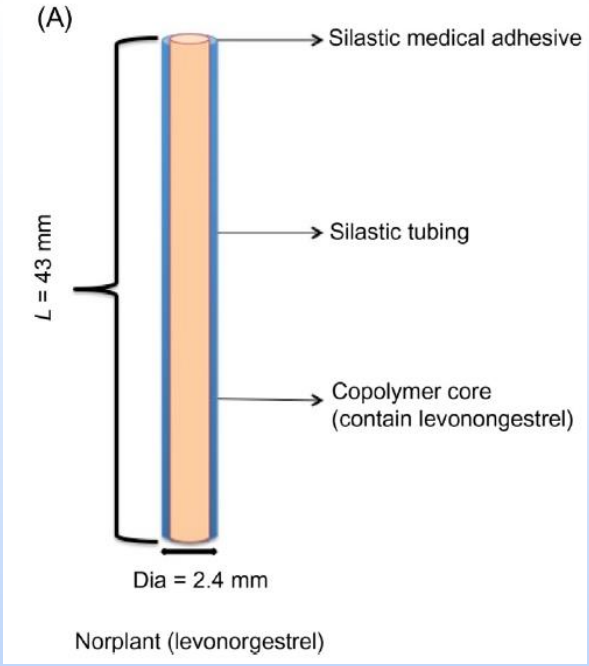
- **Passive System:** they rely on passive diffusion for drug release
  - Nondegradable Implants and
  - Degradable implants
- **Active systems:** employ some energy-dependent method for providing a positive driving force to modulate drug release

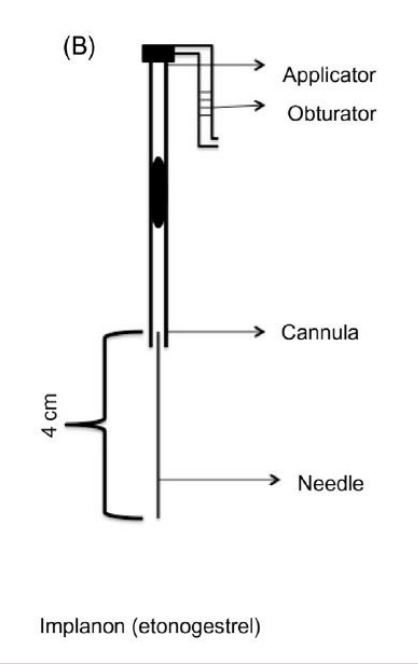
Non-Biodegradable Polymeric Implantable Systems

- These can be monolithic (drug is homogeneously dispersed in polymeric matrix) or reservoir type(drug core covered by a permeable non-biodegradable membrane).
- Polymers such as silicones, poly(urethanes), poly(acrylates) or copolymers such as poly(ethyelene vinyl acetate) are used.
- Extensively used for contraceptive delivery.

Non-Biodegradable Polymeric Implantable Systems

- A- Norplant
- B- Implanon





Non-Biodegradable Polymeric Implantable Systems

- The main drawback of non-biodegradable implants is that after depleting their drug load, they need to be removed.
- sometimes they can cause infections, tissue damage or cosmetic disfigurement
- Thus 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.

Biodegradable Polymeric Implantable Systems

- can be monolithic or reservoir type
- Polymers such as poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(caprolactone) (PCL) or their block copolymer variants with other polymers
- Biocompatible polymers are used for fabricating these delivery systems which are broken down into safe metabolites and absorbed or excreted by the body
- In biodegradable polymers, labile bonds(such as ester, amide, and anhydride bonds) are prone to degradation by hydrolysis or enzymes.
- Complete removal of the implant after postdrug release makes surgical removal of the implant unnecessary and increasing patient acceptance and compliance

Classification: Mechanism of drug release from implantable therapeutic system

1. **Diffusion Controlled System**

- Polymer membrane permeation controlled implantable delivery system
- Polymer matrix diffusion controlled implantable delivery system
- Membrane-matrix hybrid type implantable delivery system
- Microreservoir partition controlled implantable delivery system
  - Hydrophilic reservoir/Lipophilic matrix
  - Lipophilic reservoir/hydrophilic matrix

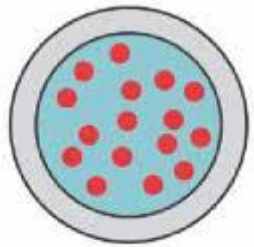
2. **Activation Controlled System**

- Osmotic pressure activated drug delivery system
- Vapor pressure activated drug delivery system
- Magnetically activated drug delivery system
- Hydration Activated drug delivery system
- Hydrolysis activated drug delivery system

Classification based on Route of Administration

- **Subcutaneous Implants**-Grafted beneath skin for prolong drug therapy ex. Norplant subdermal implant
- **Intraocular Implants/Inserts**- implanted/inserted in eye ex- Ocuserts
- **Intravaginal Implants**-inserted in vagina ex.
- **Intrauterine Implants**- inserted in uterus ex. Copper-T

Polymer membrane permeation controlled implantable delivery system



Reservoir device

Polymer membrane

- Non porous membrane
- Microporous membrane
- Semipermeable membrane

Drug

solid particles or
dispersion of the solid particles in a liquid or solid dispersing medium

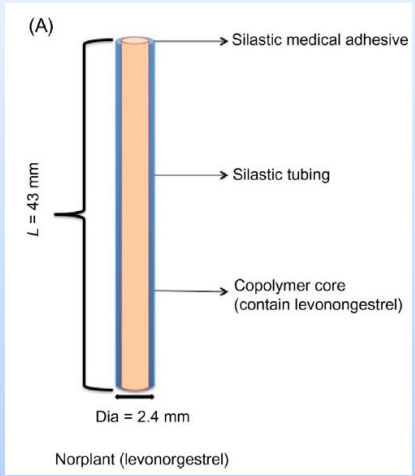
Examples

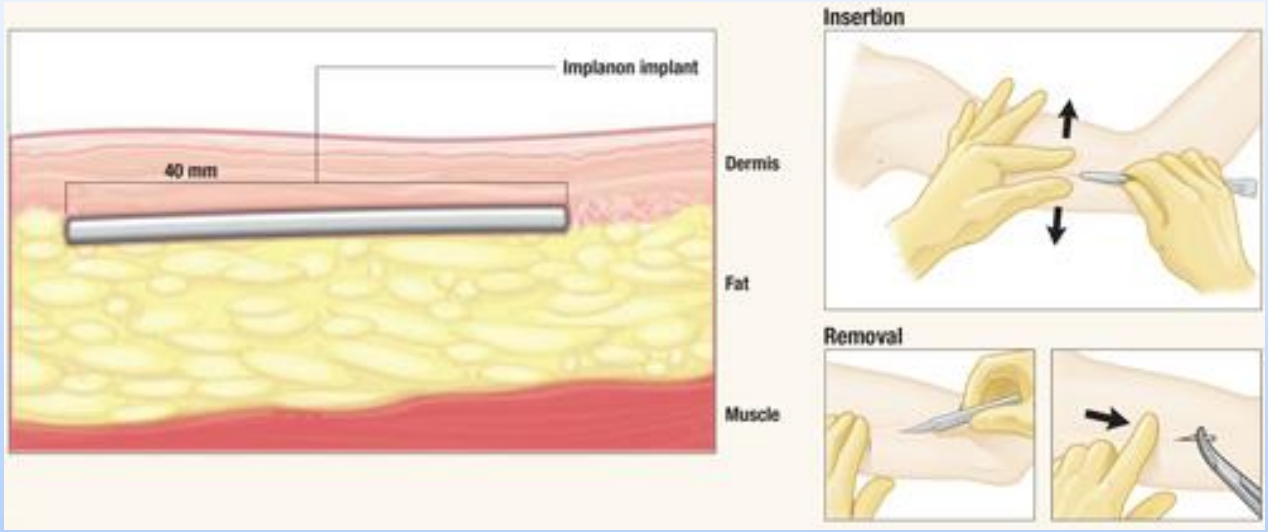
- Norplant subdermal implant
- Ocusert
- Progestasert IUD

- Drug reservoir is totally encapsulated within a capsule shaped or spherical compartment with a rate controlling polymeric membrane.
- The encapsulation of the drug reservoir system inside the polymeric membrane can be done by the encapsulation, microencapsulation, molding, extrusion etc.

Polymer membrane permeation controlled implantable delivery system

- Example: Norplant subdermal implant. Implantation of 6 units of norplant subdermal implant in the subcutaneous tissue of a human subject's arm





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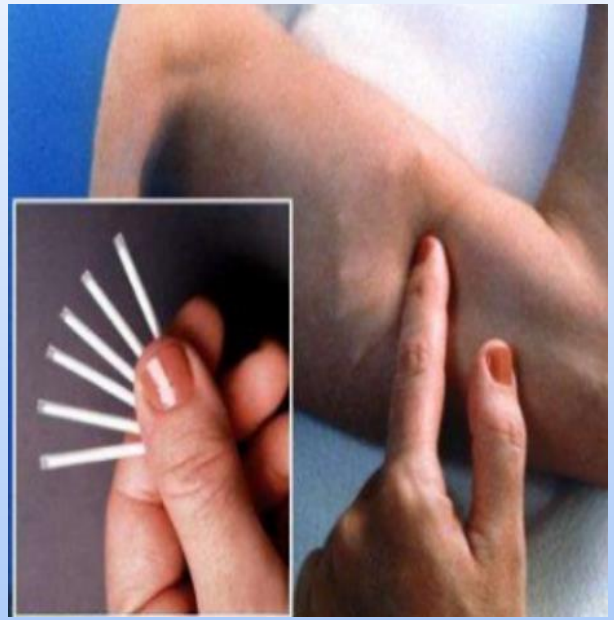
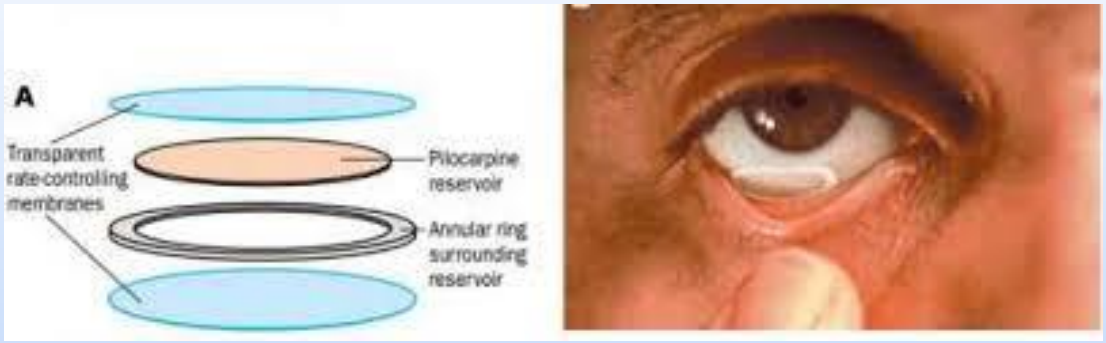


https://www.slideshare.net/MBHRY/contraception-for-undergraduate

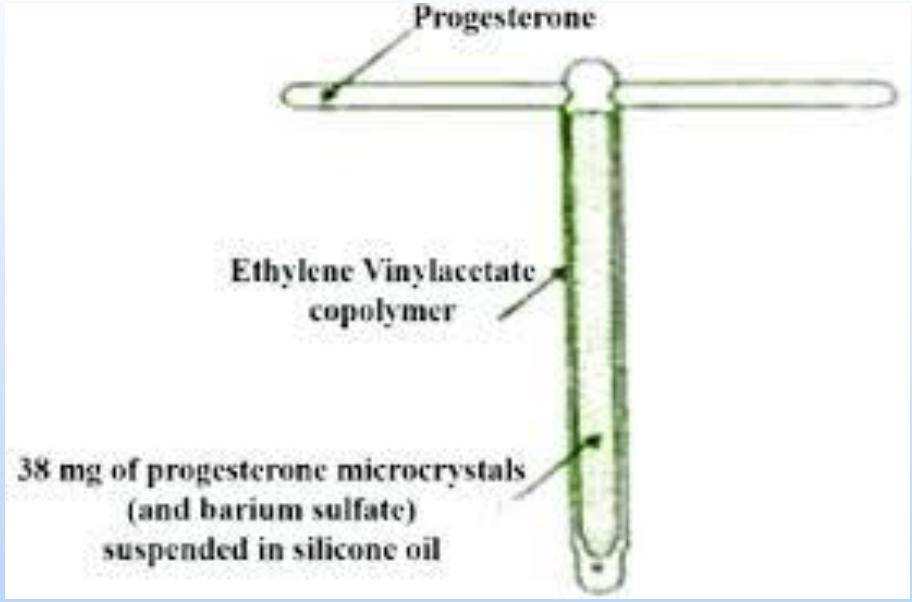
Polymer membrane permeation controlled implantable delivery system

- Ocusert



https://www.guwsmedical.info/intraocular-pressure/drug-delivery-systems.html

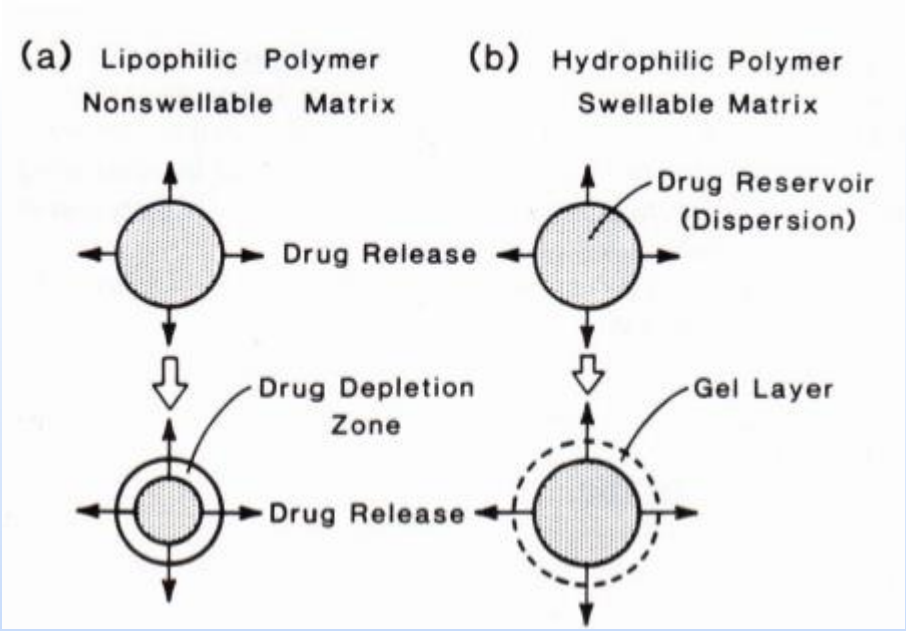
Progestasert IUD



https://www.researchgate.net/figure/Progestasert-IUD-with-structural-components-shown-adapted-from-137_fig11_343040416

Polymer matrix diffusion controlled implantable delivery system

- This type of implants are formed by dispersion of the solid particles throughout a polymer matrix
  - Lipophilic polymers nonswellable polymers ,
  - Hydrophilic swellable polymers ,
  - Porous polymers
- It can also be prepared by
  - taking drug polymer dispersions are then molded or extruded to form drug delivery devices of various shapes or
  - dissolving the drug and polymer in an organic solvent followed by conservation or solid evaporation at an elevated temperature under a vacuum to form microsphere.



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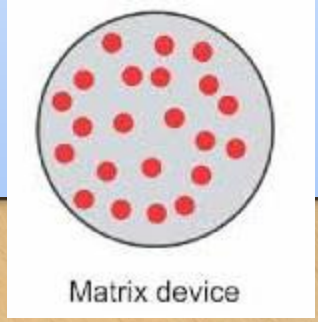
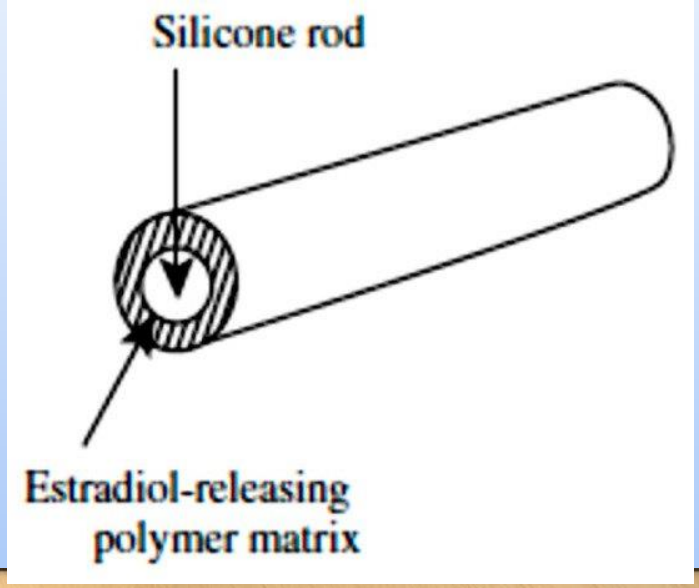


Polymer matrix diffusion controlled implantable delivery system

- **Example: Compudose implant.**
- It is a cylindrically-shape implant in which estradiol crystals are dispersed in a viscous silicone elastomer and coated in rigid (drug-free) silicone rod by extrusion that improves growth rate



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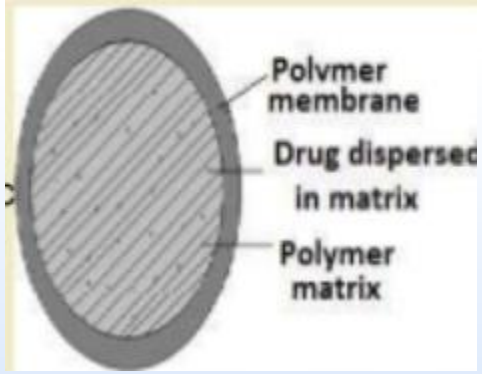
Membrane-matrix hybrid type implantable delivery system

- This delivery system is a hybrid form of polymer membrane permeation controlled delivery system and the polymer matrix permeation controlled drug delivery system.
- It shows the constant drug release kinetics just like the polymer membrane permeation controlled drug delivery system.
- These are also prepared by the homogeneous dispersion of the drug solid particles throughout a.
- this reservoir polymer matrix is encapsulated within a rate controlling polymeric membrane.
- This is actually a sandwich type implantable device.
- Example: Norplant II subdermal implant.



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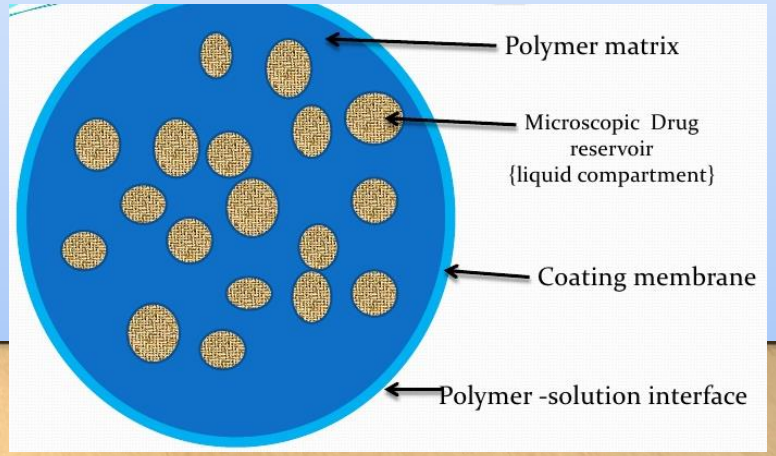
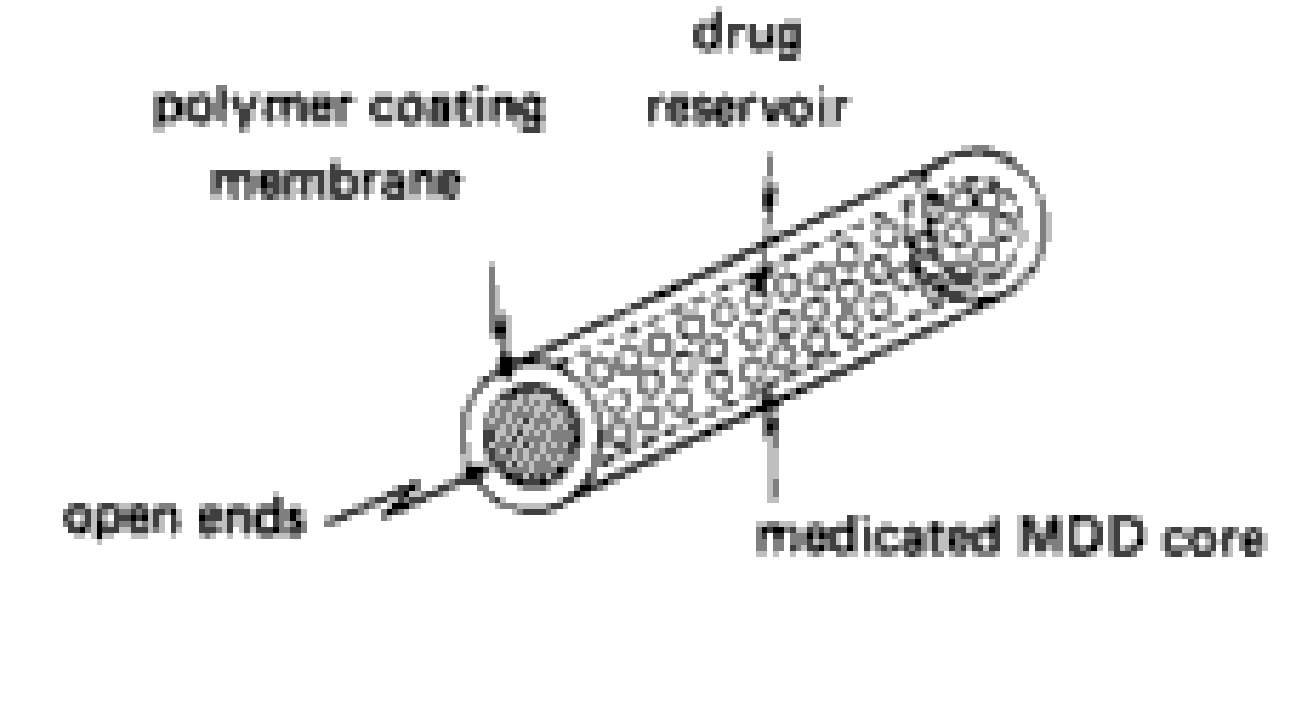
Microreservoir Partition Controlled Implantable Delivery System

- In this device the drug reservoir is a suspension of drug crystals in an aqueous solution of water miscible polymer & it also forms a homogeneous dispersion.
- Microdispersion is obtained by the high energy dispersion technique.
- size and shapes of drug delivery devices can vary
- further coated with a layer of biocompatible polymer to modify the mechanism & the rate of drug release. Example: Syncromate implant.



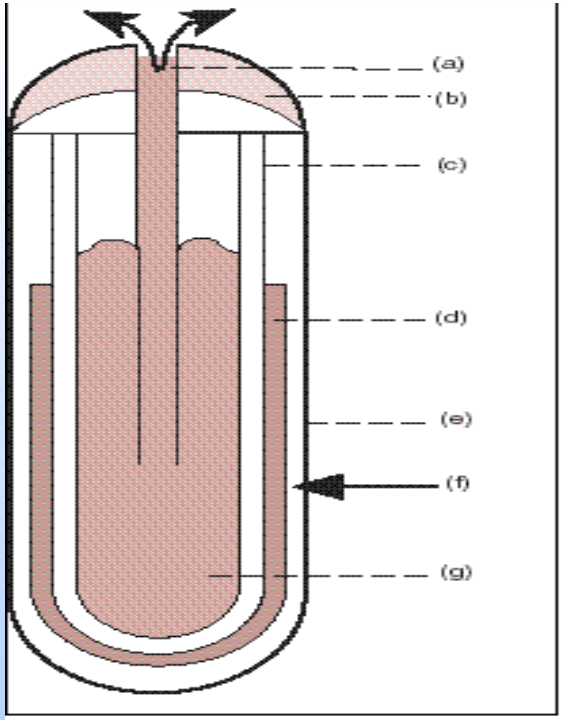
Ex. Syncro mate - c



- It is fabricated by dispersing the drug reservoir, which is a **suspension of norgestomet** in an aqueous solution of PEG 400, in a viscous mixture of silicone elastomer.

Osmotic Pressure Activated Drug Delivery System

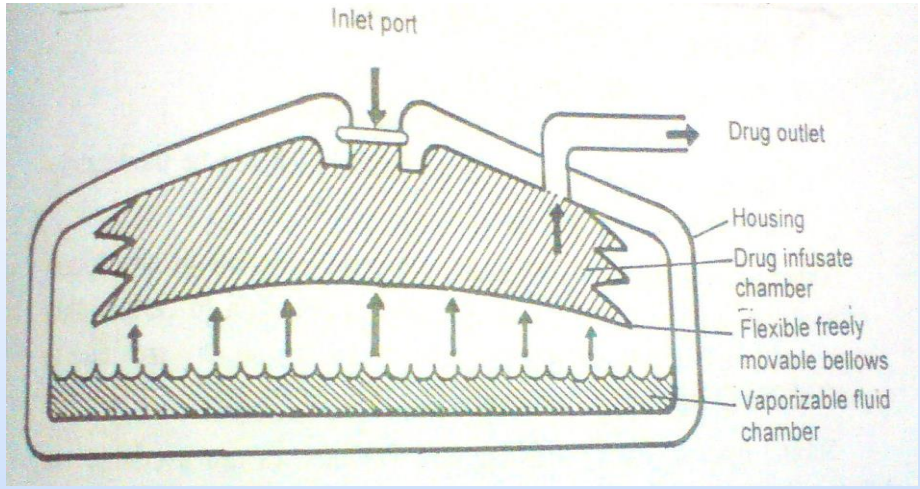
- Osmotic pressure is the main source of energy in this case to activate and modulate the delivery of drug.
- The drug reservoir is either a solution, semisolid solid formulation which is contained within a semipermeable compartment with controlled water permeability.
- Example: Alzet osmotic pump.



The elements of an osmotic pump:
(a) drug solution leaving through delivery portal;
(b) removable cap;
(c) impermeable reservoir wall;
(d) osmotic agent;
(e) semipermeable membrane;
(f) water entering through semipermeable membrane; and
(g) reservoir.

Vapour Pressure Activated Drug Delivery System

- In this device the vapor pressure is mainly used as the power source to activate the controlled delivery of drugs.
- The drug reservoir contains a solution.
- The reservoir stays inside an infusate chamber.
- Infusate chamber is physically separated from the vapour pressure chamber by freely movable bellows.
- Vapour pressure chamber contains a vaporizable fluid viz. Fluorocarbon.
- Fluorocarbon vaporizes at body temperature and & creates the vapour pressure which will forcefully move the bellow in upwards direction.
- Therefore the drug solution enters into the cannuals at a constant flow rate and we can calculate the flow rate with the help of the equation.



Magnetically Activated Drug Delivery System

- Electromagnetic energy is used as the activation source to trigger the drug delivery.
- A magnetic wave triggering mechanism is incorporated into the drug delivery device.
- Subdermally implantable, magnetically modulated hemispherical drug delivery device was fabricated by positioning a tiny donut shaped magnet at the center of a polymer matrix.
- It contains a homogeneous dispersion of a drug with low polymer permeability at a rather high drug-polymer ratio to form hemispherical pellet.
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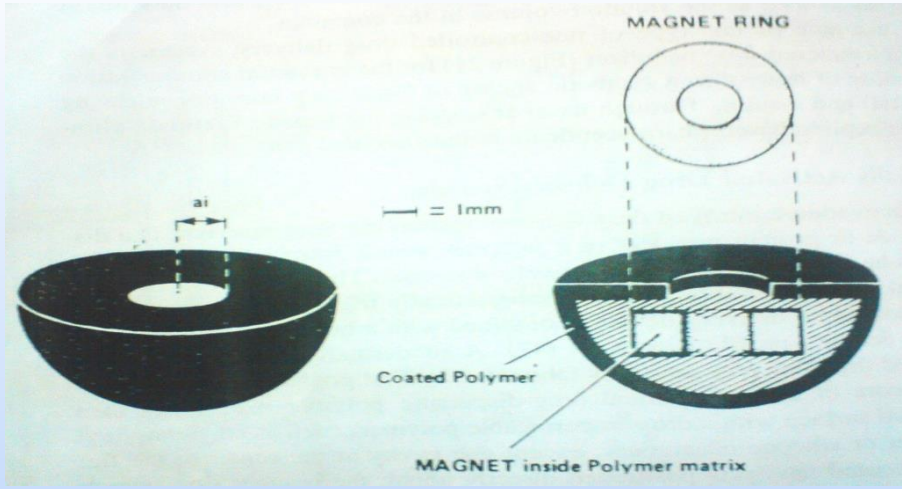
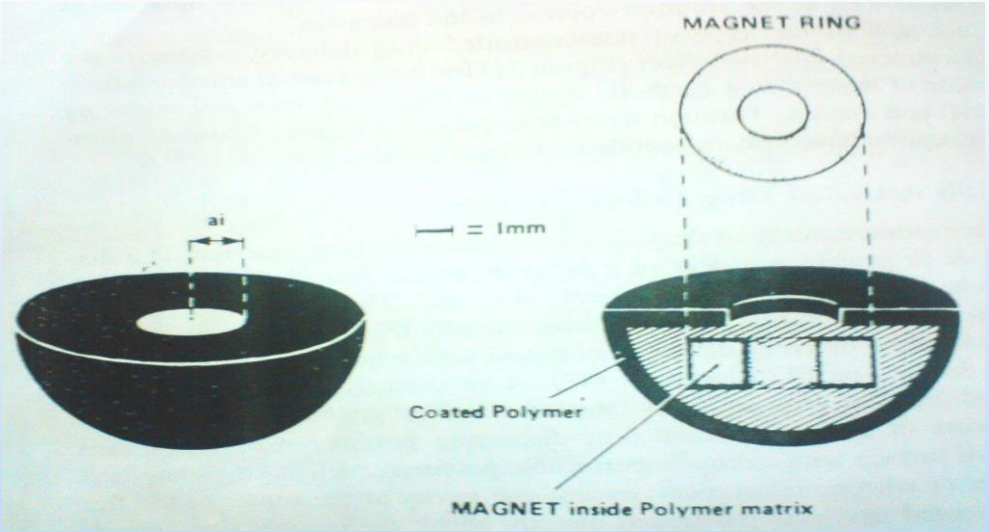


Magnetically Activated Drug Delivery System

- The external surface of the hemispherical pellet is totally covered with a pure polymer, viz. Ethylene vinyl acetate copolymer.
- By applying an external magnetic field the drugs are activated by the electromagnetic energy to release from the pellet at a much higher rate of delivery.
- Example: Bovin serum albumin (BSA) is generally given by the help of this device



Hydration Activated Drug Delivery System

- In this type of device drug molecules are released upon activation by hydration of the drug delivery device by tissue fluid at the implantation site.
- This device is generally prepared from the hydrophilic polymer.
- Drug molecules are released by the diffusion through the water saturated pore channels in the swollen polymer matrix.
- Example: Norgestomet releasing hydron implant for estrus synchronization in heifers.
- This subdermal implant is extremely small in size and can be easily implanted into the animal's ear flap (dorsal side).

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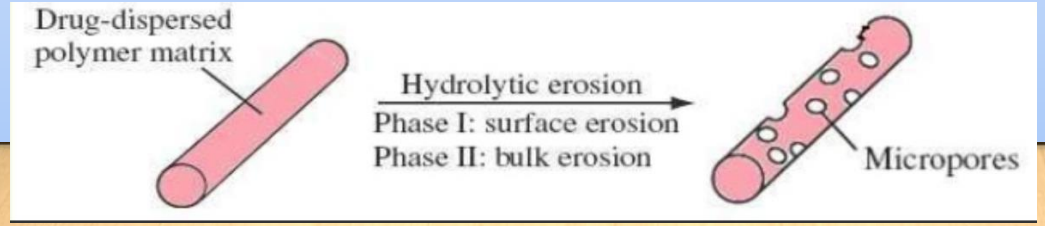
Hydrolysis Activated Drug Delivery Device

The drug release is activated by the hydrolysis.

- This hydrolysis is generally happened on the polymer base by the application of the tissue fluid at the implantation site.
- the drug delivery device is fabricated by dispersing a loading dose of drugs in micronized form in biodegradable polymer and then it is molded into a pellet or bead shaped implant.
- the rate of drug release is determined by the rate of biodegradation, polymer composition and molecular weight, drug loading and drug-polymer interaction.
- The rate of drug release is not constant and highly dependent upon the erosion process of the polymer matrix.
- Example: biodegradable naltrexone pellets fabricated from poly copolymer for the antinarcotic treatment of opoid-dependent-addicts.



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Applications

1. Biomedical application

- An implantable drug delivery system offers a great advantage injectable controlled release formulations.
- Parenteral controlled administration of drugs via subcutaneous or intramuscular drug delivery device can gain easy access to the systemic circulation to achieve a total bioavailability of drugs as well as a continuous delivery of drugs unlike transdermal, oral etc. routes of administration.

2. Human application

- Implantable drug delivery systems have been discovered with the aim to achieve continuous administration of systemically-active drugs for the long term regulation of a physiological process.
- example of human application is norplant and Norplant-II subcutaneous contraceptive drug delivery system.

Applications

- A new generation of subcutaneous contraceptive implant, “Implanon” is recently developed and it is also a sandwitch type implant device.
- Continuous heparinization in anticoagulation treatment with the help of a infusaid pump is also available today.
- Infusid pumps are also applied for the intravenous controlled infusion of insulin for the continuous treatment of diabetis. A soluble insulin preparation is used as the drug reservoir in this case.
- Nowadays several biodegradable subdermal implants has been made with the help of biodegradable polymers.
- With the help of subcutaneous injections of goserelin in solution followed by subcutaneous administration of the goserelin-releasing subdermal implalnt at three dose levels clinical evaluation of the antitumor effect is also possible.

3. Veterinary application

- Several implantable drug delivery devices have been prepared from biocompatible polymers for veterinary application.

- Biocompatibility need to be investigated, such as the formation of a fibrous capsule around the implant and, in the case of erosion-based devices there is the possible toxicity or immunogenicity of the byproducts of polymer degradation.

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