CHAPTER - 7

NOVEL DRUG DELIVERY SYSTEM

Points to be covered in this topic

- 7.1 INTRODUCTION
- 7.2 CLASSIFICATION
- 7.3 ADVANTAGES OF NOVEL DRUG DELIVERY SYSTEM
- 7.4 CHALLENGES OF NOVEL DRUG DELIVERY SYSTEM

NOVEL DRUG DELIVERY SYSTEMS

7.1 INTRODUCTION

- Novel Drug Delivery System (NDDS) refers to the **formulation, technologies and system for transporting** a pharmaceutical compound in the body as needed to fulfil the therapeutic effects.
- These new strategies, often called novel drug delivery systems (NDDS), are **based on interdisciplinary approaches** that combine polymer science, pharmaceutics, bio conjugate chemistry, and molecular biology.

7.2 CLASSIFICATION

1. **Targeted Drug Delivery System (TDDS)**

Targeted drug delivery (TDD) is a **modern method of delivering pharmaceuticals** in patients by increasing the concentration of the delivered drug exclusively in the targeted body component of interest, such as organs, tissues, or cells. It comprises of the following:

a. **Liposomes:** Liposomes are **small vesicles in bilayer** form composed of phospholipids, especially phosphatidylcholine, but may also include other lipids, such as egg phosphatidyl ethanol - amine, so long as they are compatible with lipid bilayer structure.

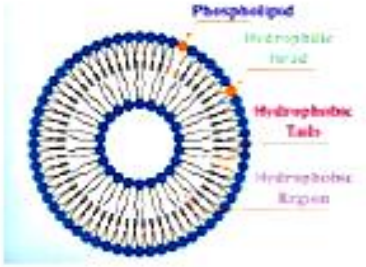


Fig 7.1: Liposomes

- Liposomes releases the drug either by **simple diffusion** or by **interacting with cell membrane.**

  Example: Enoxacin, Cytosine Arabinose etc

✓ **Advantages of liposomes**

- Liposomes are **increased efficacy and therapeutic index** of drug (Actinomycin D)
- Liposomes help to **reduce exposure of sensitive tissues** to toxic drugs.
- Liposomes have ability to **protect their encapsulated drug** from the external environment and to act as sustained release depots.

✓ Classification of Liposomes

Liposomes are classified into two types

1. Based on structural parameters

- Multilamellar Large Vesicles (MLV) – These are having particle size **more than 0.5 mm.**
- Oligolamellar Vesicles (OLV) – In this, Particle size ranges from **0.1-1 mm.**
- Small unilamellar Vesicles (SUV) – These are having particle size of **20- 100 nm.**
- Multivesicular Vesicles (MV) – These are having particle size **greater than 1mm.**

2. Based on method of preparation

- Vesicles prepared by reverse phase evaporation method (REV)
- Vesicles prepared by extrusion technique (VET)
- Vesicle prepared by dehydration-rehydration method
- Multilamellar vesicle made by REV

b. Niosomes

- Niosomes are promising vehicle for drug delivery and being non-ionic.
- Niosomes are **non-ionic surfactant vesicle** + Cholesterol or other lipids.
- Their physical properties are similar to liposomes.

Example: Tacrolimus, Naltrexone HCl

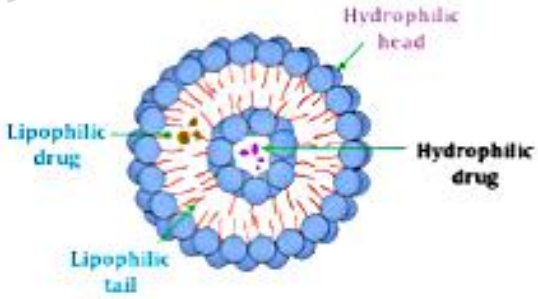
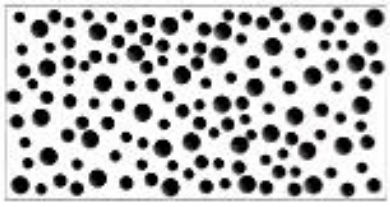


Fig 7.2: Niosomes

C. Nanoparticle

- Nanoparticles are defined as particulate dispersion, or solid particles having the size range **10- 1000 nm**. It is of the following types:



➢ **Nanotubes:** Carbon nanotubes are hollow tubes made up of 2-D hexagonal lattice that can easily penetrate cells, delivering drugs directly to the cytoplasm or nucleus.

Example: Doxorubicin, Antibodies, Genes etc.

- **Nanocantilever:** A nanocantilever is a tiny beam-like structure at the nanoscale, and MEMS involve the integration of mechanical elements, sensors, actuators, and electronics on a common silicon substrate.
  Example: Clinical diagnosis, drug screening
- **Nanoshells:** Nanoshells typically consist of a core-shell structure, where a core material is surrounded by a shell to which antibodies are attached enabling the shells to target certain cells.
  Example: Curcumin, Doxorubicin
- **Nanopores:** Nanopores are tiny openings at the nanoscale level, and they can play a role in novel drug delivery systems in which DNA molecules can pass through one strand and used to control rate of drug's diffusion in body.
  Example: Catalase, Vitamin C.
- **Gold nanoparticles:** Gold nanoparticle is solid core of a gold atom surrounded by negative reactive groups on the surface that can be functionalized by adding a monolayer of surface moieties used for drug delivery.
  Example: Folic acid, Mercaptopurine

d. Resealed erythrocytes

- Resealed Erythrocytes are **biocompatible** and **biodegradable carriers** that possess very long circulation half- life.
- It is prepared by **dipping RBCs in hypotonic media** which leads to rupturing of cell membrane and formation of small pores. When RBCs are again placed in an isotonic media at 37°C resealing of membrane takes place with drugs.
  Example: Aspirin, Steroids, Danorubicin

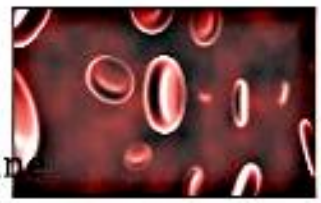


Fig 7.3: Resealed erythrocytes

✓ **Advantages of resealed erythrocytes**

- A remarkable degree of biocompatibility, particularly when the autologous cells are used for drug loading.
- Complete biodegradability and the lack of toxic product(s) resulting from the carrier biodegradation.

e. Monoclonal Antibodies

- Monoclonal antibodies (mAbs) are immunoglobulins derived from a monoclonal cell line and which have a defined specificity.

Example: Cetuximab, Rituximab etc

f. Microspheres

- Microsphere are small spherical particles, with diameters in the micrometer range typically 1 μm to 1000 μm (1 mm).

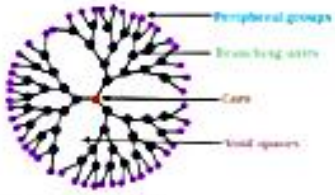
Example: Glipizide, Triptorelin etc.

✓ **Advantages of microspheres**

- They could be injected into the body due to the **spherical shape** and **smaller size**.
- Microspheres provide constant and prolonged therapeutic effect.

g. Dendrimers

- The name comes from the **Greek word (dendron),** which translates to **"tree".**
- Dendrimers are hyperbranched nanostructure with some noteworthy features such as low polydispersity index with surface functionality, versatile properties, uniformity in size, and molecular weight



2. Controlled Release Drug Delivery System (CRDDS)

Controlled release is drug delivery system which maintain constant level of drug in blood and tissue for extended period of time.

It comprises the following

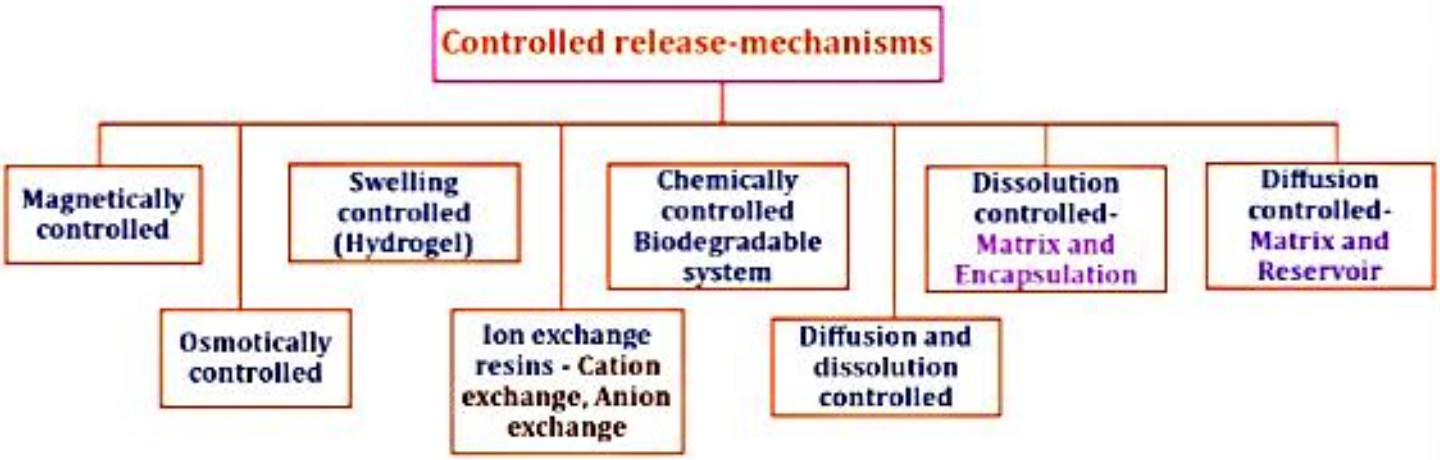


Fig 7.4: Classification of Controlled Release Drug Delivery System

a. **Diffusion Controlled System**

In diffusion- controlled release systems, drugs are trapped in and. released via diffusion through inert water-insoluble polymeric membranes (reservoir systems) or polymeric matrices. (monolithic systems or matrix systems).

➢ **Matrix diffusion -controlled system**

In a matrix diffusion-controlled system, the drug is bound to a polymeric carrier in a dispersed form.

Example: Carbopol 934, Metformin HCl etc.

➢ **Reservoir diffusion- controlled system**

Reservoir diffusion system also called as **laminated matrix device**. It is a hollow system containing an inner core surrounded by water insoluble membrane and polymer can be applied by coating or micro encapsulation.

Example: Nico 400. Nitro Bid etc.

b. **Dissolution Controlled System**

In dissolution -controlled release systems, drugs are coated with or encapsulated within slowly dissolving polymeric **membranes (reservoir systems)** or matrices **(monolithic systems),** respectively.

Example: Brompheniramine PPA, Dextromethorphan etc.

C. Dissolution and Diffusion Controlled release system

In this system, the drug is encapsulated in partially soluble membrane in which pores are formed that **permits entry of aqueous medium** into core and drug release starts by diffusion of dissolved drug out of system.

Example: Ethyl cellulose and PVP mixture dissolves in water and create pores of insoluble ethyl cellulose mixture

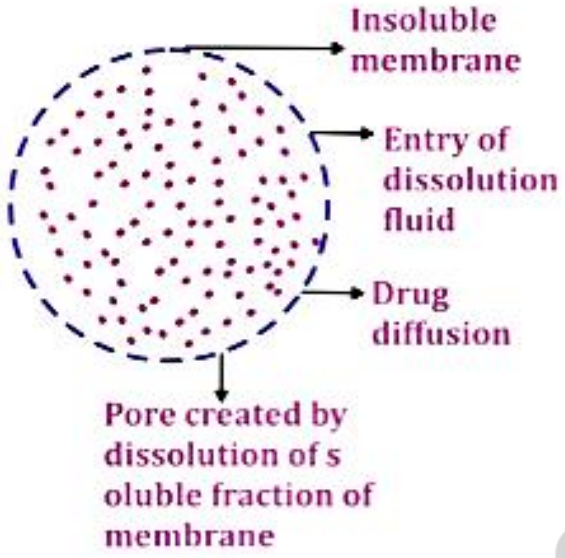


Fig 7.5: Dissolution and Diffusion Controlled Release system

d. Chemically controlled biodegradable system

- A chemically controlled biodegradable drug delivery system is a type of drug delivery system designed to release therapeutic agents in a controlled and predictable manner based on chemical properties.
- This system is particularly useful for providing sustained drug release, improving patient compliance, and minimizing side effects.

Example: Nifedipine Tablets, Zolpidem Tartrate Tablet etc.

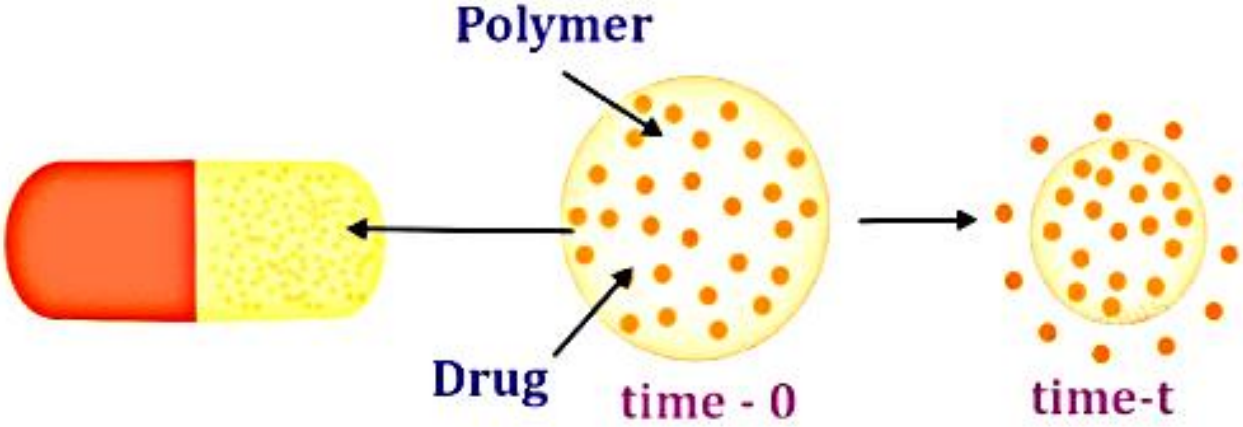


Fig 7.6: Chemically controlled biodegradable system

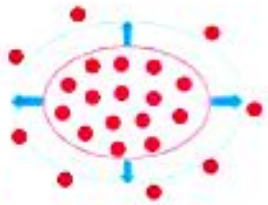
e. **Ion exchange resin**

Ion exchange is a **reversible process** in which ions of like sign are exchanged between liquid and solid when in contact with a highly insoluble body.

Example: ER Diclofenac Na, Diltiazem HCl etc.

f. **Swelling Control (Hydrogel)**

In these swelling controlled-release systems, the release of a solute (e.g., drug, dye, etc.) is controlled by one or more of the following processes: namely, the **transport of the solvent into the polymer matrix**, swelling of the associated polymer



Example: Ibuprofen, Lysozyme etc.

g. **Osmotically Controlled System**

The oral osmotic pump is developed by coating the core tablet with the **semi permeable membrane with an orifice or coat.**

Example: Albuterol Tablets, Pseudoephedrine Tablets etc.

h. **Magnetically Controlled release system**

Magnetically drug delivery system **deals with the specific delivery of therapeutic agents** to desired target area under magnetic field i.e tumor by using magnetic nanoparticle.

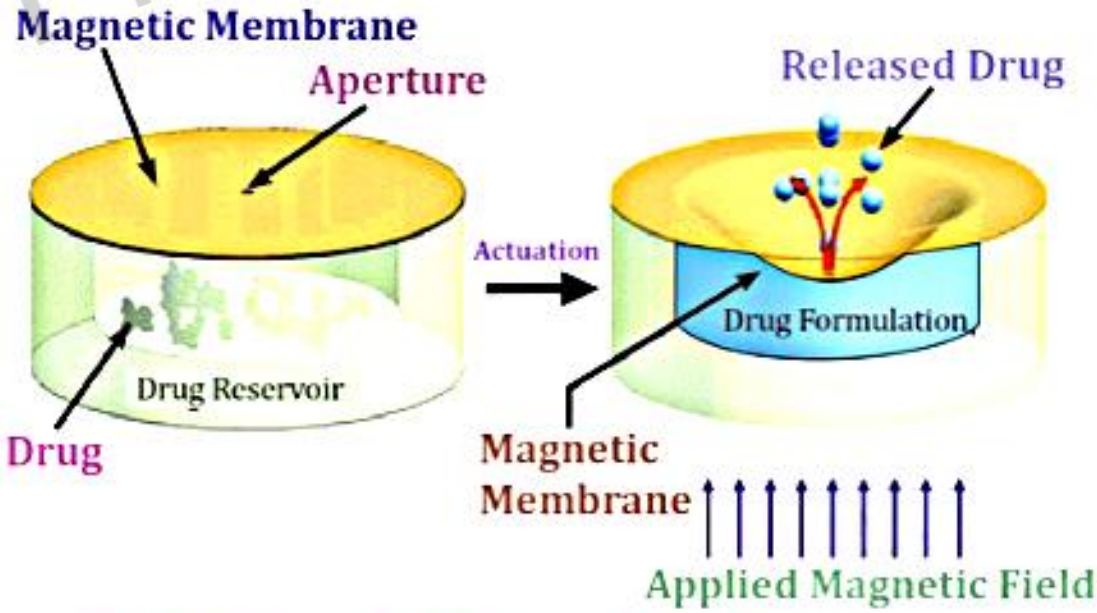


Fig 7.7: Magnetically Controlled Release System

3. **Microencapsulation**

- Microencapsulation is a process where by small discrete solid particles or small liquid droplets are surrounded and enclosed by an intact shell.
- It comprises of the following:

a. **Micro particles-** "Micro particles" refers to the particles having the diameter range **of 1-1000µm**, irrespective of the precise exterior and/or interior structures.

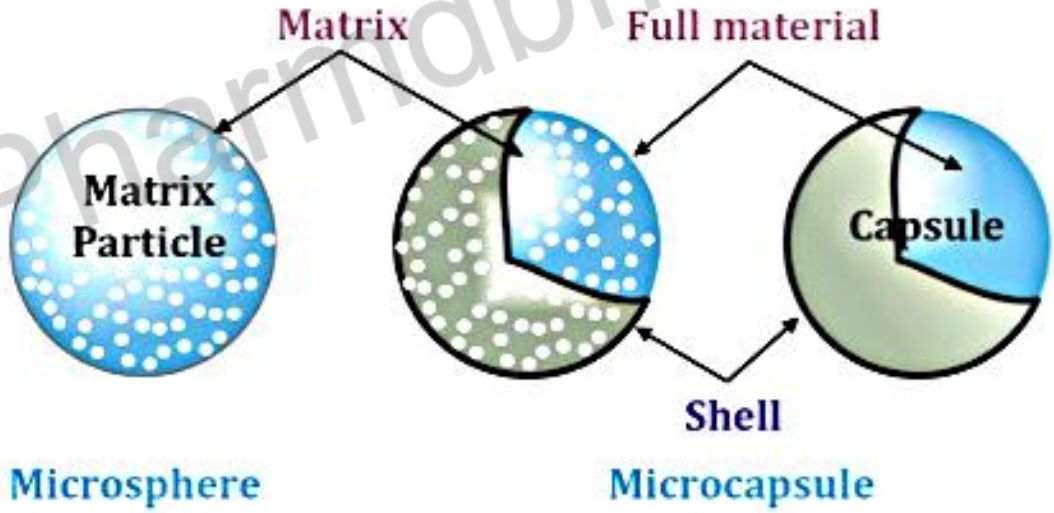
Example: Mesalamine Tablet, Olsalazine Capsule etc.

b. **Microspheres-** "Microspheres" particularly refers to the spherically shaped micro particles within the broad category of micro particles.

Example: Monoclonal antibody, Gentamicin etc.

c. **Microcapsules-** "Microcapsules" refers to micro particles having a core surrounded by the coat or wall material(s) distinctly different from that of the core or pay-load or nucleus, which may be solid, liquid, or even gas.

Example: Acetaminophen, Progesterone etc.



4. Gastroretentive Drug Delivery System (GRDDS)

- Gastroretentive dosage forms **release the drug in a controlled manner** to their specific site of action.

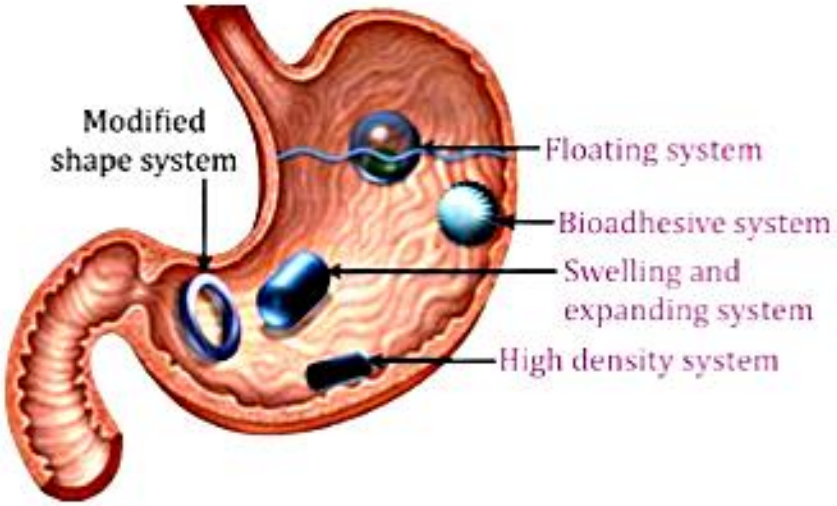
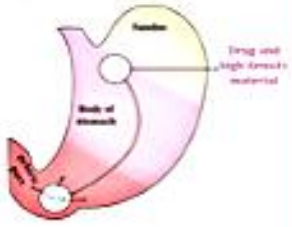


Fig 7.8: Gastroretentive Drug Delivery System

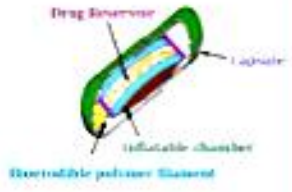
- It comprises of the following:

  a. Floating system: Floating Drug Delivery System are **hydro-dynamically controlled low-density systems** with sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.
  Example: Venlafaxine HCl Tablet, Propranolol HCl etc.

  b. High density system: A high-density system uses its weight as a retention mechanism to enhance the gastric residence of a drug in the stomach, its density must exceed the normal **stomach content (1.004 g/mL).**
  Example: Propafenone HCl Tablet, Atenolol Tablet etc.



  c. Inflatable System: This inflatable chamber contains drug reservoir which is encapsulated in a gelatin capsule.
  Example: Clarithromycin Tablet, Ciprofloxacin Tablet etc.



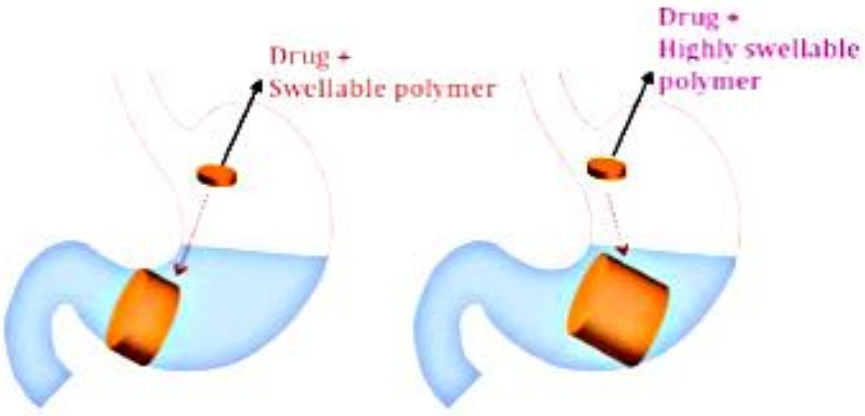


Fig 7.9: (a) Expandable Polymer (b) Superporous Hydrogels

d. **Gastro-adhesive system:** These are delivery system which **binds to gastric epithelial cell surface** or mucin by increasing the closeness and duration of contact.

Example: Acyclovir Tablet, Nizatidine Tablet etc.

5. Implantable Drug Delivery System (IDDS)

- **Implantable drug delivery systems** provide extended release of a drug for the desired duration, usually over timespans of months and years.
- It comprises the following:

a. **Implants:** Medical implants are devices or tissues that are placed inside or on the surface of the body. Many **implants are prosthetics**, intended to replace missing body parts.

Example: Norplant II subdermal implant, Paclitaxel-loaded etc.

b. **Osmotic Pump:** Osmotic pumps are controlled drug delivery devices based on the principle of osmosis.

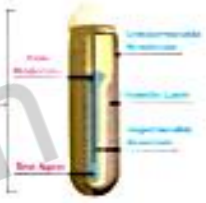


Fig 7.10: Osmotic Pump

Example: Alzet Osmotic pump, Verapamil HCl etc.

6. Nasopulmonary Drug Delivery System (NPDDS)

- Nasopulmonary Drug Delivery System is a route of administration in which patients use an inhaler to inhale their medications and drugs are **absorbed into the bloodstream** via the lung mucous membrane.
- It comprises of the following:

a. **Inhalers:** An inhaler is a device that gets medicine directly into a person's lungs. The medicine is a mist or spray that the person breathes in.

Example: Salbutamol Inhaler, Budesonide Inhaler etc.

b. **Nebulizers:** A nebulizer is an electrically powered machine that turns liquid medication into a mist so that it can be breathed directly into the lungs through a face mask or mouthpiece.

Example: Tobramycin Nebulizer, Albuterol sulphate Nebulizer etc.

c. **Nasal spray:** Nasal spray is a medication that is sprayed into the nostrils to help relieve congestion and other symptoms of allergies or a cold.

d. **Metered Dose Inhaler:** A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is usually self-administered by the patient via inhalation.

Example: Albuterol sulphate, Beclomethasone etc.

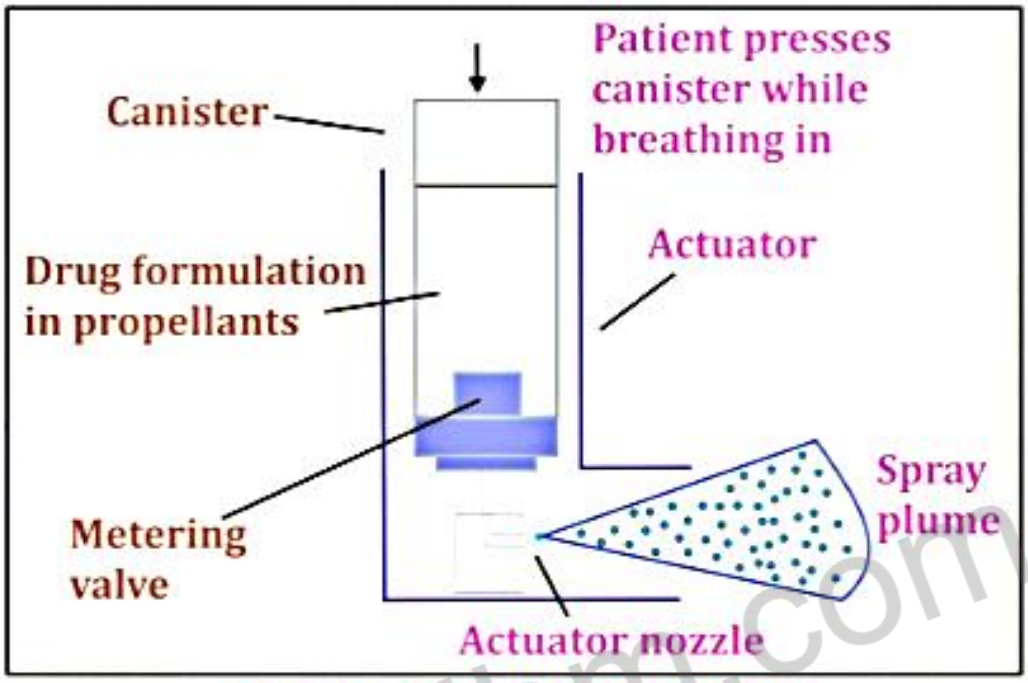


Fig 7.11: Metered Dose Inhaler

7. Mucoadhesive Drug Delivery System (MDDS)

- Mucoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption.
- It comprises of the following:

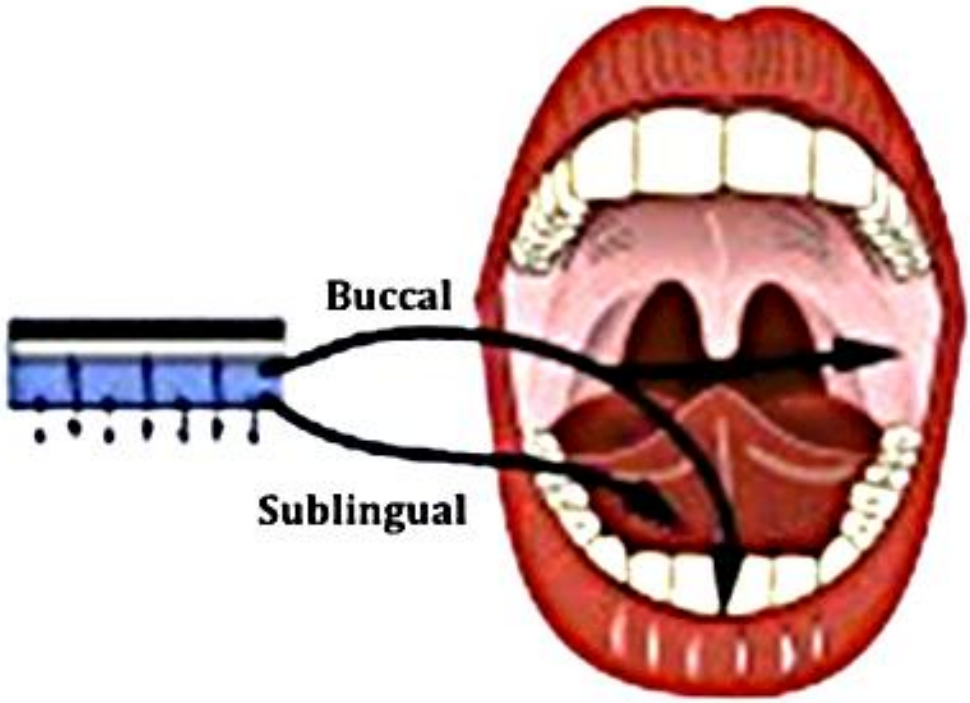
a. **Oral Delivery System:** An oral drug delivery system is thus believed to provide continuous oral release of the drug throughout the course of its gastrointestinal (GI) transit.

➢ **Buccal Delivery System:** Buccal drug delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and transmucosal (systemic effect) drug administration.

Example: Nifedipine Tablet, Omeprazole Tablet etc.

➢ **Sublingual Delivery System:** Sublingual administration involves placing a drug under the tongue. This route avoids first-pass metabolism and affords quick drug entry into the systemic circulation.

Example: Zolpidem Tablet, Nystatin Tablet etc.



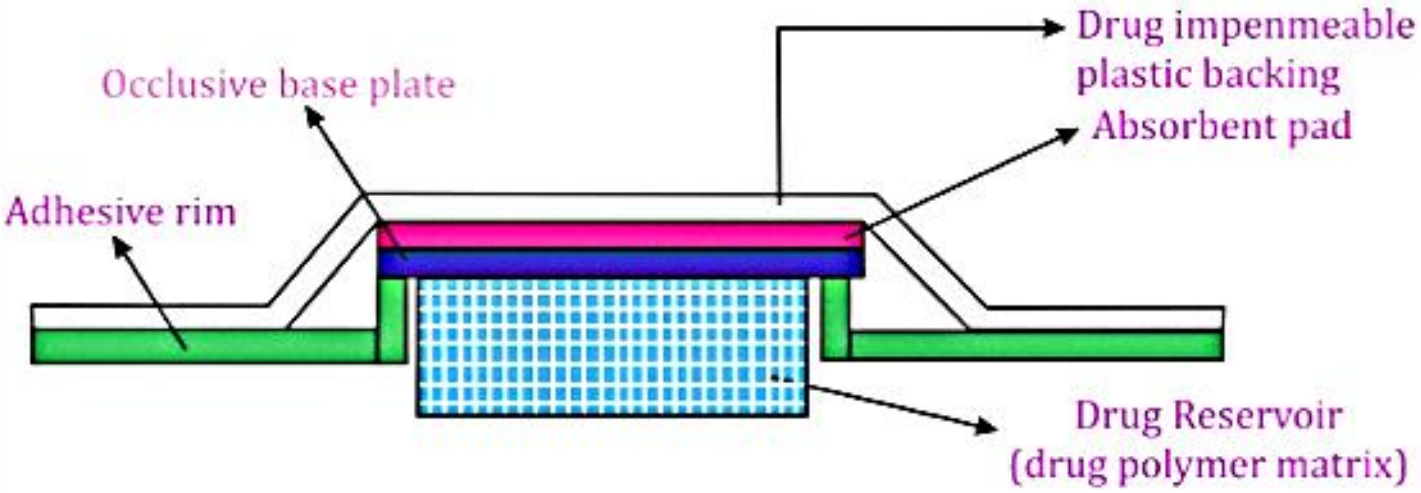
7.12: Buccal and Sublingual Drug Delivery System

a. **Rectal Delivery System:** Rectal Drug Delivery System is the **administration of drug through the rectum**. A drug that is administered rectally will in general (depending on the drug) have a faster onset, higher bioavailability, shorter peak, and shorter duration than oral administration.
Example: Zinc oxide ointment, Theophylline Film etc.

b. **Vaginal Delivery System:** Vaginal Drug Delivery System is the administration of drug through the vagina using different dosage form i.e creams, tablets, foams etc. Vaginally administered agents and formulations are mainly being developed to provide **"dual prophylaxis"** for contraception and protection against microbial infections.
Example: Nonoxynol-9, Clotrimazole cream etc.

8.Transdermal Drug Delivery System (TDDS)

- Transdermal drug delivery systems use the skin as the drug administration site **through patches.**
- The administered drug is absorbed into the **systemic circulation via blood** vessels in the skin and then circulates around the body



7.13: Transdermal Drug Delivery System

- It comprises of the following:

a. **Membrane permeation controlled TDDS:** In this type, drug is totally or partially **encapsulated with the drug reservoir.**
   - Drug reservoir may exist in the form of solid, solution, or suspension form.

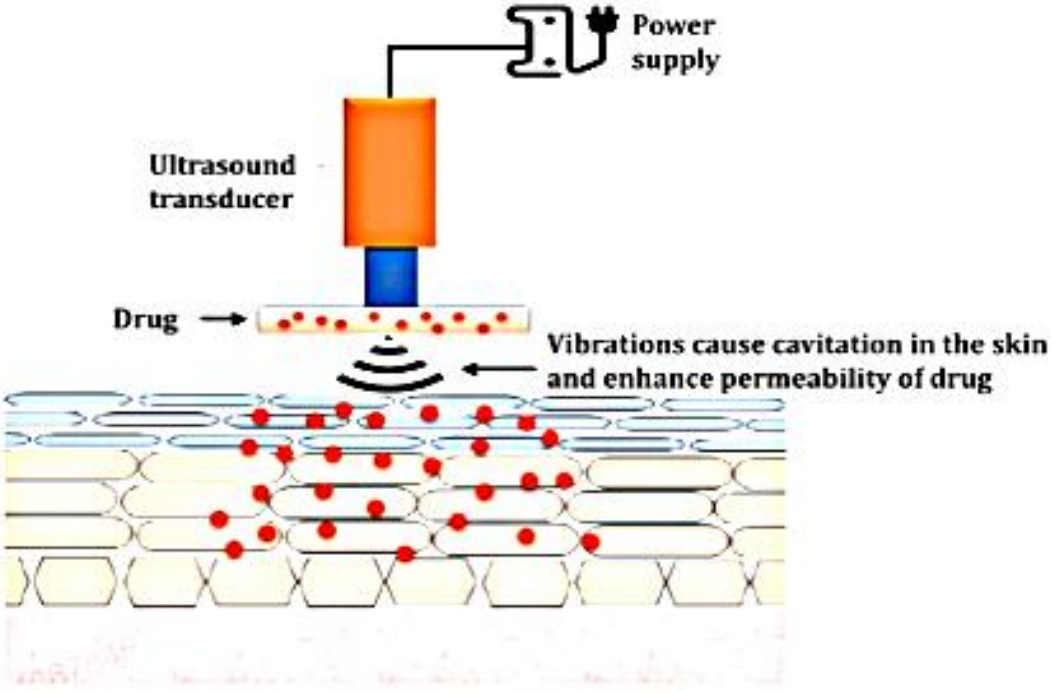
   Example: Catapress, Estraderm etc.

b. **Polymer Matrix Diffusion controlled TDDS:** In a matrix diffusion-controlled system, the **drug is bound to a polymeric carrier** in a dispersed form.
   - In this drug reservoir is prepared by dispersing the drug homogeneously in hydrophilic and lipophilic polymer matrix.

   Example: Atenolol Transdermal gel, Nitroglycerin etc.

c. **Adhesive Dispersion TDDS:** In this type, the drug reservoir is prepared by **directly dispersing the drug in an adhesive polymer** that is spread over a flat sheet of drug impermeable backing membrane.
   Example: Buprenorphine, Clonidine etc.

d. **Sonophoresis:** Sonophoresis is the movement of drug molecules through the skin under the influence of ultrasound. This technique typically uses a low-frequency pressure wave of **less than 100 kHz.**
   Example: Insulin Solution, Lidocaine solution etc.



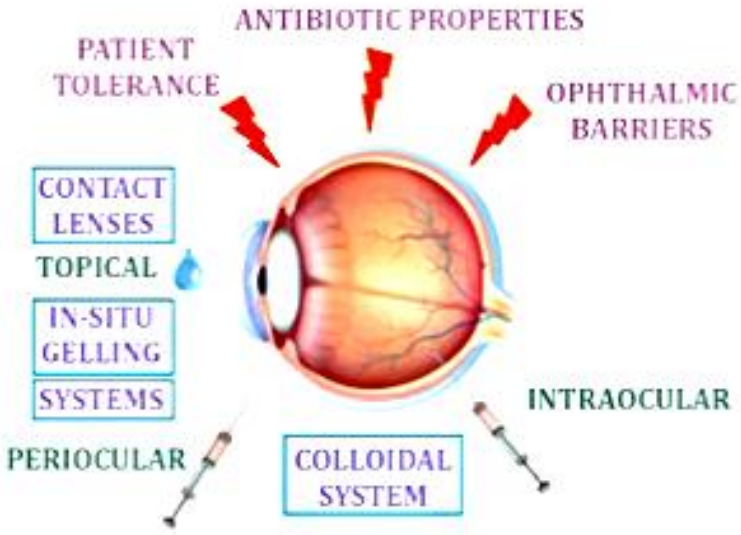
7.14: Sonophoresis

e. **Microreservoir type TDDS:** This system is the combination of reservoir and matrix diffusion type TDDS. In this, the **drug reservoir is formed by suspending the solid drug** in aqueous solution of water soluble polymer.

Example: Clonidine, Nicotine and Testosterone etc.

9. **Ocular Drug Delivery System (ODDS)**

Ocular drug delivery system (ODDS) is a dosage form, vehicle, or system intended for instilling, administering, or **delivering drug/medicine to eye** against any ailment or disorder involving or affecting vision. It ranges from simple sterile eye drop for the ocular surface to complex implants for intraocular tissue.



7.15: Ocular Drug Delivery System

a. **Artificial tear insert (ATI):** An Artificial Tear Insert (ATI) device refers to a specialized **rod -shaped device** designed for the controlled release of artificial tears, which are solutions used to lubricate and moisturize the eyes.

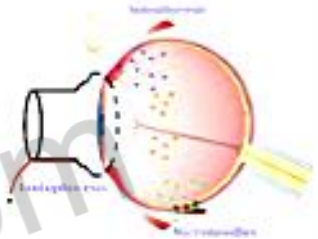
Example: Lacrisert, Succinylated Collagen etc.

b. **Contact lens:** Contact lenses are thin, round lenses that rest on the surface of your eyes to help you see more clearly.

Example: Chloramphenicol and Tetracycline, Fluorescein etc.

c. **Ocusert:** Ocuserts are sterile ocular preparations that may follow a controlled release technique to extend medication residence duration and reduce nasolacrimal discharge. **Example:** Pilocarpine ocuserts etc.

d. **Ocular Iontophoresis:** Iontophoresis refers to the non-invasive application of a low-amplitude electrical current to enhance delivery of charged drug molecules across eye.



Example: Dexamethasone Phosphate, 6-Hydroxydopamine etc.

e. **Collagen shield:** The collagen corneal shield is a newly developed, potentially multipurpose ophthalmic lens, which is made of a natural protein.

Example: Gentamycin and Dexamethasone etc.

10. Vaginal Drug Delivery System (VDDS)

- Vaginal drug delivery indicates the administration of medications within the vaginal cavity to produce local or, less frequently, systemic pharmacological effects.
- It comprises of the following

a. **Vaginal tablet:** A vaginal tablet is a solid dosage form inserted into the vagina to treat infection. Infections can be treated with a vaginal tablet which dissolves in the vagina.

Example: Clotrimazole, Itraconazole etc.

b. **Vagina gels:** Vaginal gel consist of active ingredients intended for administration in or around the vagina.

Example: Liposomes, Nonoxynol-9 etc.

c. **Vaginal ointment:** Vaginal ointments are used to applied in vulvo-vaginal area for treatment of infections.

Example: Candicidin, Tioconazole etc.

d. **Vaginal cream:** Vaginal creams are topical medications inserted into the vagina. These are used to treat a vaginal infection.

Example: Dehydroepiandrosterone Sulphate, Miconazole etc.

e. **Vaginal suppositories:** Vaginal suppositories can help with the treatment of fungal infections and vaginal dryness.

Example: Clindamycin and Clotrimazole Suppositories etc.

f. **Vaginal pessaries:** A pessary is a removable device that is inserted into the vagina (birth canal) to provide support in the area of a prolapse.

Example: Canestan

g. **Vaginal ring:** A vaginal ring is a circular ring type drug delivery device designed to release drug in a controlled manner.

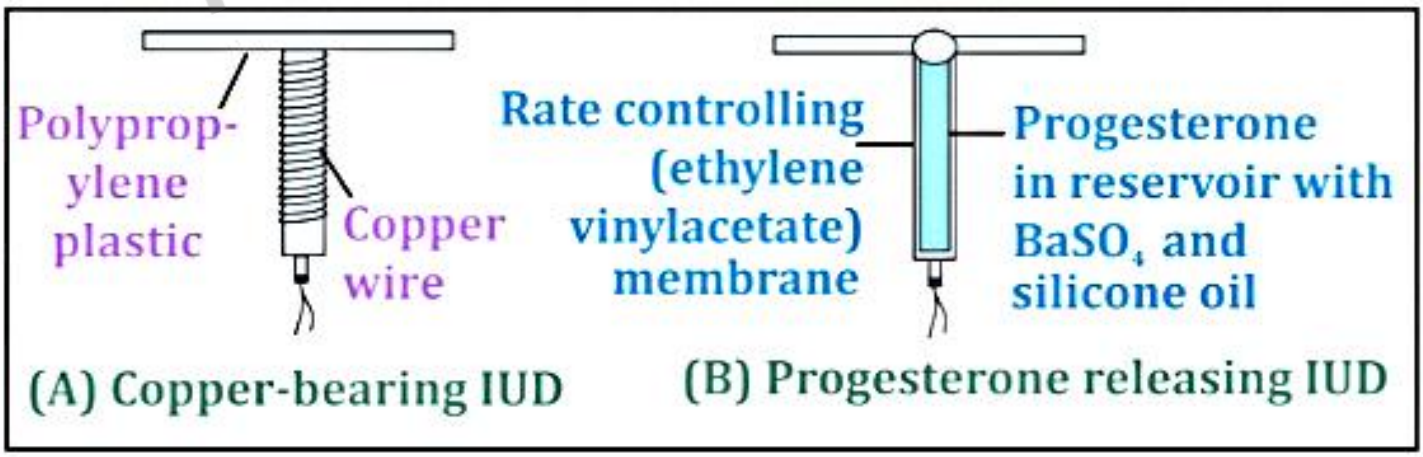
Example: Dapivurine, Estradiol etc.

11. Intrauterine Drug Delivery System (IUD)

- In intrauterine drug delivery system IUD (Intauterine Devices) are used that is inserted into the **cervix into uterus** to prevent pregnancy.
- It comprises of the following:

a. **Medicated intra-uterine device:** An intrauterine device (IUD) is a small plastic T-shaped device used to deliver the drug into the uterus.

Example: Copper bearing IUDs, Progesterone IUDs etc.



7.16: Intrauterine Devices

b. **Non-medicated IUD:** Intrauterine device (IUD) is a small, flexible plastic frame to be inserted into the uterine cavity. These devices are made of plastic or stainless steel only.

Example: Dalkon shield, Lippes Loop etc.

7.3 ADVANTAGES OF NOVEL DRUG DELIVERY SYSTEM

- It provides **optimum dose at the right time and right location.**
- It leads to **efficient use** of expensive drugs, excipients and reduction in production cost.
- It provides **better therapy** and **improved comfort** as well as standard of living.
- **Pre-determined release rates** for an extended period of time.
- Duration for **short half-life** drugs may be increased.

7.4 CHALLENGES OF NOVEL DRUG DELIVERY SYSTEM

- Novel Drug Delivery System requires **high capital investment.**
- The **major challenge** for this drug delivery system is the stability of the drug.
  - ✓ The drug which are unstable in stomach can be placed in slowly soluble form or its release must be delayed until it reached small intestine.
  - ✓ Compounds which are unstable in small intestine should demonstrate with low bioavailability when given in sustained dosage form as more drugs is delivered in small intestine hence it may get degraded.
- It is time **consuming and faces the problem of toxicity**, low efficacy, biocompatibility, side effects and degradation.