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Chapter No. 6

TRANSDERMAL DRUG DELIVERY SYSTEM AND IMPLANTS

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DEFINATION:

- Transdermal drug delivery system facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects.

- The first transdermal system, transderm Scop (Ciba, now Novartis)was approved by the food and drug administration in 1979 for prevention of nausea and vomiting associated with travel, particularly by sea.

First-generation transdermal delivery systems have continued their steady increase in clinical use for delivery of small, lipophilic, low-dose drugs.

Second-generation delivery systems using chemical enhancers, non-cavitational ultrasound and iontophoresis have also resulted in clinical products; the ability of iontophoresis to control delivery rates in real time provides added functionality.

Third-generation delivery systems target their effects to skin's barrier layer of stratum corneum using microneedles, thermal ablation, microdermabrasion, electroporation and cavitational ultrasound.

Using these novel second- and third-generation enhancement strategies, transdermal delivery is poised to significantly increase impact on medicine.

Examples of transdermal products:

The highest selling transdermal patch in the United States is the nicotine patch , which releases nicotine in controlled doses to help with cessation of tobacco smoking . The first commercially available vapour patch to reduce smoking was approved in Europe in 2007.

Two opioid medications used to provide round-the-clock relief for severe

pain are often prescribed in patch form: Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans).

Other transdermal patches for hormone delivery include the contraceptive patch (marketed as Ortho Evra or Evra) and testosterone patches for both men (Androde) and women (Intrinsa)

Nitroglycerin patches are sometimes prescribed for the treatment of angina in lieu of sublingual pills .

The anti-hypertensive drug Clonidine is available in transdermal patch form under the brand name Catapres –TTS

Vitamin B12 may also be administered through a transdermal patch. Cyanocobalamin , a highly stable form of vitamin B12, is compatible with transdermal patching.

Rivastigmine , an Alzheimer's treatment medication, was released in patch form in 2007, under the brand name Exelon

Transdermal scopolamine is commonly used as a treatment for motion sickness .

Estrogen patches are sometimes prescribed to treat menopausal symptoms as well as post-menopausal osteoporosis).


NICOPATCH®
TRANSDERMAL PATCH
NICOTINE
7mg/24hours
7 TRANSDERMAL PATCHES

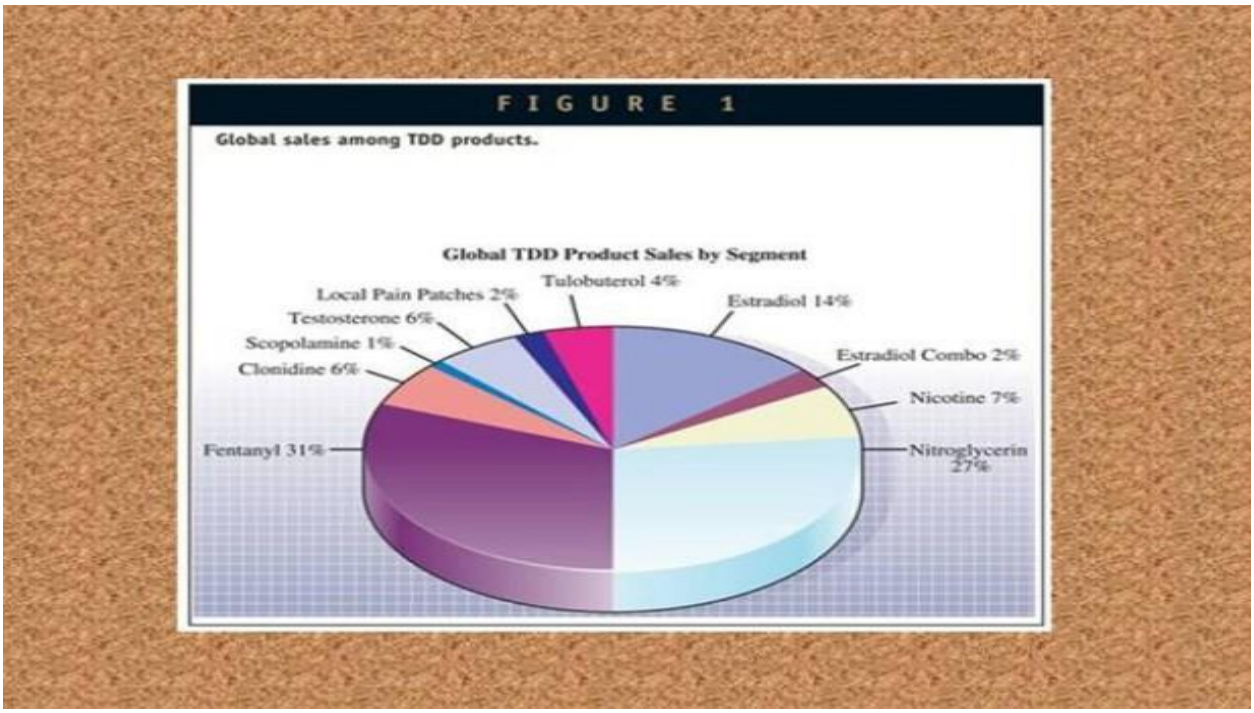


FIGURE 1
Global sales among TDD products.
Global TDD Product Sales by Segment
Tulobuterol 4%
Local Pain Patches 2%
Estradiol 14%
Testosterone 6%
Scopolamine 1%
Estradiol Combo 2%
Clonidine 6%
Nicotine 7%
Fentanyl 31%
Nitroglycerin 27%

Principles of transdermal permeation:

The various steps involved in transport of drug from patch to systemic circulation are as follows :

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through viable epidermis.
4. Uptake of drug by capillary network in the dermal papillary layer.
5. Effect on target organ.

Factors affecting the percutaneous absorption:

Not all drug substances are suitable for transdermal delivery. Among the factors playing a part in percutaneous absorption are the physical and chemical properties of the drug, including its molecular weight, solubility, partitioning coefficient and dissociation constant (pKa), the
nature of the carrier vehicle, and the condition of the skin. Although general statements applicable to all possible combinations of drug, vehicle, and skin condition are difficult to draw, most research findings may be summarized as follows

1. Drug concentration is an important factor. Generally, the amount of drug percutaneously absorbed per unit of surface area per time interval increases with an increase in the concentration of the drug in the TDDS.

2. The larger the area of application (the larger the TDDS), the more drug is absorbed.

3. The drug should have a greater physicochemical attraction to the skin than to the vehicle so that the drug will leave the vehicle in favor of the skin. Some solubility of the drug in both lipid and water is thought to be essential for effective percutaneous absorption. In essence, the aqueous solubility of a drug determines the concentration presented to the absorption site, and the partition coefficient influences the rate of transport across the absorption site. Generally, drugs penetrate the skin better in their unionized form. Nonpolar drugs tend to cross the cell barrier through the lipid-rich regions (transcellular route), whereas the polar drugs favor transport between cells (intercellular route).
For example, erythromycin base demonstrates better percutaneous absorption than erythromycin ethyl succinate.

4. Drugs with molecular weights of 100 to 800 and adequate lipid and aqueous solubility can permeate skin. The ideal molecular weight of,a drug for transdermal drug delivery is believed to be 400 or less.

5. Hydration of the skin generally favors percutaneous absorption. The TDDS acts as an occlusive moisture barrier through which sweat cannot pass, increasing skin hydration.

6. Percutaneous absorption appears to be greater when the TDDS is applied to a site with a thin horny layer than with a thick one.

7. Generally, the longer the medicated application is permitted to remain in contact with the skin, the greater is the total drug absorption.

These general statements apply to skin in the normal state. Skin that is abraded or cut permits drugs to gain direct access to the subcutaneous tissues and the capillary network, defeating the function of the TDDS.

Care taken while applying Transdermal patch:

The part of the skin where the patch is to applied should be properly

cleaned.
Patch should not be cut because cutting the patch destroys the drug delivery system.
Before applying a new patch it should be sure that the old patch is removed from the site.
Care should be taken while applying or removing the patch because anyone handling the patch can absorb the drug from the patch.
The patch should be applied accurate to the site of administration

Properties that influence Transdermal delivery of the drug:

Release of the medicament from the vehicle.

Penetration through the skin barrier.

Activation of the pharmacological response

Components of transdermal patch:

- The main components of a transdermal patch are:
- Liner- protects the patch during storage. The liner is removed prior to use.
- Drugs- drug solution in direct contact with release liner.
- Adhesive- serves to adhere the components of the patch together along with adhering the patch to the skin. The peripheral adhesive system is less elegant and have several layers, Manu. Is more difficult than the face adhesive system. Ex: Polyisobutylenes, acrylics and silicones.
- Membrane- controls the release of the drug from the reservoir and multi-layer patches.
- Backing- protects the patch from the outer environment. Aluminum foil, poly urethanes, etc.
- Permeation Enhancer-these are permeation promoter for drugs, which increases delivery of drug.

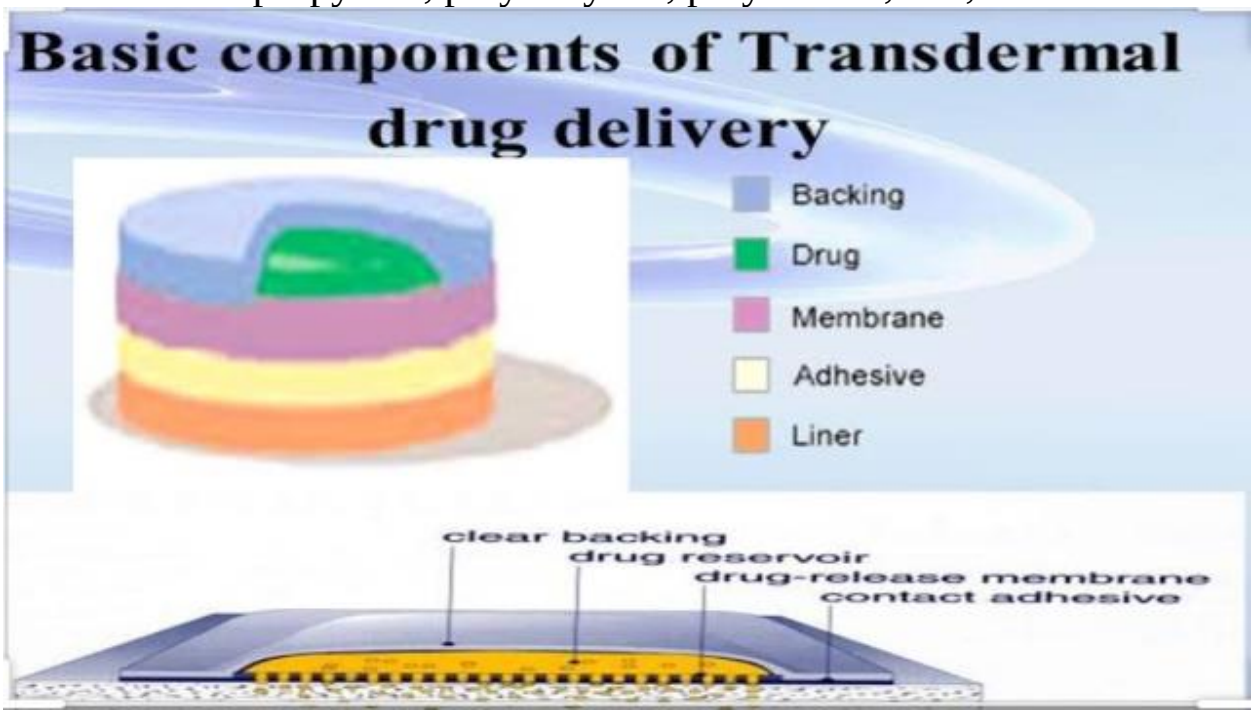
a) Solvent: Methanol , ethanol, dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide, poly propylene glycol, glycerol, silicon fluids, iso propyl palmitate, etc.,

b) Surfactant: i) Anionic: Dioctyl sulphosuccinate, Sod. lauryl sulfate, etc.,

ii) Non ionic: Pluronic F127, Pluronic F68, etc.,

iii) Bile salts: Sod. tauroglycolate, Sod. taurocholate, etc.

- Polymer matrix:
  - (i) Mol. wt., glass transition temp. and chemical functionality of the polymer should able to release the drug.
  - (ii) Should be Stable, non-reactive with the drug and should be easily fabricated.
  - (iii) Polymer and its degradation products must be non-toxic to the host.
  - (iv) Natural: Ex: Cellulose, zein, shellac, waxes, proteins, gums, natural rubbers, etc.,
  - (v) Synthetic Elastomers: Ex: polybutadienes, poly siloxanes, silicon rubber, nitrile, acrylonitrile, butyl rubber, styrene-butadiene rubber, etc.,
  - (vi) Synthetic polymers: Ex: PVA, PVP, polyethylene, poly propylene, poly acrylate, polyamides, etc.,



Biopharmaceutical parameters in drug selection for transdermal patch:

Dose should be low i.e <20mg/day.
Half-life should be 10 h or less.
Molecular weight should be <400.
Partition coefficient should be Log P (octanol-water) between 1.0 and 4.
Drug should be non-irritating and non-sensitizing to the skin.
Oral bioavailability should be low.
Therapeutic index should be low.

Desirable features for transdermal patches:

Composition relatively invariant in use.
System size reasonable.
Defined site for application.
Application technique highly reproducible.
Delivery is (typically) zero order.
Delivery is efficient

Approaches used in development of TDDS:

Membrane permeation- controlled system
Adhesive dispersion- type system
Matrix diffusion- controlled system
Micro reservoir type- controlled system.

- **Membrane permeation- controlled system:**
  Drug reservoir (solid or viscous liquid in silicon fluid) is encapsulated totally in a shallow compartment from drug impermeable metallic plastic laminate and rate controlling polymeric membrane which may be micro porous or non-porous e.g., Ethylene vinyl acetate (EVA) copolymer.

A thin layer of drug compatible, hypoallergenic adhesive polymer.

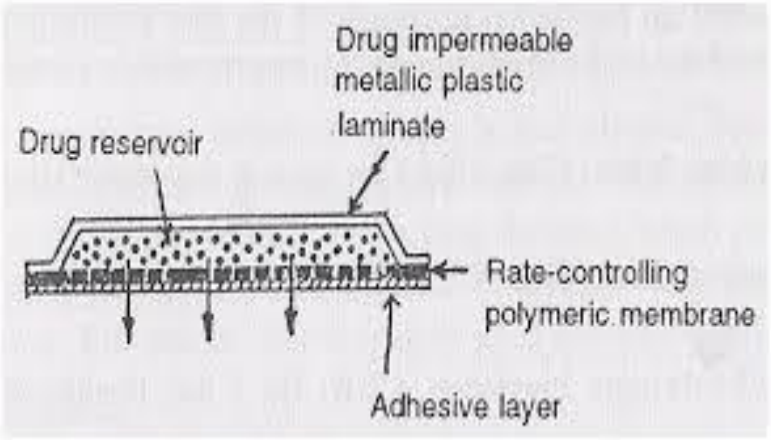


Fig: 2 Membrane moderated transdermal drug delivery system

- **Adhesive dispersion- type system**:
  The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g., poly isobutylene or polyacrylate.
  Spread evenly the medicated adhesive by solvent casting or hot melting onto a flat sheet of drug impermeable metallic plastic.
  then onto top of the drug reservoir layer, thin layer of non-medicated, rate- controlling adhesive polymer and constant thickness.

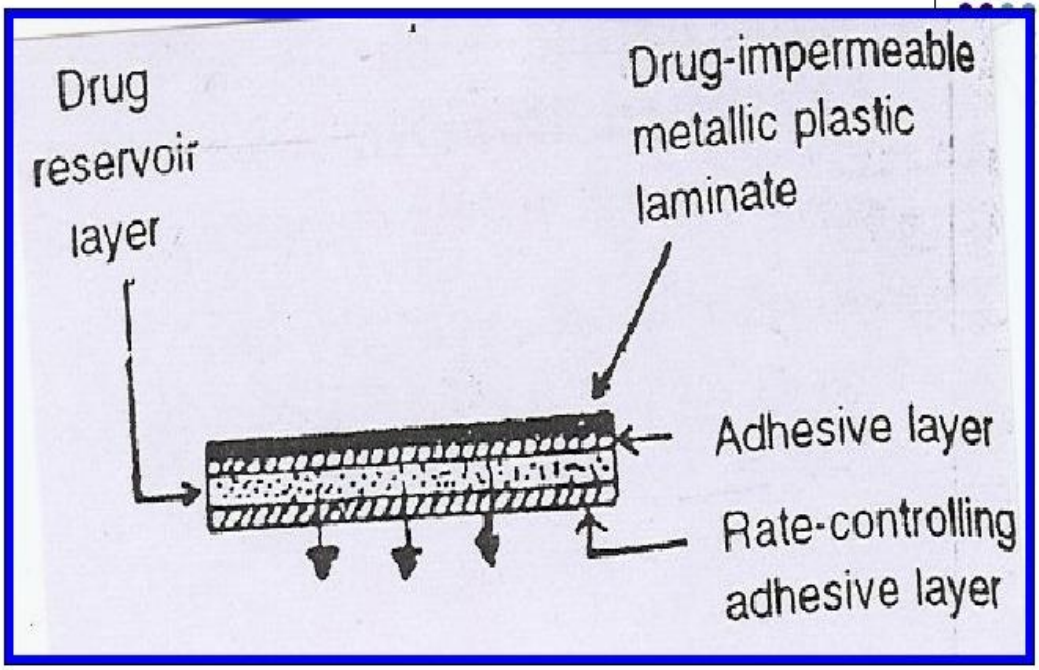


Fig. Adhesive dispersion type Transdermal drug delivery system

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- **Matrix diffusion- controlled system:**
  The drug reservoir is prepared by homogeneously dispersing drug particles in a hydrophilic or lipophilic polymer matrix then moulded into medicated disc at elevated temperature.
  The drug reservoir can also prepared by mixing drug + polymer in common solvent followed by solvent evaporation at elevated temperature under vaccum.
  This drug reservoir containing polymer disc is then plated drug impermeable plastic film.
  Then the adhesive polymer is spreaded along the circumference to form a strip of adhesive rim around the medicated disc.

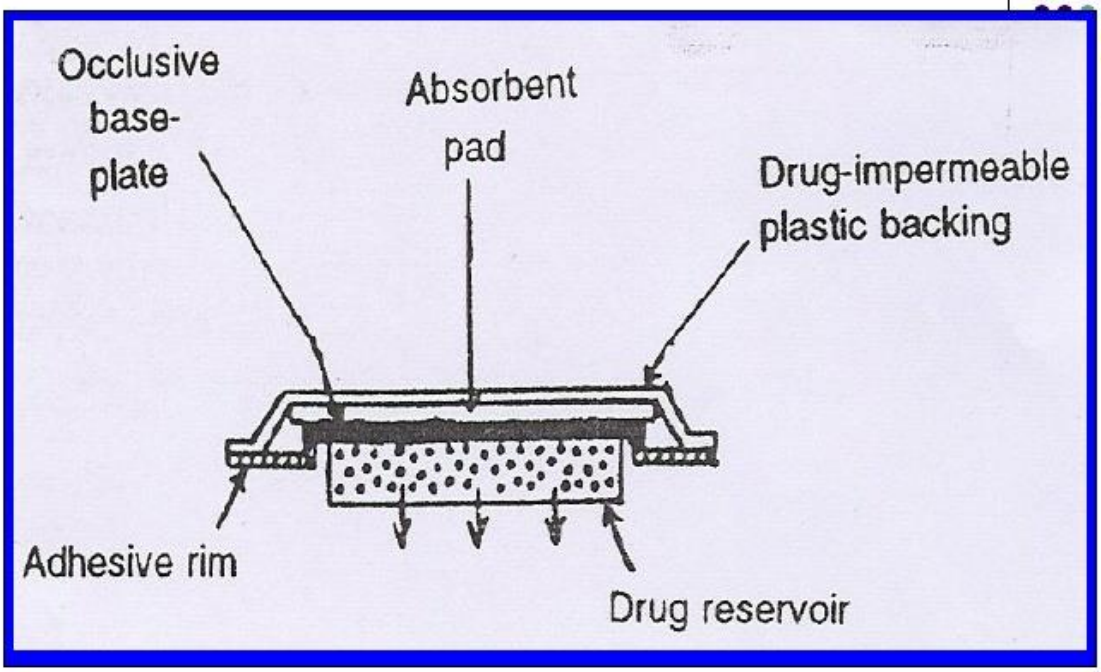


Fig. Matrix diffusion controlled Transdermal drug delivery system

- **Microreservoir type- controlled system:**
  Consisting of both reservoir and matrix diffusion DDS.
  The drug reservoir is formed by suspending drug in an aq. solution of water soluble polymer.
  Then dispersed in a lipophilic polymer by high energy dispersion techniques to form a several discrete, unleachable microspheres of drug reservoir and get cross-linking polymer chain which produces the medicated disc.
  This is then coated with layer of biocompatible polymer and surrounded by adhesive rim.

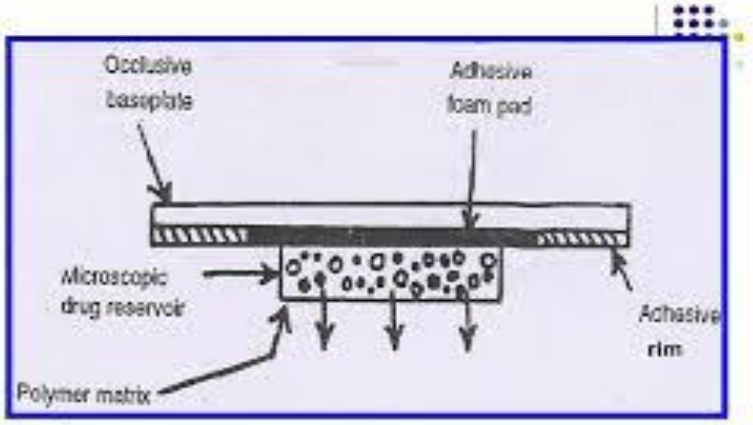


Fig. Micro reservoir dissolution-controlled transdermal drug delivery system

Advantages:

a) Can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.

b) Can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.

c) To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.

d) Noninvasive, avoiding the inconvenience of parenteral therapy.

e) They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Transdermal clonidine 7 day.

f) The activity of drugs having a short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.

g) Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.

Disadvantages:

a) Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
b) Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's impermeability.
c) Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
d) Long time adhere is difficult.

IMPLANTS

DEFINATION:

Implants are small sterile solid masses consisting of a highly purified drug (with or without excipients) made by compression or molding or extrusion.

They are intended for implantation in the body (usually subcutaneously) for the purpose of providing continuous release of the drug over long periods of time.

Implants are administered by means of a suitable special injector or surgical incision. They are packaged individually in sterile vials or foil strips.

Advantages:

- Unattended continuous delivery within the therapeutic window
- Avoids the highly variable peak and trough concentrations
- Enhanced drug efficacy
- Minimized side effects
- Termination of therapy as and when required
- Patient compliance is also a benefit of continuous dosing with these implants as they operate for long period of time once implanted
- Targeted drug delivery
- Improved stability of drugs

- Improved availability of drugs
- By pass first pass metabolism

Disadvantages:

- Reaction between host and implant
- Implantation procedure is difficult in case of larger implants
- Mini-surgery is needed(painful)
- There is no concomitant danger with this therapy that the device may for some reason fail to operate. which again requires surgical intervention to correct.
- Systems have a limited loading capacity so that often only quite potent drugs such as hormones may be suitable for delivery by implantable devices.

Ideal properties of implants:

- Biostable.
- Biocompatible.
- Easily removable.
- Nontoxic & non carcinogenic.
- Minimum surface area & smooth texture.

  Rate controlled release of the drug.

Types of implants:

3 main categories:-

Biodegradable & Non-biodegradable polymeric implants. Implantable pump system. Atypical class of implants.

Non-biodegradable implants

- The drug is dispersed homogeneously, inside the polymeric matrix through which the drug diffuses slowly providing sustained release
- This type of system has several disadvantages, the outer membrane is non degradable.

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.

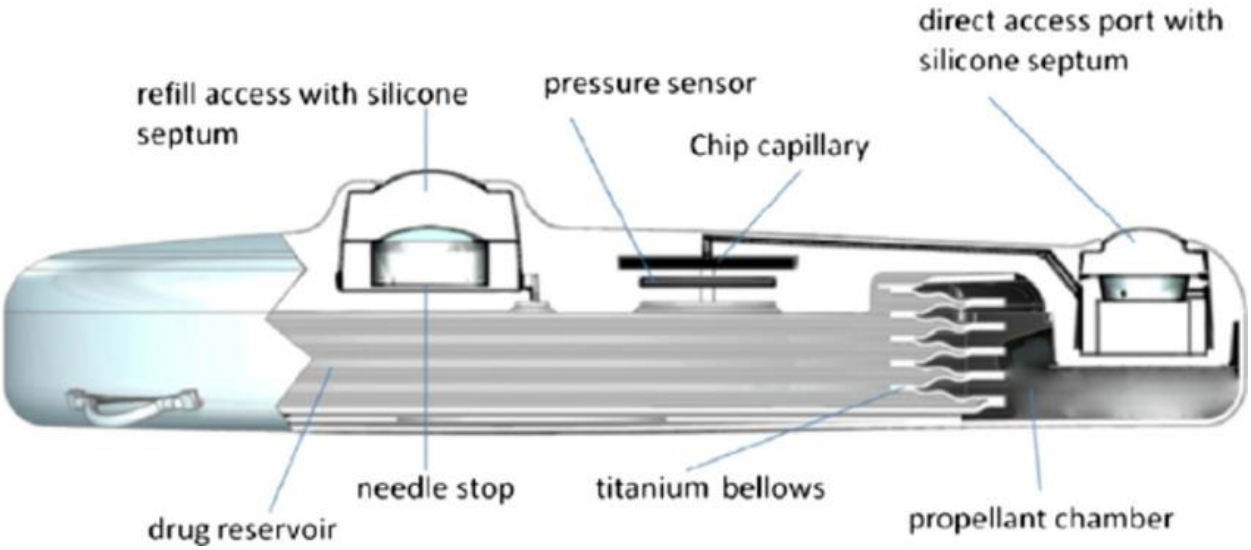
Biodegradable implants

The inert polymers, used are eventually absorbed or excreted by the body.
No need for surgical removal of the implant after the conclusion of therapy.
Drug is dispersed in to a biodegradable polymer matrix like poly vinyl methyl ether and is coated with immobilized urease in a neutral PH. In the presence of urea, ammonia is released causing increase in PH at which polymer degrades leading to drug release.

Implantable pump system

Controlled release- achieved by utilizing micro technology of electronic systems & remote controlled flow rate manipulation by maintaining constant pressure difference .

- **Infusion pump** The drug reservoir is in a solution formulation inside an infusate chamber.
  Infusion pump for infusion of heparin for anti-coagulation therapy, insulin for antidiabetic.



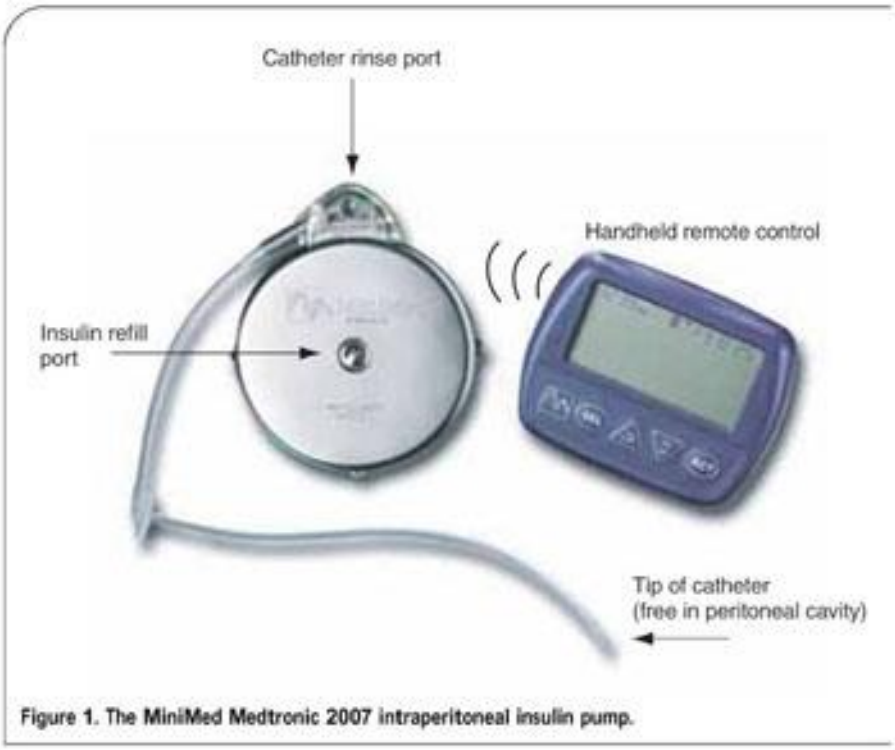
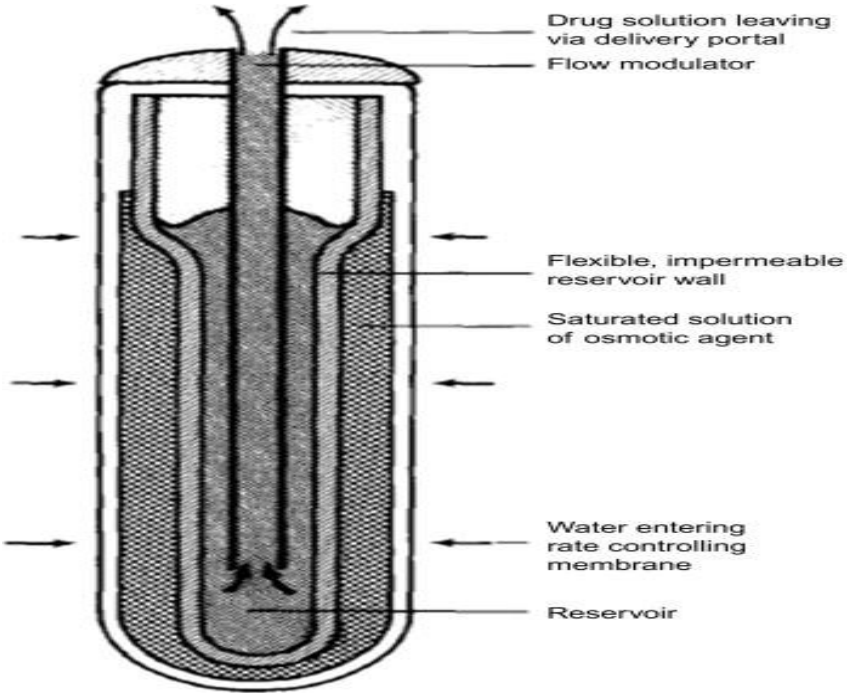


Figure 1. The MiniMed Medtronic 2007 intraperitoneal insulin pump.

- **Osmotic pump:**
  The osmotic pressure is used as the energy source in this device.
  Drug reservoir-flexible wall(inert impermeable)
  Outside- osmotic sleeve, cylinder(Nacl high conc.)

Eg: An example of this type of drug delivery is the Alzet osmotic pump of angiotensin- II manufactured by Alza Corporation.



Atypical systems

Differ from typical implant with respect to administration, mechanism & technology.

- **Ceramic composite system** CDDS- to deliver protein, polypeptide, steroids, amino-acids, vaccine & antibiotic. Inorganic bone meal or oseograft. Alumino Ca phosphorous oxide ceramics. Hydroxyapatite ceramics

- **Intrauterine implant Progestasert**- deliver constant progesterone dose in uterine cavity. T-shaped polyethylene support vertical arm→fitted with sleeve containing the steroid. Sleeve→ Inner- Reservoir of steroid & silicone polymer. Outer- Rate regulating layer of PEVA.

- **In-situ gel-forming formulation Liquid formulation**→ generate semisolid depot after S.C injection.

Application-
Less invasive & painful.
Localized or systemic drug delivery for prolonged period of time. Various therapeutic agent incorporated by simple mixing.
Several mechanism for in-situ implant formation-
Solvent exchange or polymer precipitation. Water insoluble polymer + water miscible solvent. On contact with body fluid- solvent diffuses out of polymer while water permeates the liquid polymer matrix. Due to insolubility in water, the polymer precipitates, results in formation of solid polymeric implant.
Thermally induced gelling. e.g.; Oncogel (paclitaxel)
Thermoplastic pastes.

- **Responsive drug delivery implants**.
  Marker- indicative of disease state & subsequently delivering the type & dose of drug most appropriate for treatment. This system located inside the patient's body & continuously detect the early onset of crisis & respond immediately with countermeasure.
  Eg; Antibiotic-PVA hydrogel (peptide linker)-S.aureus

- **Bio artificial muscle implants**.
  Retrievable DDS- for long term delivery of therapeutic proteins. Muscle precursors cell (myoblast) are genetically engineered to secrete proteins. Cell- fabricate with 3D muscle like structure that can be implanted.

Preparation of implants:

- **Materials :**

Although many polymers can by used to prepare rate-limiting membranes for controlled release relatively few are employed for implantation purpose because in addition to being a good rate-limiting barrier the polymer should also be biocompatible and sterilizable. Several nonpolymeric materials such as fatty substances (e.g. cholesterol) and metals (e.g. titanium, stainless steel 316) may be used in implantation devices.

- **Silicone polymers**

Silicone polymers are among the most widely used polymers in controlled drug delivery. They provide several advantages such biocompatibility, ease of fabrication, resistance to heat sterilization and high permeability for many lipophillic drugs.
Therapeutic products prepared with silicone elastomers include Norplant a subdermal implant to deliver levonorgestrel for contraception a dual-release vaginal ring and certain Transdermal patches.

Polyethylene-vinyl acetate

Ethylene vinyl acetate (EVAc) copolymers have been used for many investigational and commercial devices. The vinyl acetate of the copolymer can vary from very small amounts to 40%. Increasing the vinyl acetate content increase elasticity permeability and glass transition temperature and reduces crystalline. The polymer is being used in the Alza ocular insert (Ocusert) and in IUD reservoir-type systems (Progestasert).

Cellulose acetate

Various cellulose derivatives are used in controlled drug delivery devices application to implants is usually restricted to cellulose acetate. Cellulose acetate is formed by the acetylation of the hydroxyl groups in the glucose backbone. Commercial cellulose acetate is available with 36 to 43 %

acetylation. Because of their high water permeability and low salt permeability cellulose acetate membranes have been used extensively in the Alzet osmotic pumps.

Processes:

Processes used in manufacturing these devices depend on the type. In any case implants need to be sterile and therefore they are prepared aseptically or under reduced bioburden and then sterilized most commonly using gamma radiation.

Traditional steroid implants are prepared by compressing large crystals of drug under high pressure or by the solidification of molten drug in cylindrical molds. Diffusion-controlled polymeric devices can be prepared by a variety; of techniques. Membrane type polymeric devices may be prepared by coextrusion of the drug core and the polymeric membrane as in the case of silicone capsules. Spherical membrane-coated devices are prepared with conventional pharmaceutical coating equipment such as a pan coater or a Wurster coating apparatus, Many specialized techniques have been developed for coating microcapsules. Matrix-type devices are simpler to prepare: techniques include compression under high pressure with or without heat solvent casting of drug dispersion in polymer solution meltextrusion and in situ polymerization.

Regulatory assessment

All novel drug delivery systems are considered new drugs requiring complete new drug applications as a basis of approval. Besides the safety and efficacy demonstration plasma-blood level variation and drug pharmacodynamics need to be established. Establishment of the reproducibility of release, both in vivo and in vitro demonstration of the absence of dose dumping and a well-defined pharmacokinetic profile to support drug labeling is needed.

Application:

Cancer Treatment

Gliadel Wafer: Delivers carmustine for the treatment of brain tumours directly at the site of tumour to prevent reccurrence of tumours.

Depocyte: cytarabine releasing implantable DDS used to treat acute leukemia

Duros osmotic pump: Non-biodegradable implantable DDS used to deliver Leoprolide acetate in the treatment of prostate cancer

Isomed: - To deliver Fluxuridine in the treatment of colorectal liver cancer & to deliver Morphine to spinal fluid in the treatment of chronic intrathecal pain related to cancer

Eligard : insitu forming implant system developed by Atrix Labs is used to deliver Leuprolide Acetate
Alzamer Depot: Devoloped by ALZA corporation is similar to Eligard but claimed to have reduced burst effect.

Zoladex : PLGA- based biodegradable implant used to deliver Goserilin acetate in the treatment of prostate carcinoma.

Osteoporosis Microchips: This device used to deliver Forteo drug used to increase bone density in patients suffering from severe osteoporosis.

Contraceptives Norplant: delivers Norgestrol to achive contraception.

Ocular Diseases:

- **Lacrimedics:** These are collagen implants used to treat dry eye syndrome by partially blocking tear removing canals and they dissolve within 7-10 days.
- **Vitrasert:** delivers ganicyclovir used to treat AIDS related retinitis.

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