IMPLANTABLE THERAPEUTIC SYSTEMS

Dr.D.VARUN

Professor & Academic Director

SRI INDU INSTITUTE OF PHARMACY

Hyderabad

HISTORICAL DEVELOPMENT

- The concept of implantable therapeutic systems for long term continuous drug administration pioneered with the development of subcutaneously implantable drug pellet

- Application of biocompatible polymers to the construction of implantable therapeutic systems for achieving a better control of drug release in terms of duration of drug activity and precession of long term dosing, was not realized until accidental discovery of the controlled drug permeation characteristics of silicon elastomers.

✓Implant systems was developed when the paths of two unrelated experiments unexpectedly converged.

- In a trail to treat experimental heart block with thyroid harmone pellet that would release a minute dose of the harmone locally at steady rate.

- In other trail experimenting with the heart valves fabricated from silicon elastomers, studying how well these silicon valves performed under stress in turbulent water.

✓ For photography purposes, an attempt was made to stain the transluscent valves with various types of dyes. Then observed that certain oil soluble dyes such as Rhodamine and Sudan III would penetrate the lipophilic silicone valves and stain them easily…, Where as water soluble dyes like methylene blue and Chlorazol balck would not..

- This observation triggered the imagination of applying the reversible sorption of lipophilic dyes into and out of the silicone elastomer as a means to control the release of drugs for long term medication.

- The following drugs are successfully evaluated for release through implants…

Thyroid harmone powder, Isoproterenol, Digoxin , EDTA, Histamine , Atropine, Progesterone , Radiolable steroids….

- All of these historical developments have explored the potential of using silicone capsules as the implantable therapeutic systems to control the duration of drug activity and the precession of long term continual dosing.

- Later, concentrated effort was made to expand the silicone elastomer based implantable therapeutic technology to other biocompatible polymers, which one can be applied to control the release of water soluble molecules.

Some of the Implantable Therapeutic Systems that have been evolved……

- Micro porous membrane made from Ethylene / Vinyl acetate co-polymer for the ocular controlled administration of Pilocarpine

- The bio-degradable (Lactic / Glycolic) co-polymer for subcutaneous and intramuscular controlled administrations of narcotic antagonists.

- Bioerodable Polysaccharide polymers for Occular controlled administration of Anti-inflammatory steroids

- Hydrogels for the subcutaneous controlled administration of estrus synchronizing agents.

- The SC implantation of drug pellets is known to be the first medical approach aiming to achieve prolonged and continuous administration of drugs.

- The first generation of Implantable therapeutic systems was produced by compressing drug crystals with or without pharmaceutical ingredient into a tiny, cylinder shaped solid pellet that can be readily implanted into a SC tissue by means of a KEARNS PEELET INJECTOR or by making a small incission.

- Subcutaneous tissue is essentially a sheat of aereolar tissue lying directly underneath the skin, it is rich in fat but poor in nerve network ….which is the ideal location for implantation and prolonged drug administration because of its ready access to implantation, slow drug absorption, and low reactivity to the insertion of foreign materials.

APPROACHES TO THE DEVELOPMENT OF IMPLANTABLE THERAPEUTIC SYSTEMS

- Controlled Drug Release by Diffusion
- Controlled Drug Release by Activation

CONTROLLED DRUG RELEASE BY DIFFUSION

- **Membrane permeation controlled drug delivery using…**
  - Non porous membranes
  - Micro porous membranes
  - Semi permeable membranes
- **Matrix diffusion controlled drug delivery using….**
  - Lipophilic polymers
  - Hydrophilic (swellable) polymers
  - Porous polymers
- **Microreservoir dissolution controlled drug delivery using…**
  - Hydrophilic reservoir / Lipophilic matrix
  - Lipophillic reservoir / Hydrophilic matrix

CONTROLLED DRUG RELEASE BY ACTIVATION.

- Osmotic pressure activated drug delivery
- Vapour pressure activated drug delivery
- Magnetism activated drug delivery
- Ultrasound activated drug delivery
- Hydrolysis activated drug delivery

MEMBRANE PERMEATION CONTROLLED DRUG DELIVERY

C_p – Solubility of the drug in the polymer phase

C^1_p – Concentration of the drug in the polymer / solution interface

C_p – Concentration of the drug in the solution / diffusion layer interface

C_b - Concentration of drug in the bulk of the solution

δ_m – Thickness of polymeric membrane

δ_d – Thichness of hydrodynamic diffusion layer.

$$dQ / dt = C_R / 1 / P_m + I / P_d$$

$$P_m = K_{m/r} D_m / \delta_m$$

$$P_d = K_{a/m} D_a / \delta_d$$

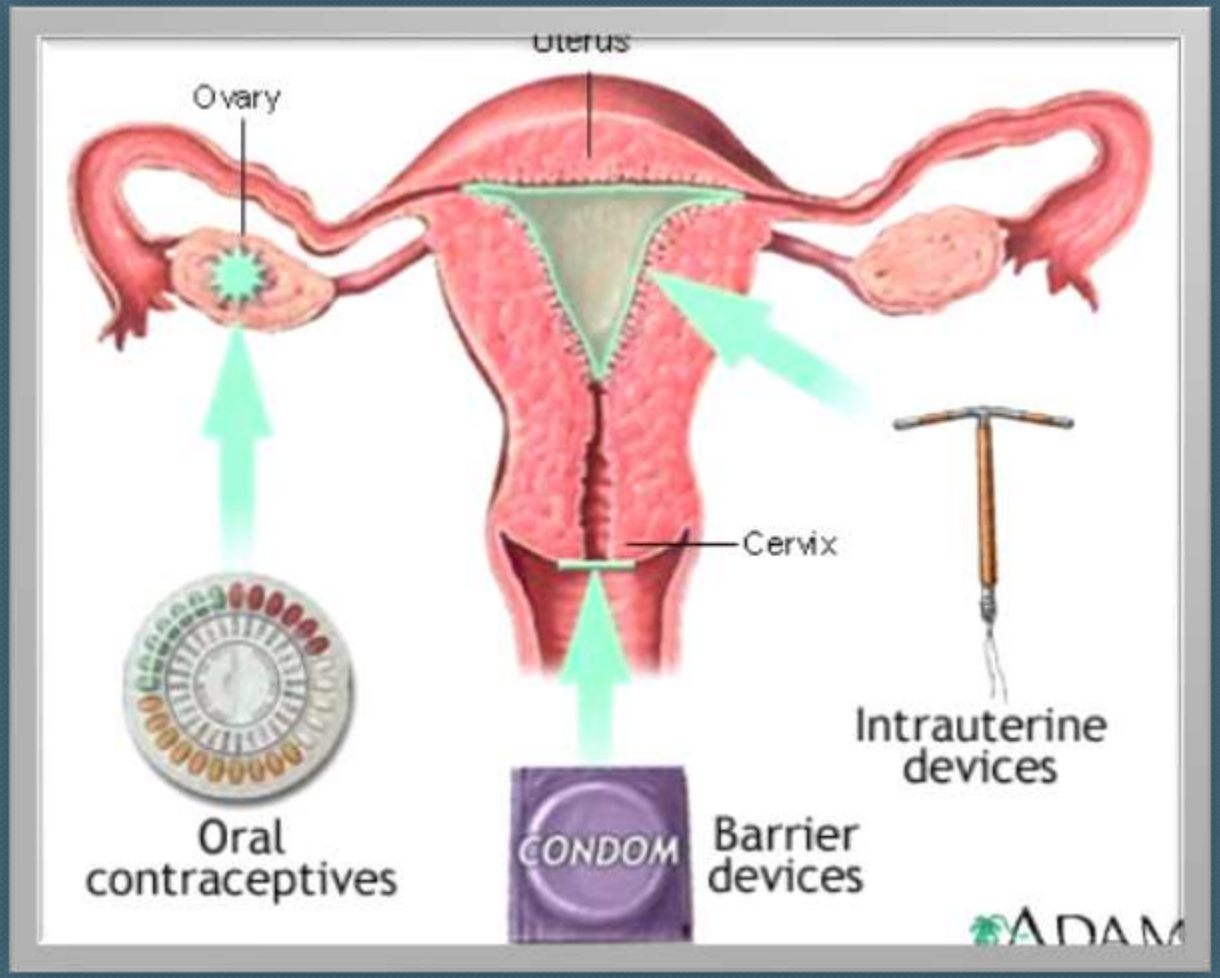
Examples //

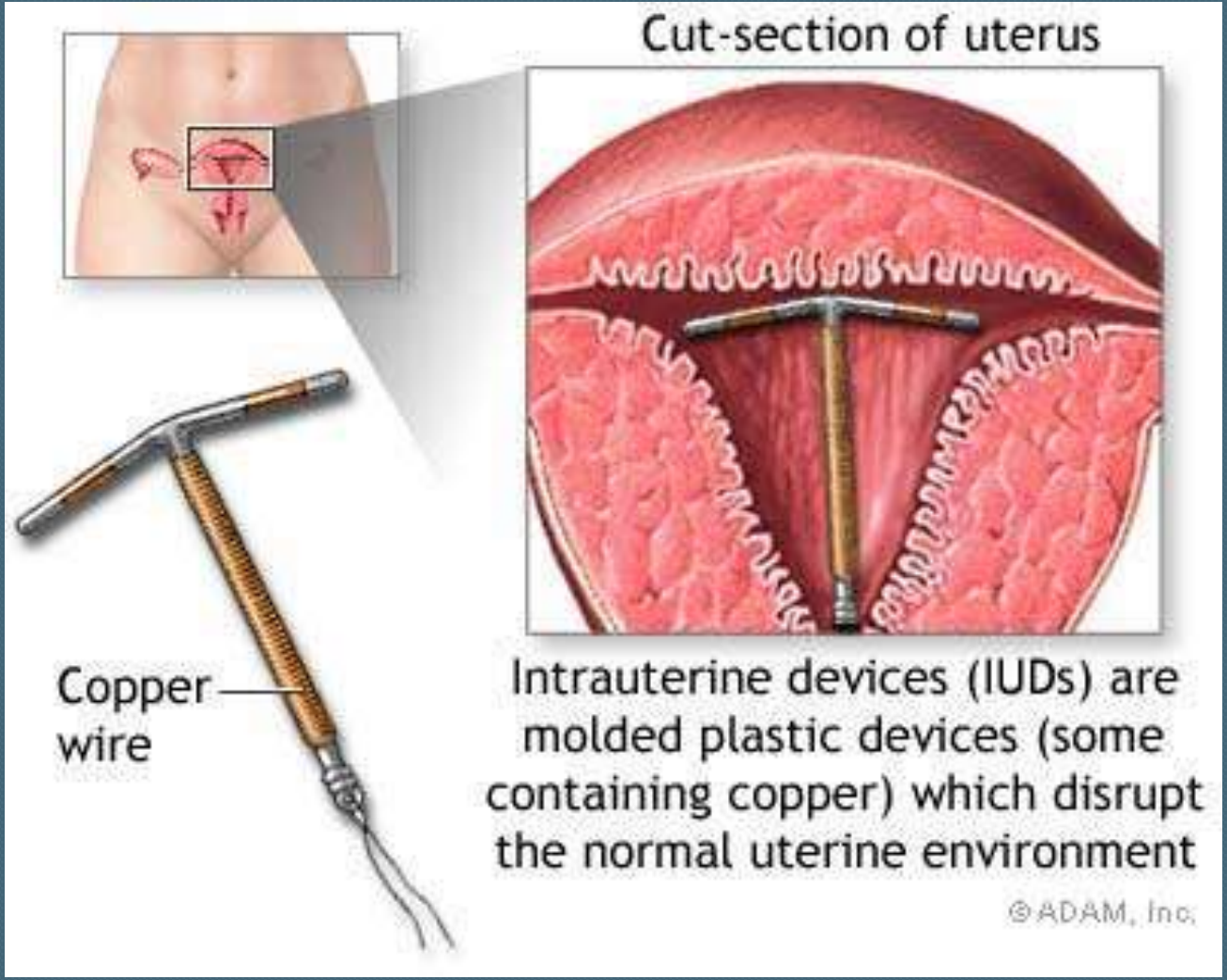
- **PROGESTASERT IUD**

In this device, drug reservoir is a suspension of Progesterone crystals in liquid silicone polymers is encapsulated in a T shaped intrauterine device enclosed by non porous membrane of ethyl- vinyl acetate co-polymer

Fabricated to release 65 mcg / day of progesterone locally in the uterine cavity to achieve contraception for one year.

PROGESTASERT IUD




Cut-section of uterus
Copper wire
Intrauterine devices (IUDs) are molded plastic devices (some containing copper) which disrupt the normal uterine environment
©ADAM, Inc.

▫OCCUSERT SYSTEM

In this device, drug reservoir is a thin disc of Pilocarpine alginate is sandwitched between two transparent sheets of microporous membrane fabricated from ethyl- vinyl acetate co-polymer

It is designed to permit the tear fluid to penetrate the microporous membranes, to dissolve and too carry out Pilocarpine at a constant rate of 20-40 mcg / hr for weekly management of Glaucoma

MATRIX DIFFUSION CONTROLLED DRUG DELIVERY

A – Initial amount of the drug solids impregnated in a unit volume of polymeric martix

C_p – Solubility of the drug in the polymer phase

C^1_p – Concentration of the drug in the polymer / solution interface

C_p – Concentration of the drug in the solution / diffusion layer interface

C_b ~ Concentration of drug in the bulk of the solution

δ_d & δ_d– Thickness of drug depletion zone in the matrix and of the hydrodynamic diffusion layer

$$dQ / dt = [AC_p D_p / 2t]^{1/2}$$

Examples //

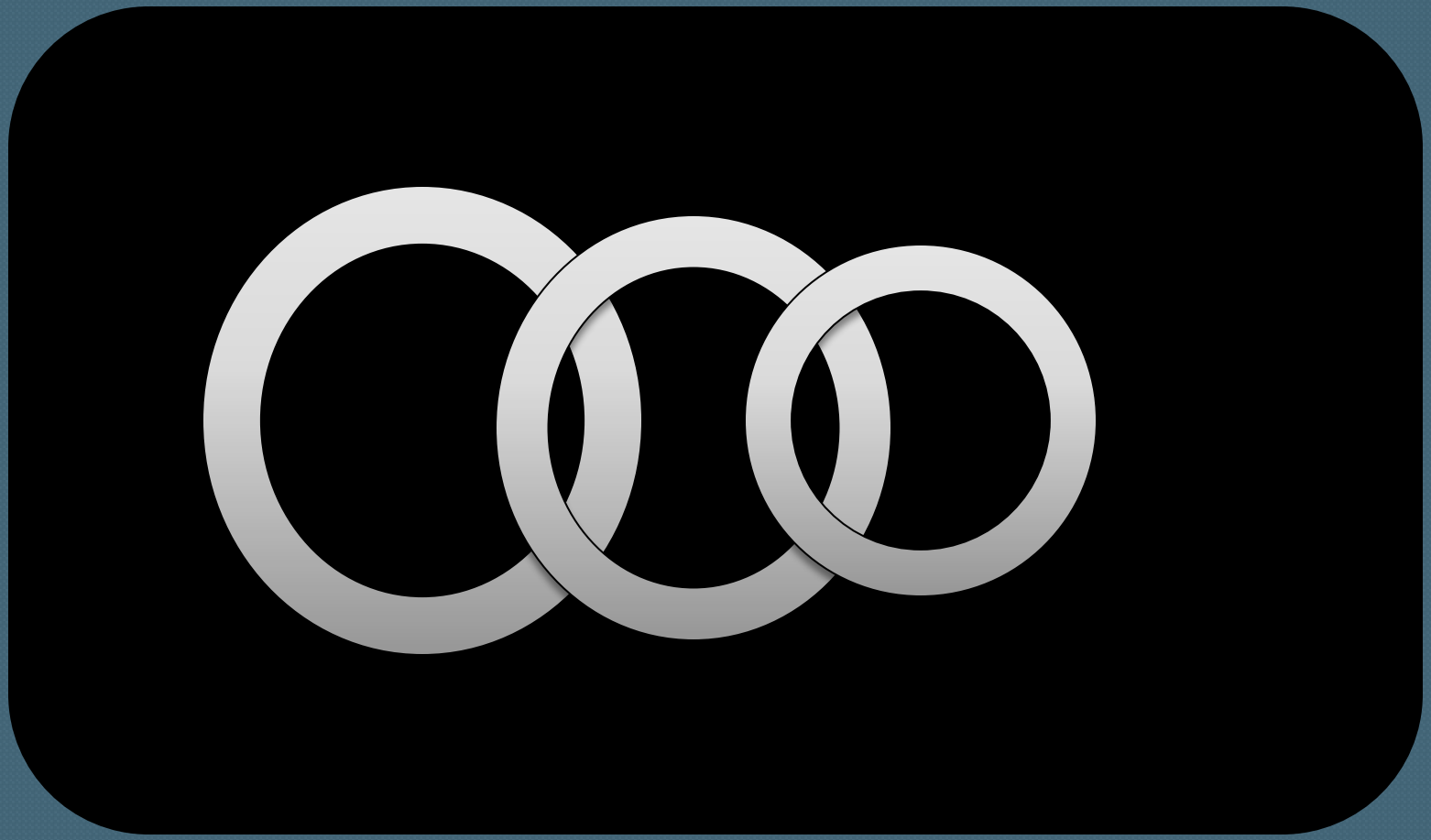
- **CONTRACEPTIVE VAGINAL RING**

It is fabricated by dispersing a contraceptive steroid Medroxyprogesterone acetate as micronized solid particles in a viscous mixture of silicone elastomer and catalyst and then extruding the steroid polymer dispersion into mould to form a donut shaped vaginal ring

It is designed to insrt into the vagina and positioned around the cervix for 21 days to achieve a constant plasma progestin level and cyclic intravaginal contraception.

-

CONTRACEPTIVE VAGINAL RING



❑COMPUDOSE IMPLANT

It is fabricated by dispersing micronized Estradiol crystals in a viscous mixture of silicone elastomer and catalyst and then coating the Estradiol - polymer dispersion around a rigid silicone rod by extrusion technique to form a cylinder shaped implant

It is designed for subcutaneous ear implantation in steers for 200 – 400 days and to release a controlled quantity of Estradiol for growth promotion.


COMPUDOSE®
Estradiol
AH-0370-020
200 DAY CONTROLLED RELEASE IMPLANTS


ENCORE & COMPUDOSE
VetLife
COMPUDOSE
Estradiol
CONTROLLED
RELEASE IMPLANTS 20 IMPLANTS
ACTIVE DRUG INGREDIENT: Each silicone rubber implant
contains 25.7 mg estradiol and is coated with not less than
0.5 mg of oxytetracycline powder as a local antibacterial.
For subcutaneous ear implantation in steers and heifers only.
See enclosed literature for complete directions for use.
WARNING: Keep out of reach of children.
COMPUDOSE is a registered trademark of Ivy Animal Health, Inc.
Manufactured for VetLife by Ivy Laboratories
Overland Park, KS 66214, USA
VetLife and Ivy Laboratories are divisions of Ivy Animal Health, Inc.
Questions or comments call 1-888-462-3493
Manufactured by a non-sterilizing process.
NADA 118-123, Approved by FDA
LOT 12602
EXP NOV 09

MICRORESERVOIR DISSOLUTION CONTROLLED DRUG DELIVERY

Examples //

Dual release Vaginal Contraceptive Ring –

It is fabricated by dispersing the drug reservoir which is suspension of Progestin and Estrogen in a aqueous solution of PEG 400, to form many microscopic drug reservoirs in a viscous mixtures of silicone elastomers and is polymerized by heat to form a donut shaped Vaginal ring.

It is designed to permit the users to insert the ring themselves and to release both the Progestin & Estrogen at a specific ratio in the vagina for 21 days to achieve a cyclic intravaginal contraception.

CONTROLLED DRUG RELEASE BY ACTIVATION

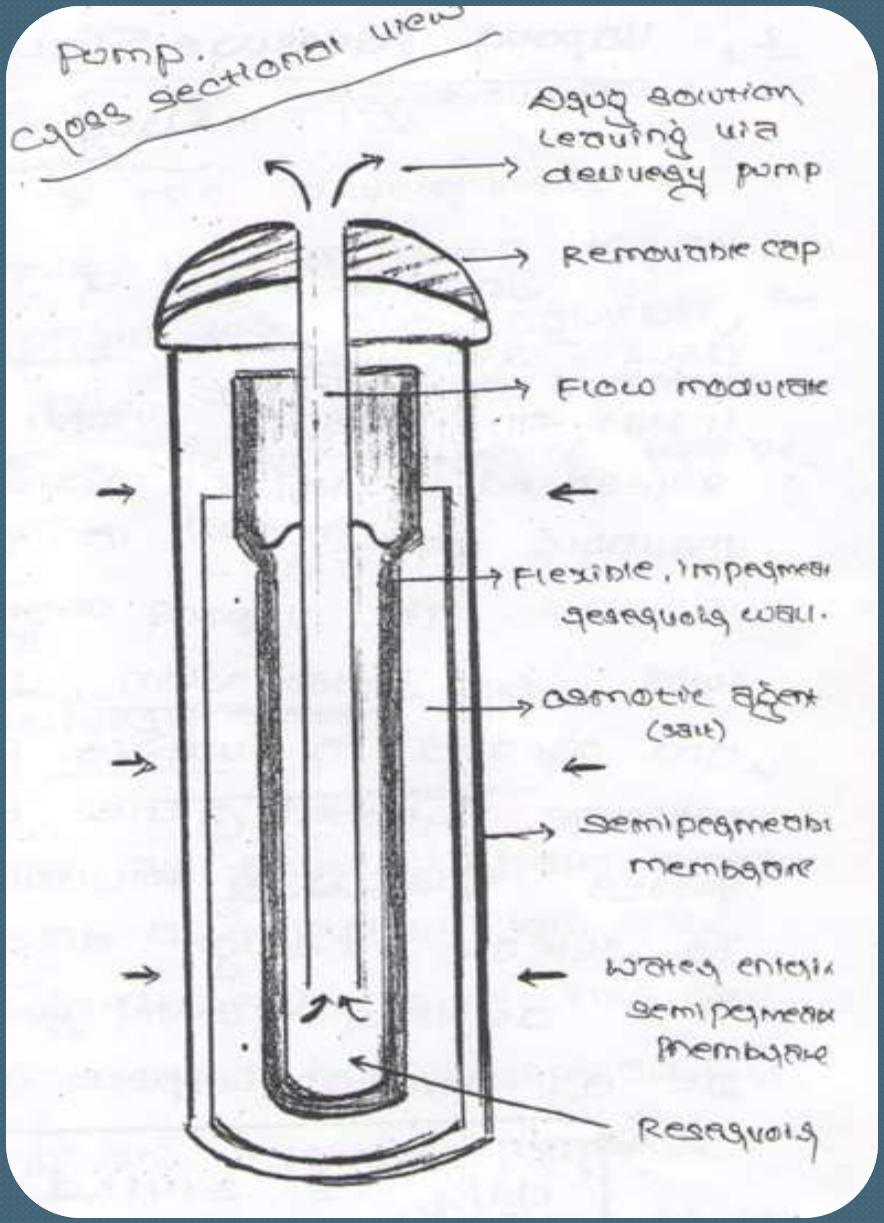
- **OSMOTIC PRESSURE ACTIVATED DRUG DELIVERY**

In this mode of controlled drug delivery, the drug is released in solution form at controlled, constant rate under the osmotic pressure gradient.

$$dQ / dt = P_w A_w / h_m (\pi_s - \pi_e)$$

- **Alzet Osmotic Pump**

ALZET OSMOTIC PUMP



VAPOUR PRESSURE ACTIVATED DRUG DELIVERY

- In this mode of controlled drug delivery, the drug is released in solution form is contained inside an infusate chamber, which is physically separated from the vapour chamber by a freely movable bellows.

$$dQ / dt = 3.1416\, d\, 4\Delta P / 128\mu l$$

Example //

Infusaid – an implantable infusion pump for the constant infusion of Heparin for anticoagulation, treatment of insulin for antidiabetic medication and of morphine for patients suffering from the intensive pain of terminal cancer

MAGNETISM ACTIVATED DRUG DELIVERY

- Macromolecular drugs like peptides have been known to release only at a relatively low rate from a polymeric drug delivery device.

- This low release rate have been improved by incorporating a magnetism triggering mechanism into a polymeric drug delivery device.

ULTRASOUND ACTIVATED DRUG DELIVERY

- Ultrasonic waves can also be utilized as an energy source to facilitate the release of a drug at a higher rate fro polymeric drug delivery containing a bioerodible polymer matrix.

Example – Poly [bis (p-carboxyphenoxy) alkane anhydrade]

HYDROLYSIS ACTIVATED DRUG DELIVERY

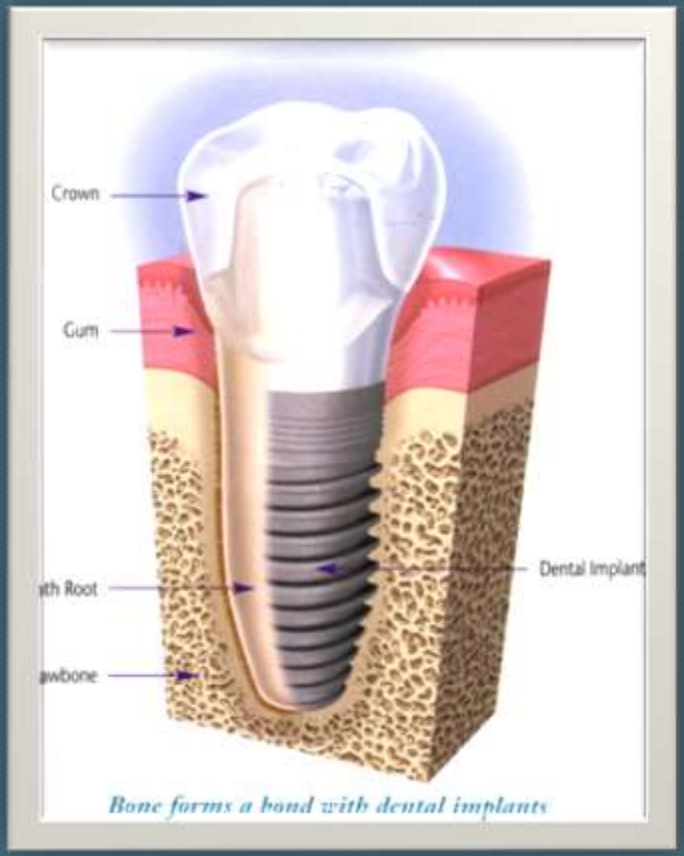
- This is fabricated by dispersing a loading dose of solid drug, in micronized form homogeneously throughout a polymer matrix made from bioerodible or biodegradable polymer, which is then moulded into a pellet or bead shaped implant

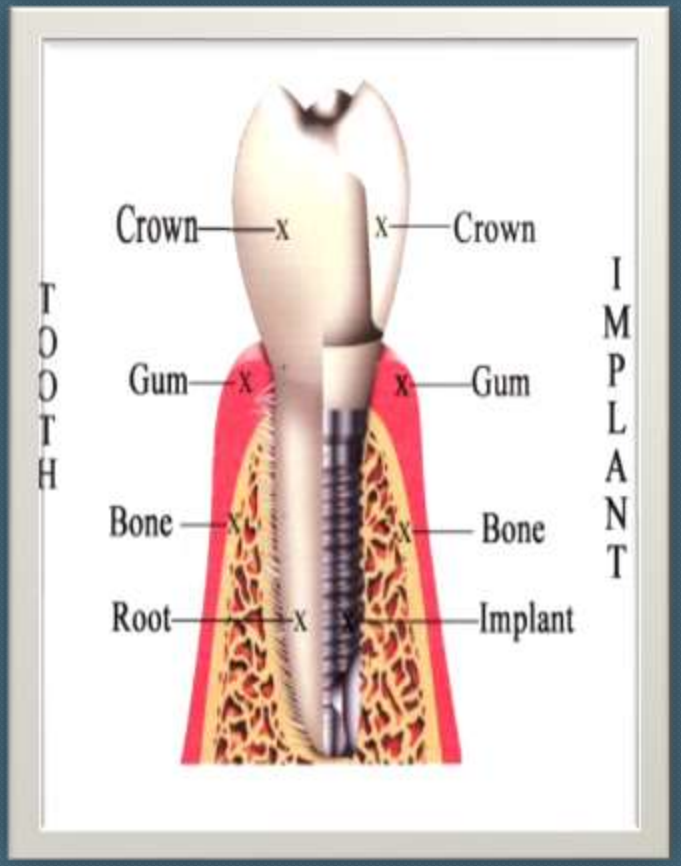
- The controlled release of the embedded drug particles is made possible by the combination of polymer erosion through hydrolysis and diffusion through polymer matrix.

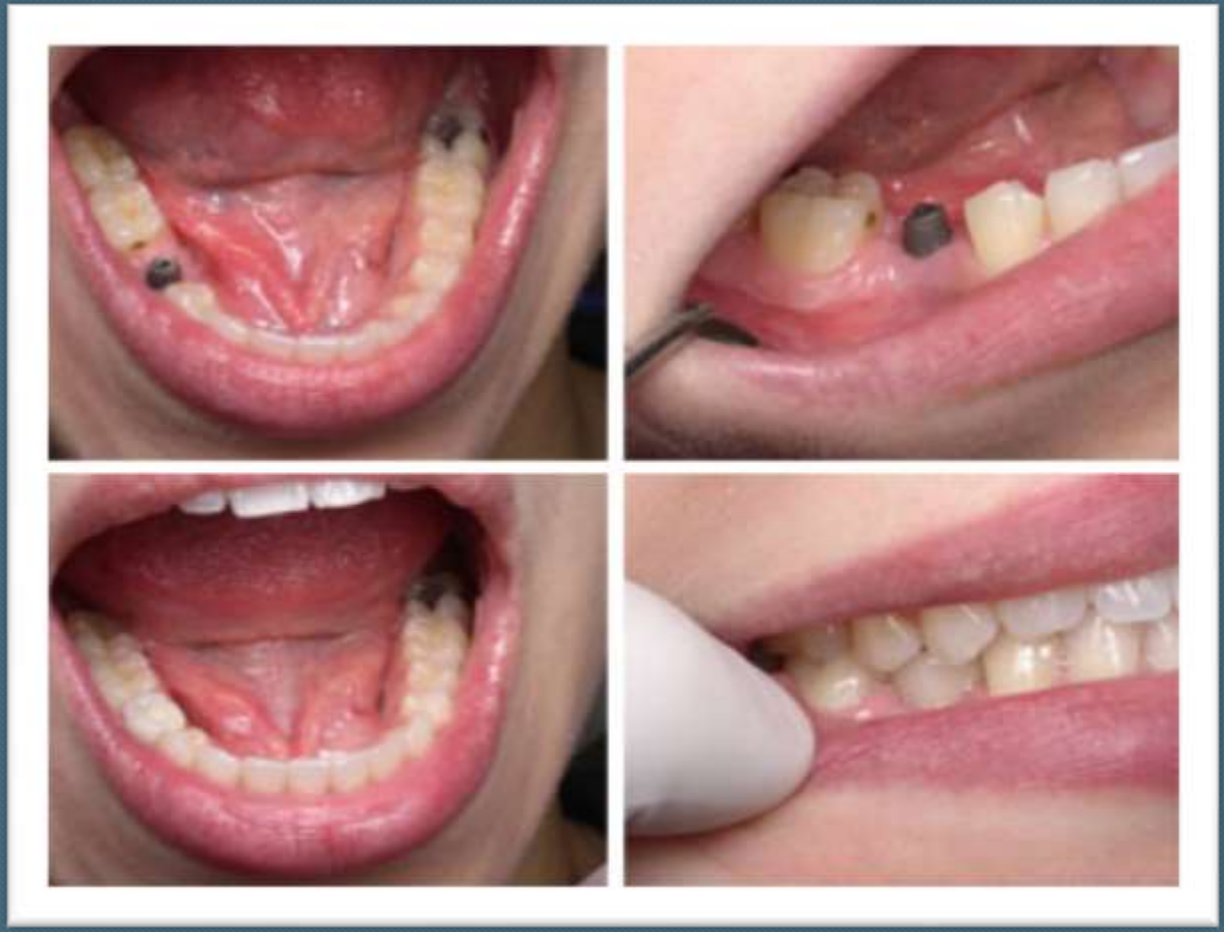

Implanon

DENTAL IMPLANT

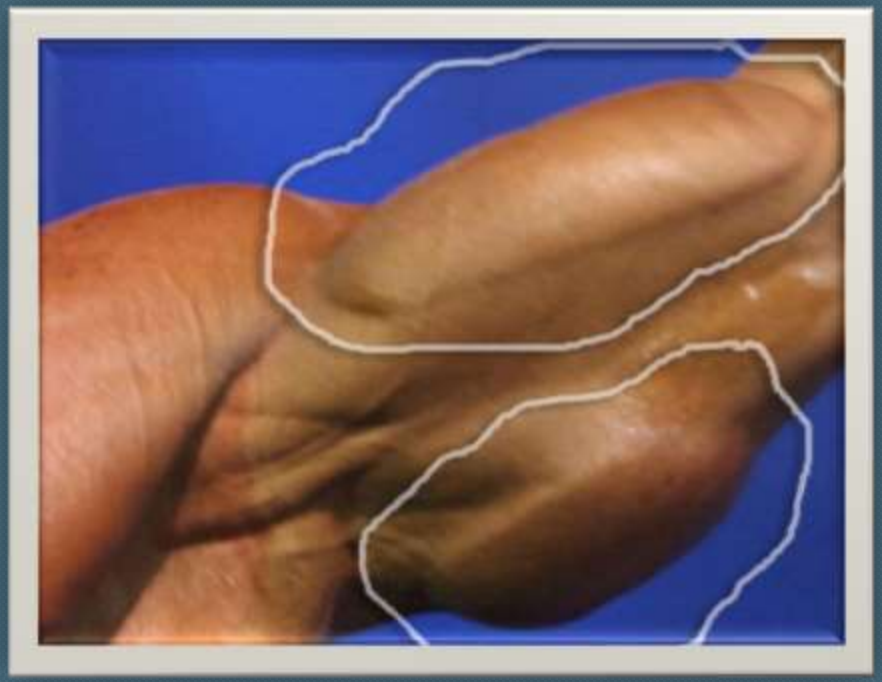
DENTAL IMPLANT



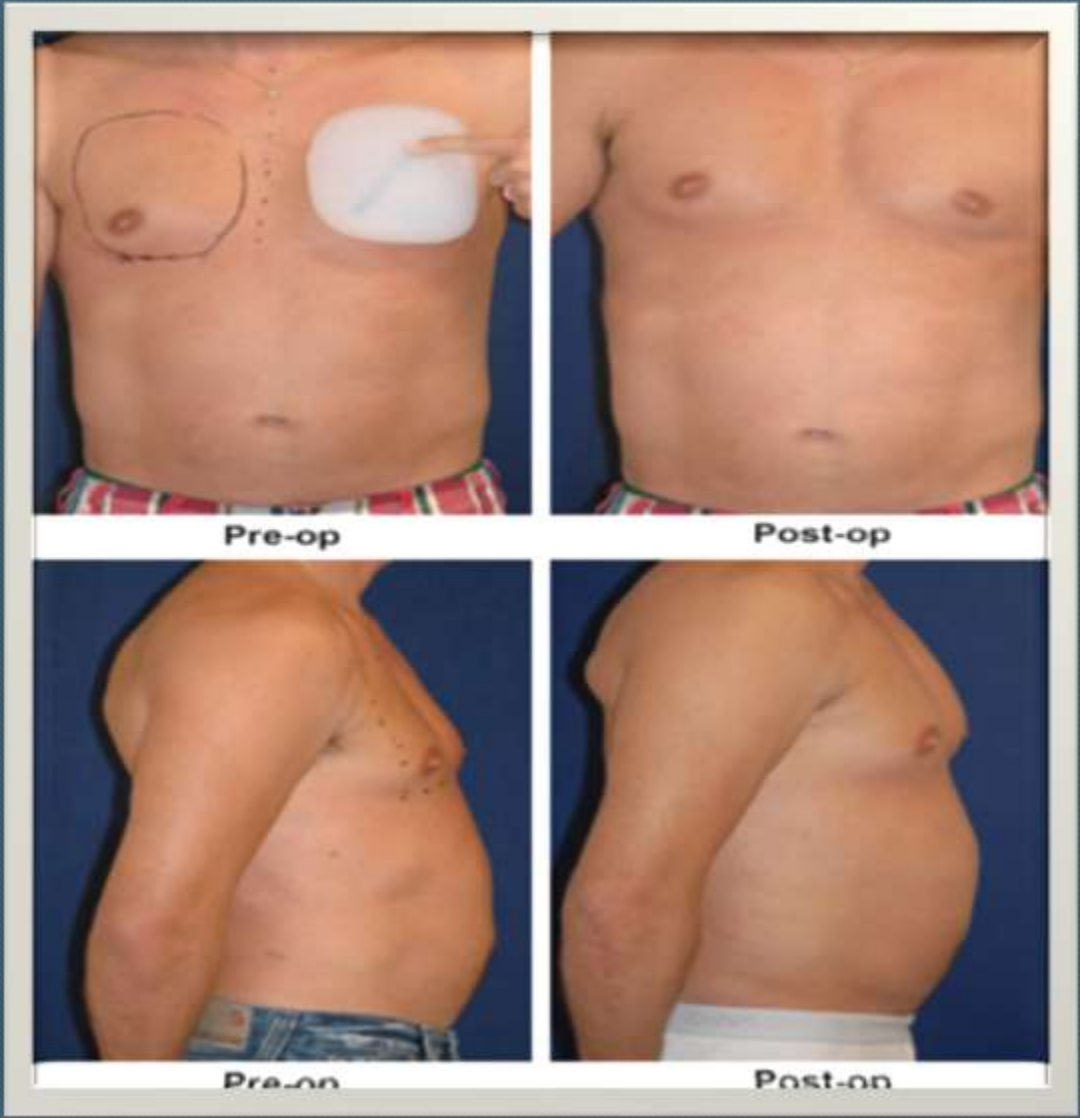


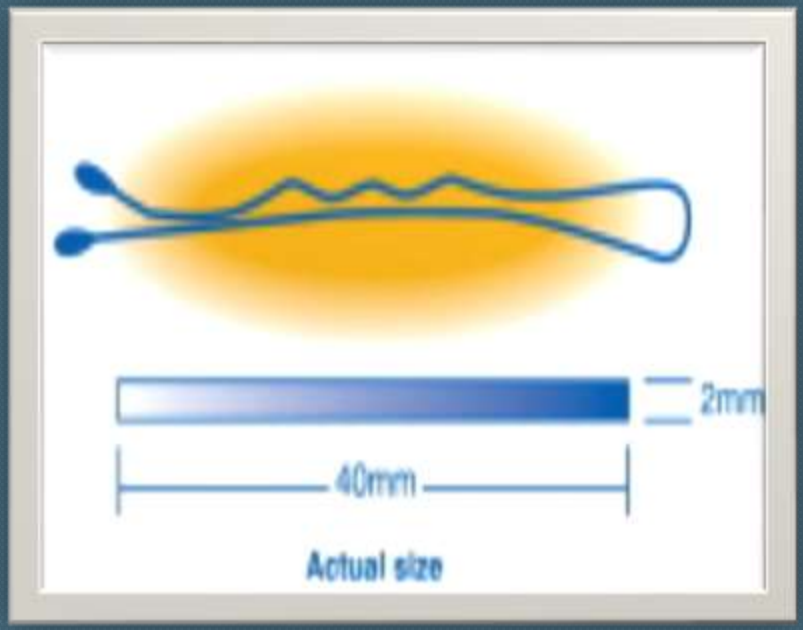



PillWatch.com

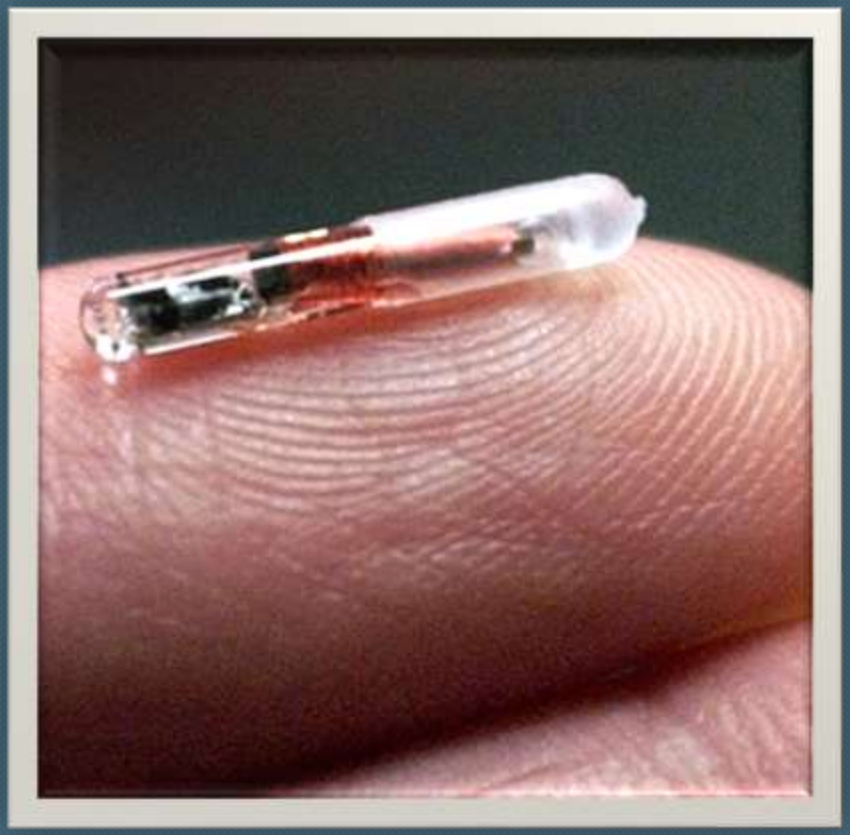


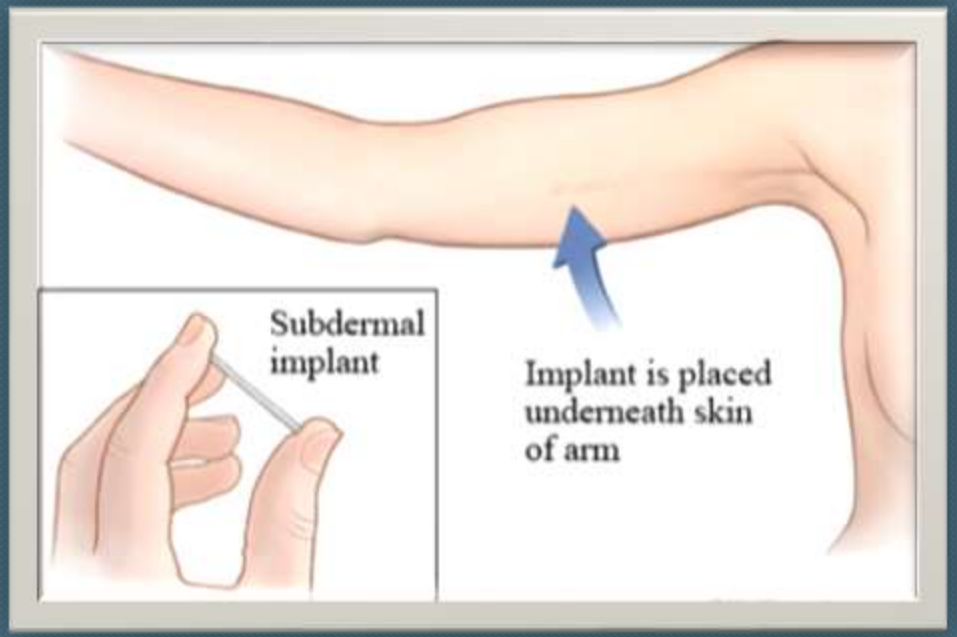
PECTORAL IMPLANTS


Pre-op
Post-op


2mm
40mm
Actual size

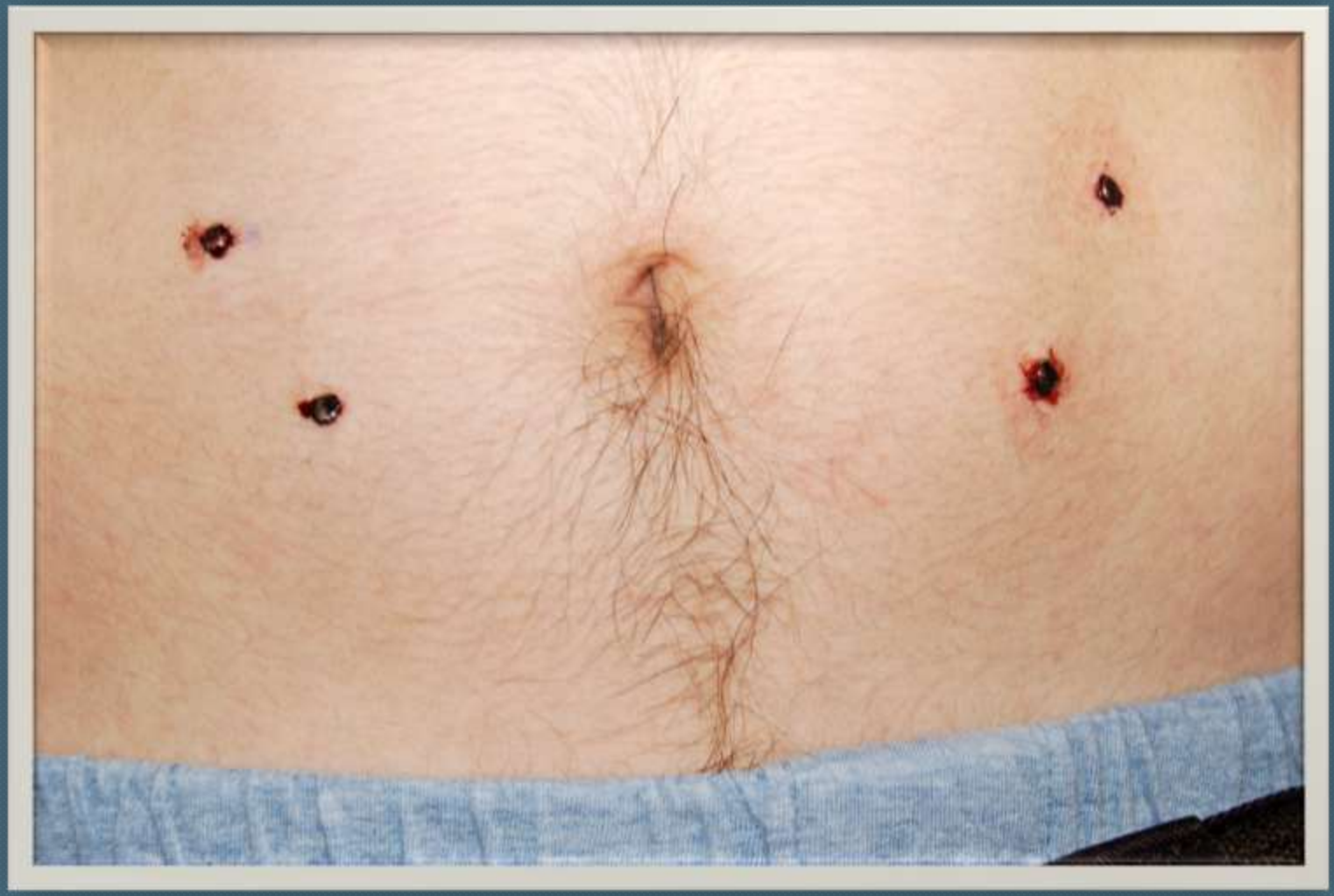

Implanon
Implanon




Subdermal implant
Implant is placed underneath skin of arm


155
168
170
175
180
180
185
190
200
210

MICRODERMAL IMPLANTS

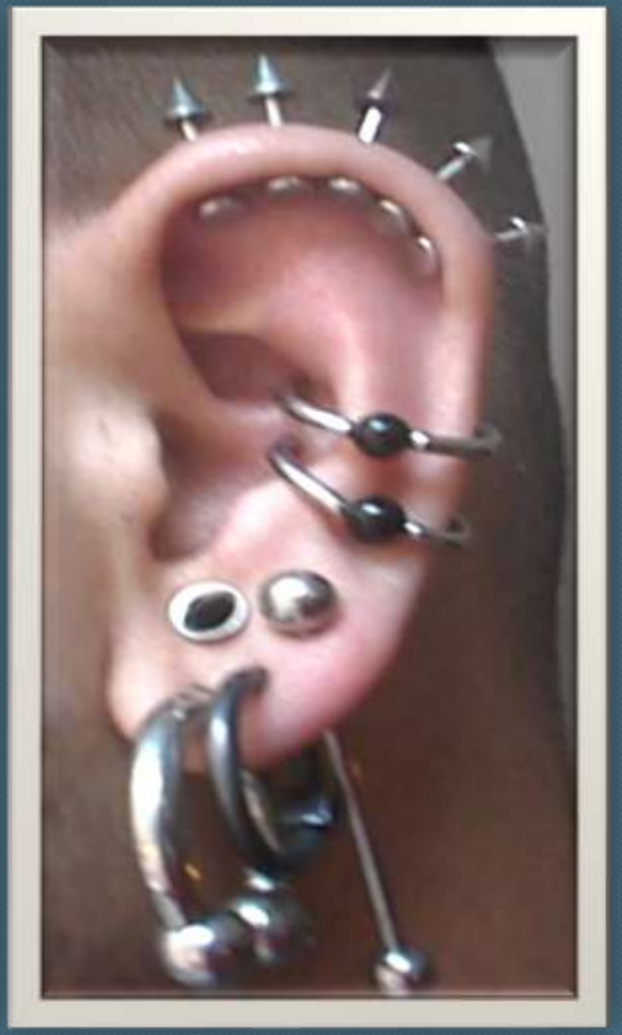


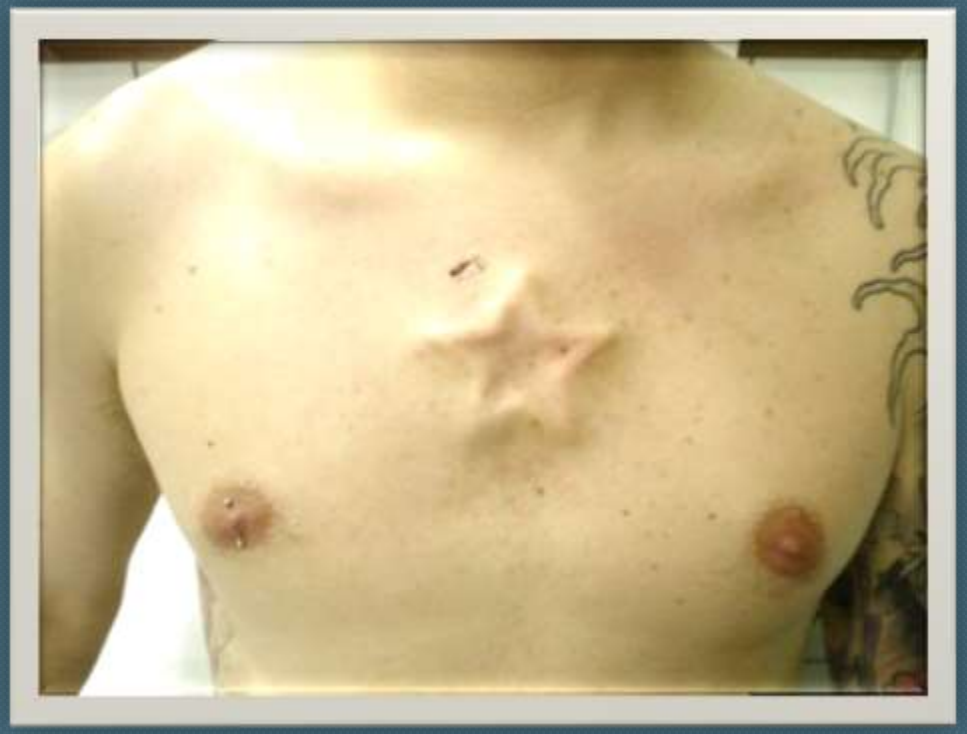
CHIN IMPLANTS

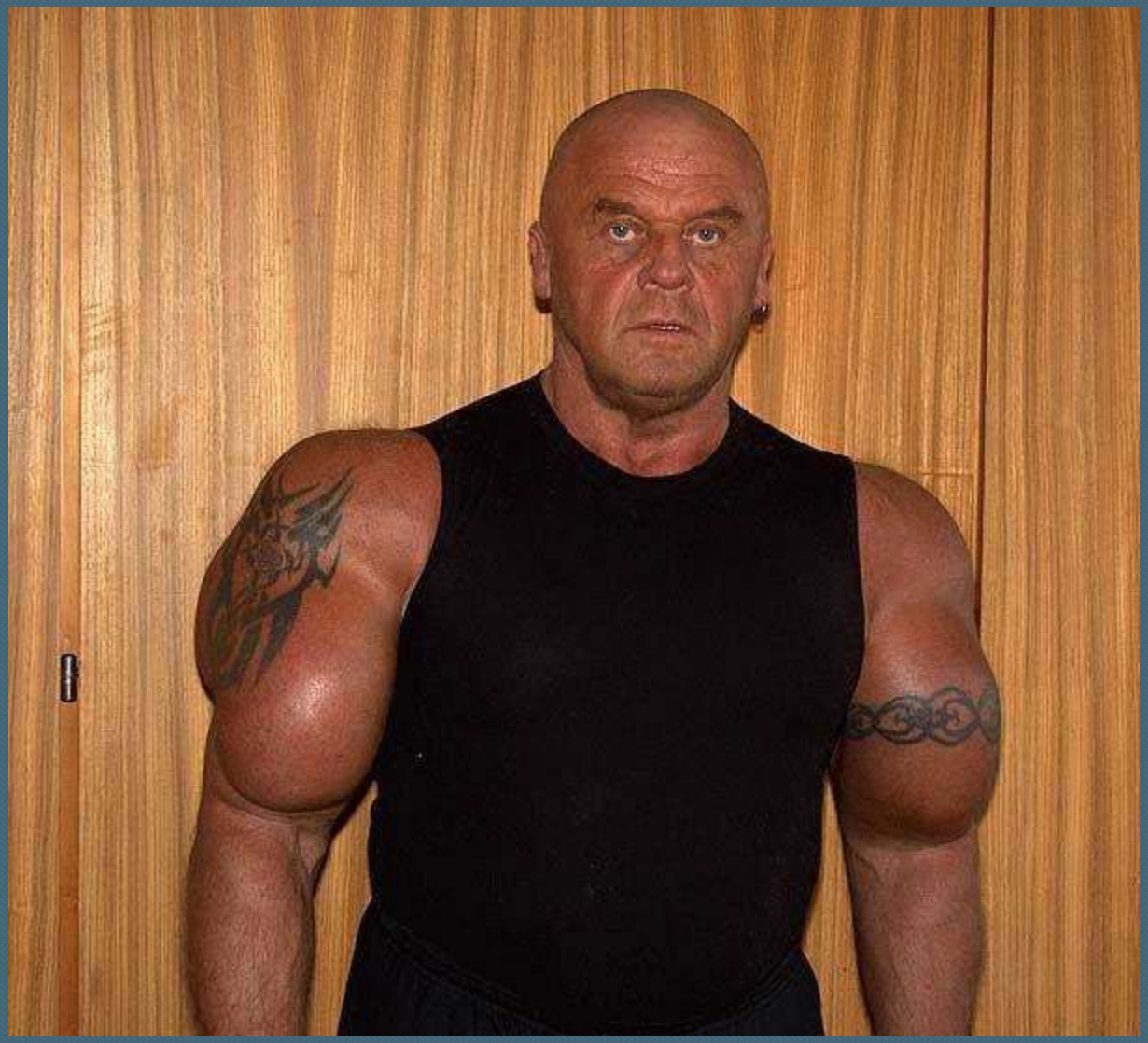

Before
After

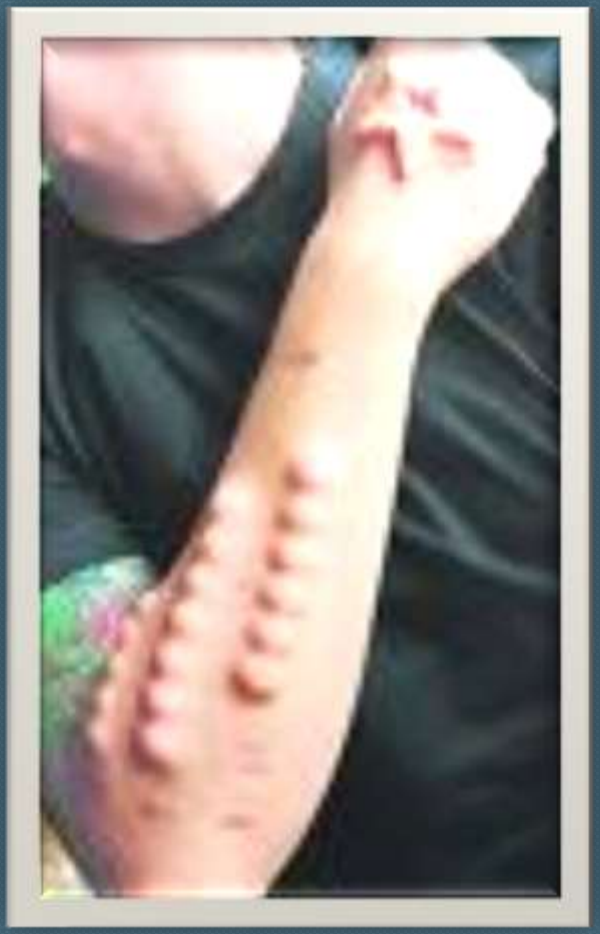

BEFORE

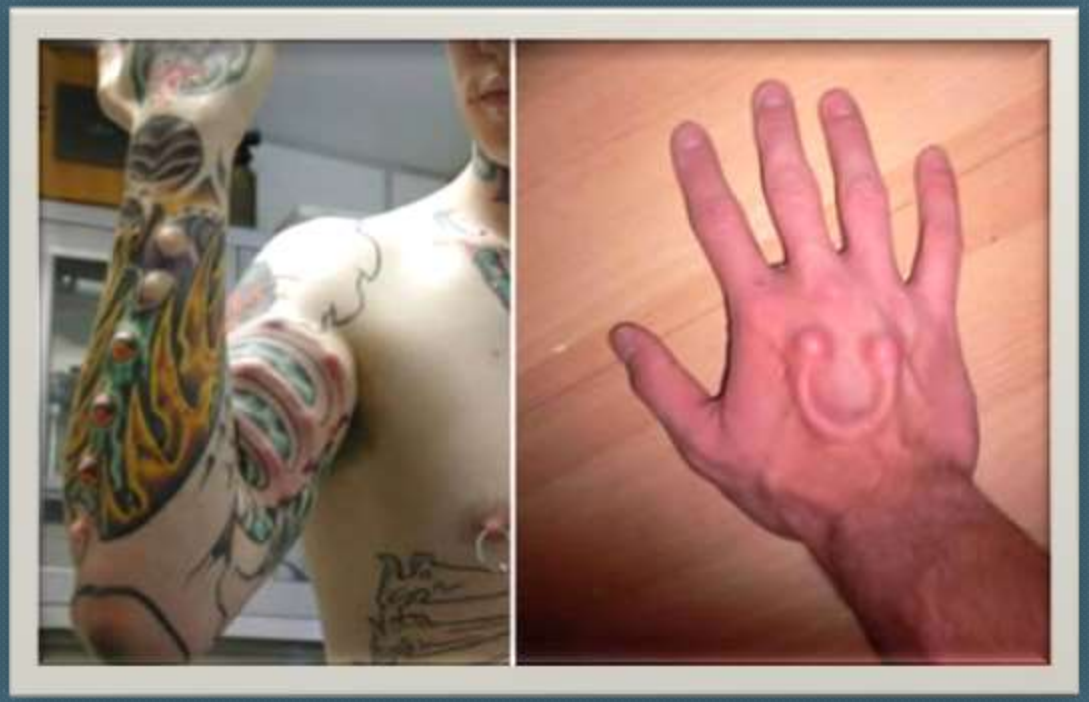
WHEN IMPLANTS GO WRONG ?!!!











CONCLUSION

φ An ideal implantable therapeutic system should be biostable, biocompatible with minimal tissue implant interactions, non ~toxic, non~ carcinogenic, removal if required and should release the drug at a constant programmed rate for predetermined duration of medication.