UNIT – 5 OCULAR DRUG DELIVERY SYSTEM

Points to be covered in this topic

- ☐ INTRODUCTION
- ☐ INTRA OCULAR BARRIERS
- ☐ METHODS TO OVERCOME BARRIERS
- ☐ OCULAR FORMULATIONS
- ☐ OCUSERTS

OCULAR DRUG DELIVERY SYSTEM

INTRODUCTION

- The novel approach in which drug can be instilled on the **cul-de-sac cavity of eye** is known as **ODDS**.
- Ophthalmic preparations are specialized **sterile preparations** of dosage forms designed to be instilled onto the **external surface of the eye (topical)**, **administered inside (intraocular)** or **adjacent (periocular)** to the eye or used in conjunction with an ophthalmic device.
- The most commonly administered dosage forms are **solutions, suspensions and ointments**.

- Poor bioavailability of drugs from ocular dosage forms is mainly due to the **precorneal loss factors** which include:
    - Solution drainage
    - Lacrimation
    - Tear dynamics
    - Tear dilution
    - Tear turnover
    - Conjunctival absorption
    - Nonproductive absorption
    - Transient residence time in the cul-de-sac
- The relative **impermeability of the corneal epithelial membrane** are the major challenges.
- ODDS can be mainly prepared as **gels, ointments, microspheres, ocular inserts and nanoparticles**, etc.

Advantages

✓ It increases accurate dosing.

✓ It provides sustained and controlled drug delivery system.

✓ It increases the ocular bioavailability of drug by increasing the corneal contact time.

✓ It provides targeting within the ocular globe so as to prevent the loss to other ocular tissues.

✓ It provides comfort, better compliance to the patient and improves therapeutic performance of drug.

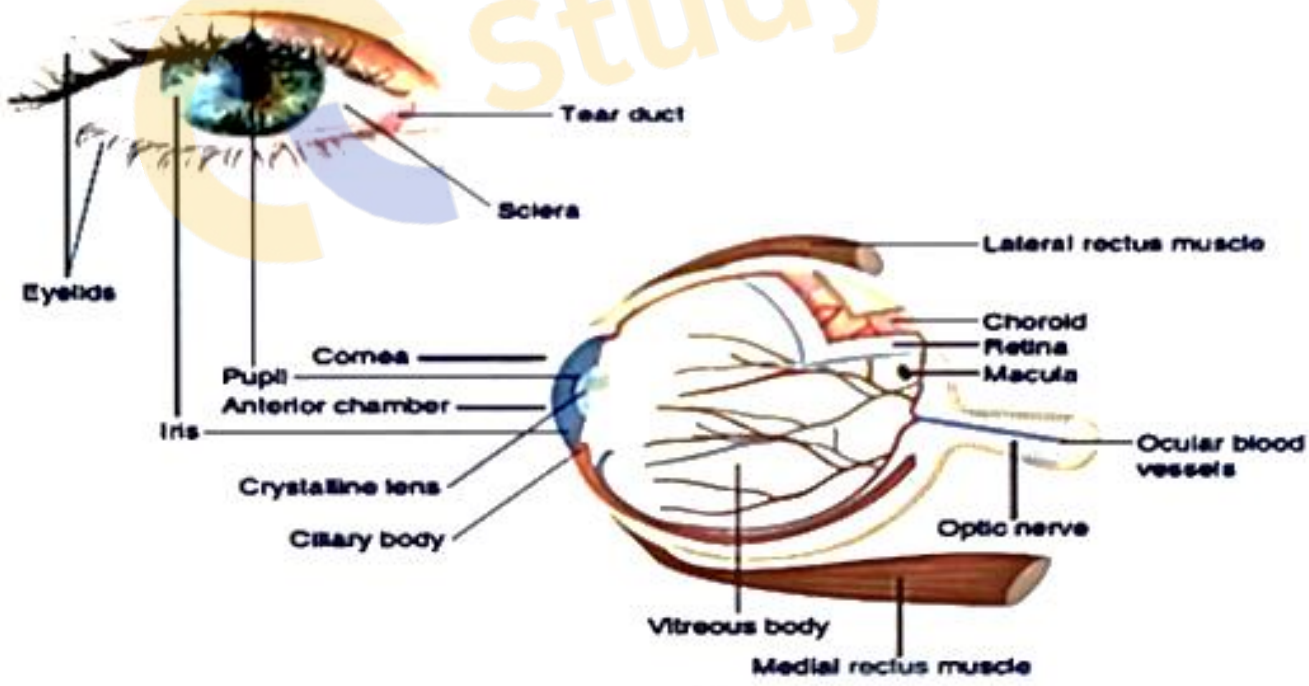
Disadvantages

✓ Dosage form cannot be terminated during emergency.

✓ It interferes with vision.

✓ It is difficult in placement and removal.

✓ There is occasional loss during sleep or while rubbing eyes.

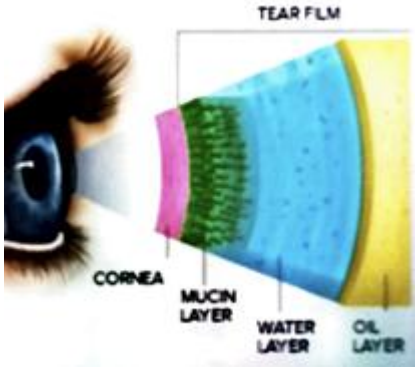


Anatomy of eye

INTRA OCULAR BARRIERS

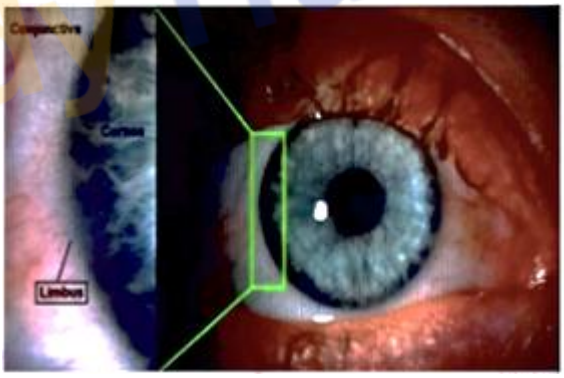
1. Tear

- The precorneal barrier is **tear film** which reduces the effective concentration of the administered drugs.
- Due to dilution by the tear, accelerated clearance and binding of the drug molecule to the tear proteins.
- The dosing volume of instillation is generally **20–50 µl**, whereas the size of cul-de-sac is only **7–10 µl**.
- The excess volume may spill out onto the cheek.



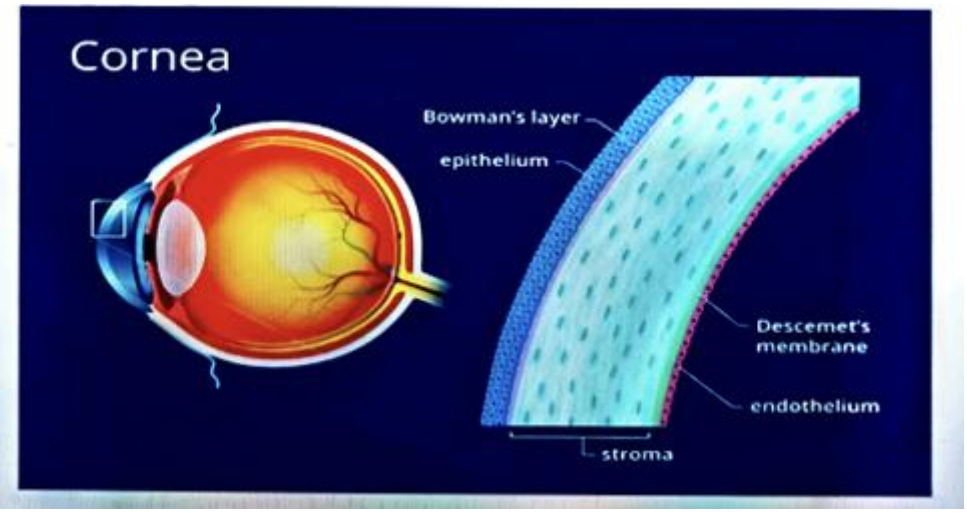
2. Cornea

- The cornea consists of **three layers** such as:
  - **Epithelium**
  - **Stroma**
  - **Endothelium**



- A mechanical barrier to **inhibit transport of exogenous substances** into the eye.
- **Corneal epithelium** is lipophilic in nature and tight junctions are formed to restrict **paracellular drug permeation** from the tear film.
- **Stroma** is composed of collagen fibrils. The highly hydrated structure of the stroma acts as a **barrier to permeation of lipophilic drug molecules**.

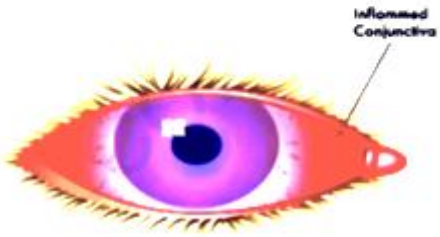
- **Corneal endothelium** is the innermost monolayer of hexagonal shaped cells and acts as a **separating barrier** between the stroma and aqueous humor.



3. Conjunctiva

- Conjunctiva of eyelids and globe is a **thin and** transparent membrane which is involved in the **formation and maintenance of the tear film**.

- The conjunctiva or episclera is **highly** supplied with capillaries and lymphatics.

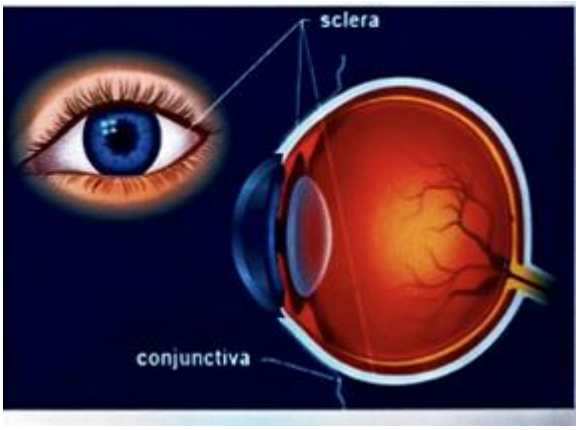


- The conjunctival blood vessels do **not form a tight junction barrier** which means **drug molecules can enter into blood circulation** by **pinocytosis** and **convective transport** through paracellular pores in the **vascular endothelial layer**.

4. Sclera

- The sclera mainly consists of **collagen fibres** and **proteoglycans** embedded in an **extracellular matrix**.

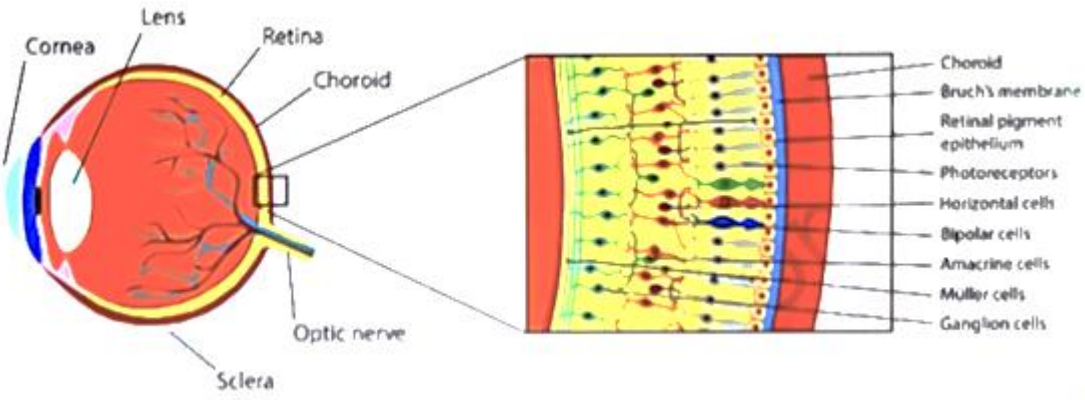
- Scleral permeability depends on the **molecular radius**.
- The increase of **hydrophobic/lipophilic character** of drugs shows **lower permeability in sclera**.



- **Hydrophilic drugs** may diffuse through the **aqueous medium of proteoglycans in fibre matrix pores** more easily than lipophilic drugs.
- The **charge of drug molecule** may affect its permeability across the sclera.

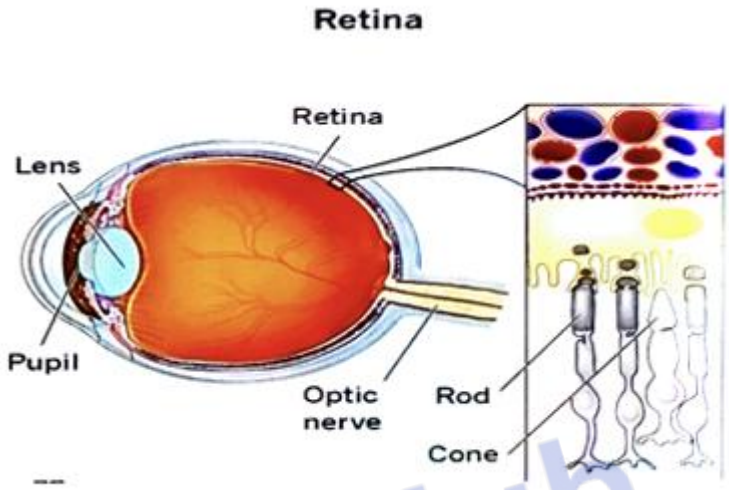
5. Choroid / Bruch's Membrane

- Choroid is one of the most **highly vascularized tissues** of the body to supply the blood to retina.
- Bruch's membrane (BM) causes **thickening with age**.
- These changes cause **increased calcification of elastic fibres** and **increased crosslinkage of collagen fibres**.



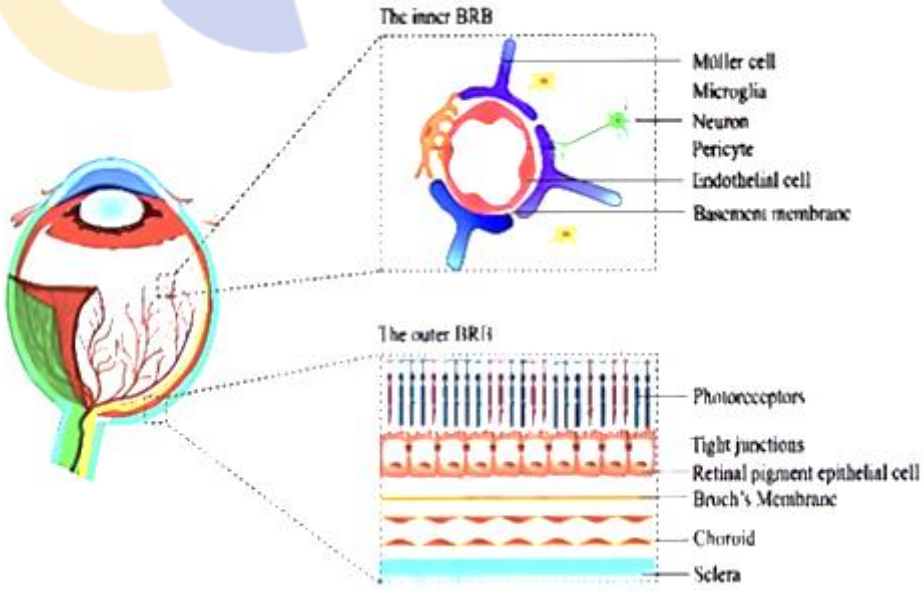
6. Retina

- The barriers restricting drug penetration from the vitreous to the retina is the **internal limiting membrane (ILM)**.
- The **ILM separates the retina and the vitreous** and is composed of **10 distinct extracellular matrix proteins**.
- Drug transport across the **retinal pigment epithelium (RPE)** takes place by **transcellular and paracellular routes**.



7. Blood–Retinal Barrier

- Blood retinal barrier (BRB) restricts drug transport from blood into the retina.
- BRB is composed of **tight junctions of retinal capillary endothelial cells and RPE**.



METHODS TO OVERCOME BARRIERS

I. PHYSICAL METHODS

- Physical force-based methods generally require a **power-driven physical device** to deliver energy to the barriers, thereby **enhancing transient drug transport**.

Iontophoresis

- It is the process in which **direct current drives ions into cells/tissues**.
- Iontophoresis, application of a **low-intensity electrical current**, enhances drug delivery across biological membranes.
- By causing **electrorepulsion** and **electro-osmosis** of drug molecule.
- Ocular iontophoresis offers a drug delivery system that is **fast, painless, safe** and in most cases results in the delivery of **high concentration of drug at specific site**.

Sonophoresis / Ultrasound

- It involves the application of a **sound field at frequencies higher than 20 kHz** to improve drug transport across biological membranes, including ocular barriers.
- The mechanisms for ultrasound-enhanced drug delivery take into account **non-thermal effects** (e.g. cavitation, acoustic streaming and mechanical stress) and **thermal effects** with ultrasound parameters, co-administration of microbubbles and drug characteristics, all having an effect on delivery efficacy.

Microneedles

- Microneedles (MLs) are **micrometer sized needles**, or arrays of such, fabricated by adapting microelectronics tools.
- Applying MLs to biological membranes can create **tiny transport pathways**, thereby allowing drugs to permeate across these barriers.
- Enhanced drug delivery into the **cornea and anterior segment of the eye** can be achieved by insertion of MLs across the **corneal epithelium**.

II. CHEMICAL APPROACHES

- **Chemical modification of drugs** to improve therapeutic efficacy and to enhance various **physicochemical properties** such as solubility, stability, permeability, and evasion of efflux pump is an established approach in therapeutic drug delivery.

The most important strategies in chemical approaches for ocular delivery are:

- Designing ocular drugs that are **inactive at sites other than the eye (prodrugs)**
- Designing drugs that undergo **sequential metabolic conversion** and finally reach the target (**retro-metabolic design**)

Chemical modification

✓ Chemical modification of a known inactive metabolite or analog to restore the therapeutic activity that transforms back into the inactive metabolite in a predictable one-step biotransformation (SD)

OCULAR FORMULATIONS

I. Drug delivery systems to anterior segment of the eye

II. Drug delivery systems to posterior segment of the eye

III. Advanced delivery system

IV. Vesicular drug delivery system

I. Drug delivery systems to anterior segment of the eye

1. Eye-Drops

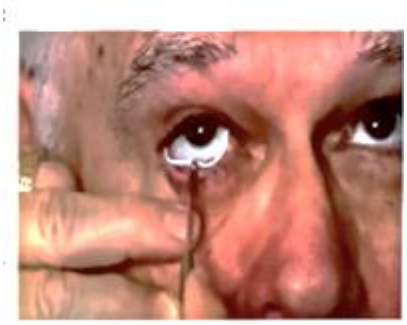
✓ Drugs which are active at eye or eye surface are widely administered in the form of **solutions, emulsion and suspension**.

✓ Generally eye drops are used for anterior segment disorders as adequate drug concentrations are not reached in the posterior tissues using this drug delivery method.

✓ Various properties of eye drops like **hydrogen ion concentration, osmolality, viscosity and instilled volume** can influence retention of a solution in the eye.

2. Ophthalmic Inserts

✓ Ophthalmic inserts are **sterile preparations** with a **solid or a semisolid consistency**, and



✓ Whose size and shape are specially designed for ophthalmic application.

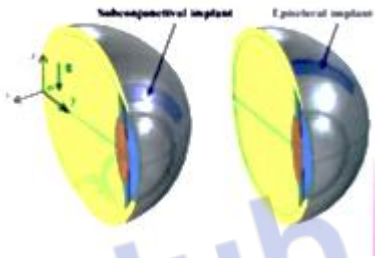
✓ The inserts are placed in the **lower fornix** and less frequently, in the **upper fornix or on the cornea**.

3. Punctal Plugs

✓ To prolong the retention time and increase absorption and efficacy after instillation of eye drops, inhibition of drainage through nasolacrimal system using punctual plug into the puncta is a long standing approach.

4. Subconjunctival / Episcleral Implants

✓ Scleral plug can be implanted at the **pars plana region of eye** made of biodegradable polymers and drugs and it gradually releases doses of drugs for several months upon biodegradation.



✓ The implant is flat on the bottom in contact with the episclera and the top is rounded in contact with anterior surface.

5. Ointment and Gels

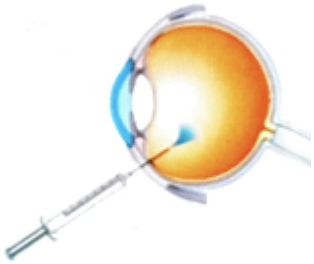
✓ Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointments and gels.

✓ Hence prolonging duration of action and enhancing ocular bioavailability of drugs is possible by gels and ointments.

II. Drug delivery systems to posterior segment of the eye

1. Intravitreal Implants

✓ An intravitreal implant is a drug delivery system, injected or surgically implanted in the vitreous of the eye.



✓ For sustained release of a pharmacologic agent to the posterior and intermediate segments of the eye.

III. Advanced delivery system

1. Cell encapsulation
2. Gene therapy
3. Stem cell therapy
4. Protein and peptide therapy
5. Scleral plug therapy
6. siRNA therapy
7. Oligonucleotide therapy
8. Aptamer
9. Ribozyme therapy

IV. Vesicular system

1. Liposomes
2. Niosomes

OCUSERTS

✓ Ocuserts (ocular inserts) are defined as **sterile preparations**, **multilayered**, **solid or semisolid devices** placed in **cul-de-sac or conjunctival sac** and

✓ Size and shape are designed especially for ophthalmic application.

✓ Delivers at constant rate by **diffusion mechanism**.

✓ Ocuserts increase corneal contact time, **prolongs duration of action, improve bioavailability, reduces the frequency of administration** and thus achieve patient compliance.

All types of ocuserts consist of 3 components namely:

1. A central drug reservoir
2. Rate controlling membrane
3. An outer annular ring meant for easy handling

CLASSIFICATION OF OCULAR INSERTS

Insoluble ocular inserts

a. Diffusional inserts

b. Osmotic inserts

c. Hydrophilic contact lenses

Soluble ocular inserts

a. Natural polymeric inserts

b. Synthetic insert

Bio erodable inserts

a. Soluble ocular drug inserts

b. Lacrisert

c. Minidiscs

d. Collagen shields

UNIT – 5 INTRAUTERINE DRUG DELIVERY SYSTEM (PART - 2)

Points to be covered in this topic

- INTRODUCTION
- ADVANTAGES
- DISADVANTAGES
- DEVELOPMENT OF INTRAUTERINE DEVICE
- APPLICATIONS

INTRAUTERINE DRUG DELIVERY SYSTEM

INTRODUCTION

• New intrauterine drug delivery products, which are designed to provide improved methods for the prevention and treatment of gynecological conditions, improvements to

birth control methods, and higher levels of safety, user acceptability, compliance, and quality of life for women.

• The development of frameless intrauterine systems is such an attempt to improve on the performance and acceptability of established intrauterine contraception.

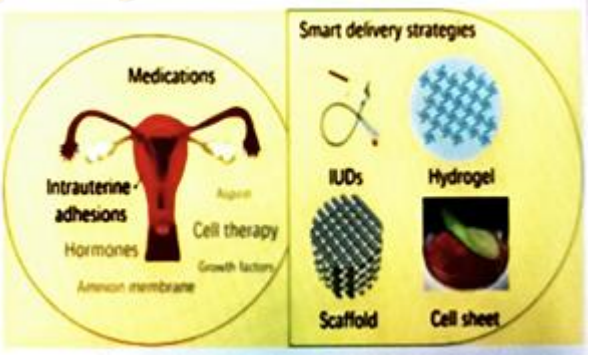
• An intrauterine drug delivery system (IUDDS) is used for the **controlled release of a drug having progestogenic activity** over a prolonged period of time and at a level required for contraception.

• It is a small object that is **inserted through the cervix and placed in the uterus** to prevent pregnancy.

• A small string hangs down from the IUD into the upper part of the vagina. The IUD is not noticeable during intercourse.

• IUDs can show pharmacological efficacy for about **1–10 years**.

• They work by **changing the lining of the uterus and fallopian tubes**, affecting the movements of eggs and sperm so that fertilization does not occur.



ADVANTAGES

• They are more than **99 percent effective** in preventing pregnancy.

• They last for a long time.

• They are safe to use if you are breastfeeding.

• No medications stop them from working.

• It provides another contraceptive choice if there is difficulty taking the hormone oestrogen.

• There is **no vaginal bleeding at all or a light regular period** after use.

DISADVANTAGES

• It does not protect against sexually transmitted infections (STIs).

• IUDDS is not useful if a uterus that is not the usual shape and pelvic infection.

• It is not suitable in case of **heavy periods, low iron levels, and endometriosis**.

• It may increase the likelihood of ectopic pregnancy.

• There are risks during insertion and removal.

• IUDDS may cause systemic contraindications like **copper allergy, immunodeficiency disorders, immunosuppressive therapy, Wilson's disease, acute liver disease or liver carcinoma and breast carcinoma**, especially for hormonal IUD, multiple sexual partners for the patient or her partner.

DEVELOPMENT OF INTRAUTERINE DEVICE

• Intrauterine Device (IUD) is a small object that is **inserted through the cervix and placed in the uterus** to prevent pregnancy.

• IUD usually is a **small, flexible plastic frame**.

• A small string hangs down from the IUD into the upper part of the vagina.

• The IUD is not noticeable during intercourse.

• IUDs can last **1–10 years**.

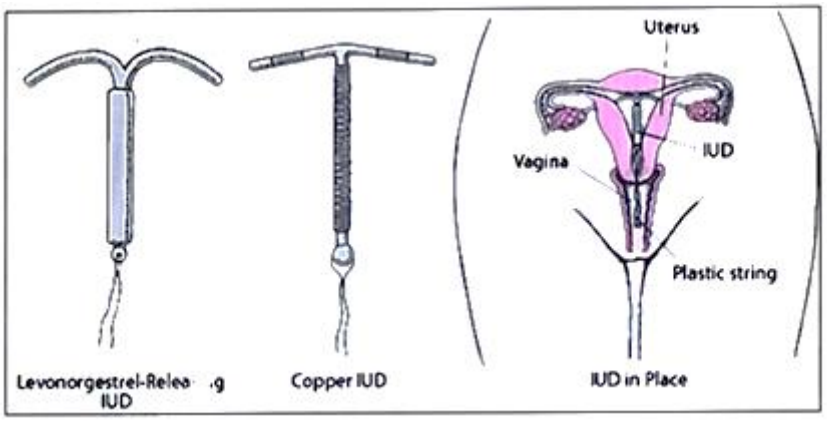
• They **affect the movements of eggs and sperm** to prevent fertilization.

• They also **change the lining of the uterus and prevent implantation**.

• IUDs are **99.2–99.9% effective** as birth control.

• They **do not protect against sexually transmitted infections**, including HIV/AIDS.

• Insertion of an IUD takes only about **5 to 10 minutes**.



ADVANTAGES

✓ It is highly effective in preventing pregnancy.

✓ It is inexpensive.

✓ It does not interrupt sex.

✓ It does not require partner's involvement.

✓ It can be used for a long period of time.

✓ It can be used as an emergency method of birth control.

✓ An IUD provides **long-term contraception for 3 to 5 years** and is cost-effective.

DISADVANTAGES

✓ It does not protect against sexually transmitted infections (STIs).

✓ It may increase the likelihood of ectopic pregnancy (pregnancy outside the uterus).

✓ It can cause heavier and more painful periods.

✓ Cramping and discomfort occurs during and **24–48 hours after insertion**.

✓ There are risks during insertion and removal.

APPLICATIONS

• IUD is effectively useful in contraception similar or better than female sterilization. IUDs are safe to use for many years. They may even remain somewhat effective past their recommended end date. **It provides long-term contraception**.

• For people with severe health conditions that make pregnancy dangerous, an IUD **can be life-saving**. IUD protects against pregnancy-related health issues.

• IUDs can be **safely placed immediately after abortion or 6 weeks postpartum** with high contraceptive benefits. **Copper IUD is recommended as the most effective option for emergency contraception**.

• IUD benefit is the fact that it can be used as an **adjunctive treatment modality for intrauterine adhesions**. IUD can be beneficial in patients with intrauterine adhesions or **Asherman's syndrome**, especially when combined with other ancillary treatments.

• IUDs include the treatment of **menorrhagia, anemia, dysmenorrhea and pelvic pain associated to endometriosis**, and endometrial protection during hormone replacement.