OCULAR CONTROLLED RELEASE SYSTEMS

INTRAVAGINAL AND INTRAUTERINE SYSTEMS

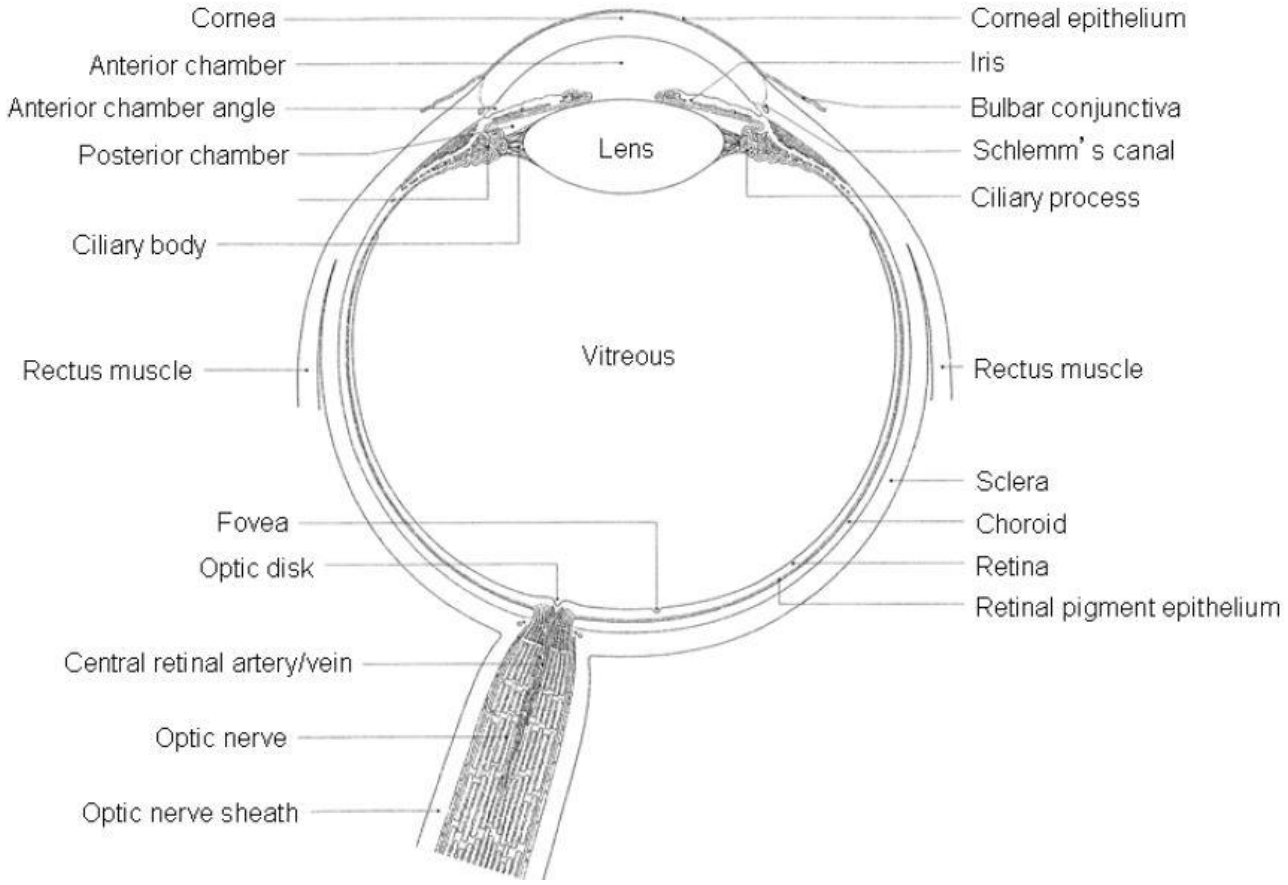
NASAL CONTROLLED RELEASE SYSTEMS

13. WEEK

OCULAR CONTROLLED RELEASE SYSTEMS

The eye is a complex organ with an unique anatomy and physiology. The structure of eye can be divided into two main parts:

- Anterior segment, and
- Posterior segment.



- Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion.
- Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor.
- The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract.

- For the treatment of the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea), usually topical ocular eye-drops are used.
    - An eye-drop, irrespective of the instilled volume, often eliminates rapidly within five to six minutes after administration, and only a small amount (1–3%) of an eye-drop actually reaches the intraocular tissue.
    - Thus, it is difficult to provide and maintain an adequate concentration of drug in the precorneal area.
    - More than 75% of applied ophthalmic solution is lost via nasolachrymal drainage and absorbed systemically via conjunctiva, hence ocular drug availability is very low.

- To increase ocular bioavailability and prolong the retention time on the ocular surface, numerous ophthalmic dosage forms such as viscous solutions, suspensions, emulsions, ointments, aqueous gels, and polymeric inserts, have been investigated for topical application to the eye.
- In general, topical applied drugs do not reach the posterior segment of the eye (retina, vitreous, choroid), therefore, systemic administration, periocular or intraocular injections of drugs are normally applied in clinical therapeutics.

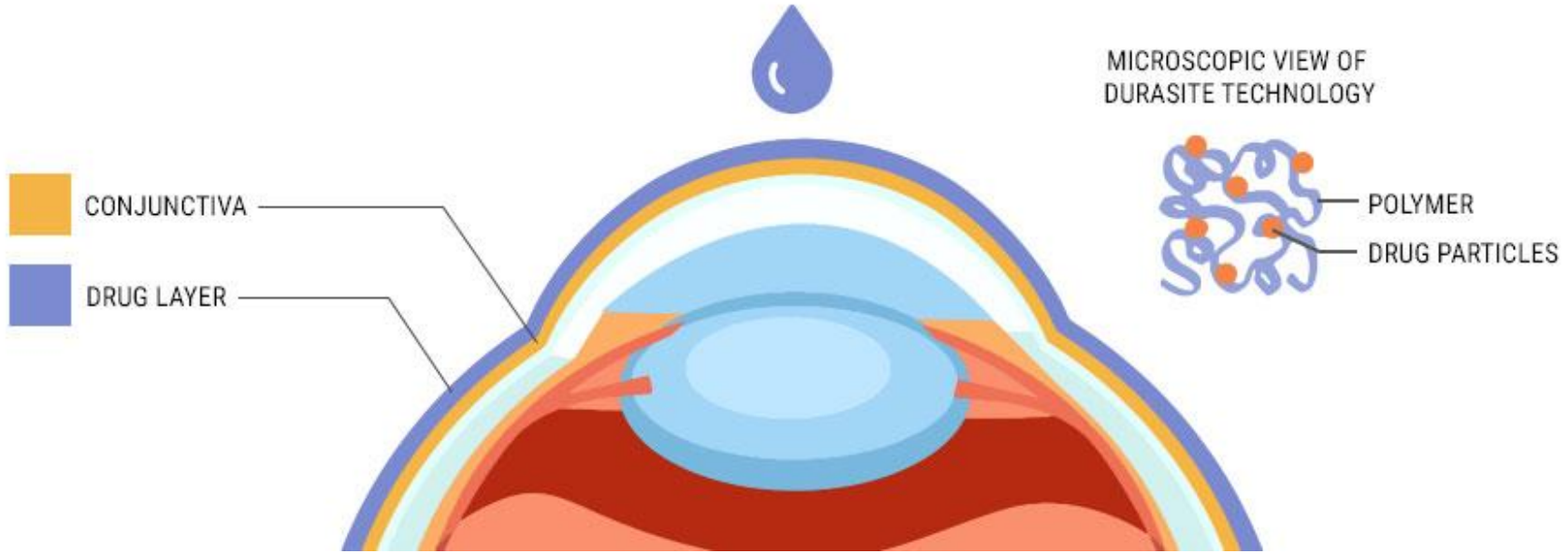
- However, the unique anatomy and physiology of the eye and its protective barriers prevent the administrated drugs from penetrating into the target tissues. Currently there is also rapidly growing interest in drug delivery systems to the posterior segment of the eye. This trend is toward a polymeric depot system implanted or injected directly into the vitreous, to obtain long-term, sustained release of drugs.

Drug Delivery Systems to Anterior Segment of Eye

❖ Eye Drops:

To prolong the retention time of topically applied drugs, anterior drug delivery systems for eye-drops utilizing interaction between drug carrier (excipients) and physiological environment of cornea and/or subconjunctiva are being developed.

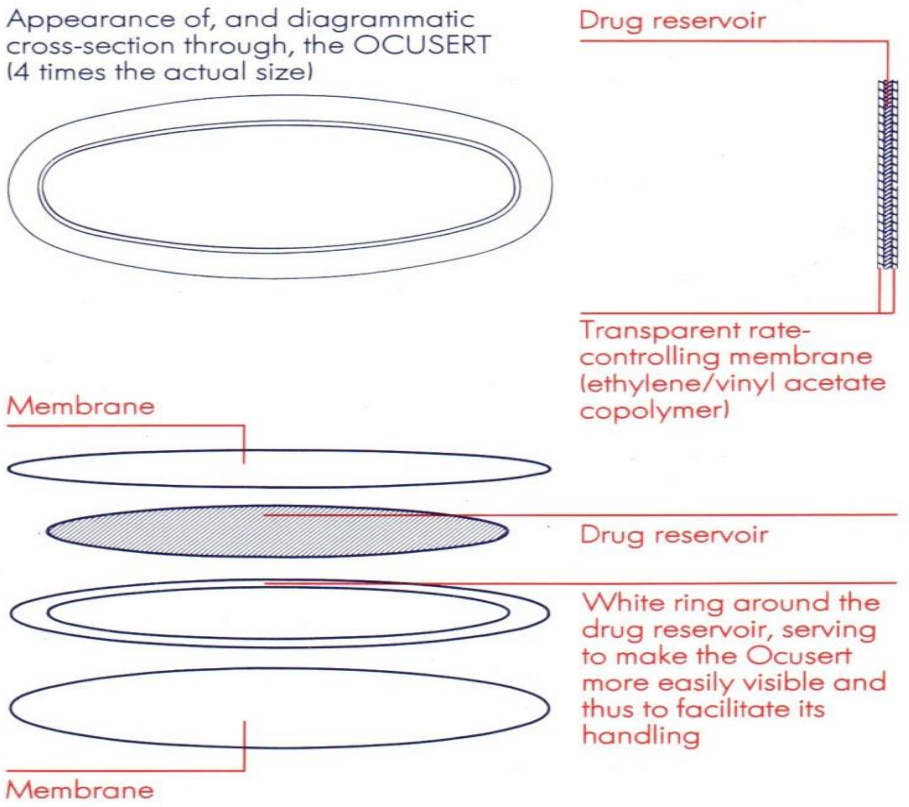
- **Durasite® DDS** (InSite Vision Inc., Alameda, CA, U.S.) is based on a polycarbophil aqueous solution. Polycarbophil is polyacrylic acid cross-linked with divinyl glycol, and forms hydrogen-bonding with the mucus, and corneal and conjunctival epitheliums, which are all negatively charged, to extend the effects of drug to several hours.



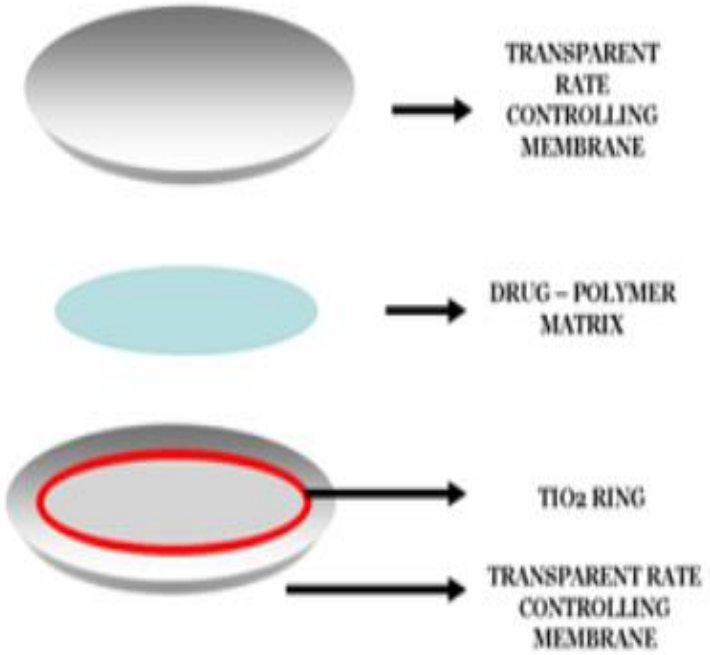
❖ Cul-de sac Inserts:

- **Ocusert®** was the first controlled-release polymer system to be used clinically. It was developed by ALZA Corporation. It was designed to improve therapy for glaucoma, one of the world's leading causes of blindness. The conventional treatment for this disease was for the patient to use eyedrops containing pilocarpine (which reduces intraocular pressure) four times a day.

- These eyedrops were often painful and patient compliance was sometimes poor. The Ocusert ® was designed to deliver pilocarpine continuously over a one-week period. The implant was placed in the lower eyelid's conjunctival cul-de-sac, where it floated in the tear film.



- The Ocusert ® is a reservoir system which utilizes a membrane composed of ethylenevinyl acetate copolymer as a rate-limiting barrier.



- **Lacrisert®** was the second ocular controlled-release system. It was recently introduced for use as artificial tears. The system is a hydroxypropylmethyl cellulose rod which is inserted with a special device beneath the tarsus of the lower eyelid.

- The rod slowly dissolves over a one day period, providing continuous lubrication and tear film stability to the eye. This system has received approval by the Food and Drug Administration and was introduced clinically in 1981.

Drug Delivery Systems to Posterior Segment of Eye

- Intravitreal Implants:
  - **Durasert™ Technology System** (pSivida Corp., Watertown MA, U.S.) uses a drug core with one or more surrounding polymer layers, and delivers drugs for predetermined periods of time ranging from days to years. The drug release is controlled by permeability of the polymer layers.

- Using the Durasert™ system, an antiviral drug, ganciclovir loaded intravitreal implant (Vitrasert®, Bausch & Lomb Inc., Rochester, NY, U.S.) for the treatment of cytomegalovirus retinitis, has been developed as the first intravitreal drug delivery system that avoids systemic side effects and does not involve frequent intravitreal injections. This implant is made of EVA and PVA, and releases ganciclovir by passive diffusion through a small opening in EVA at the base of the device for 6–8 months.

INTRAVAGINAL AND INTRAUTERINE SYSTEMS

Vagina is route for administration for contraceptives, anti-fungal, and antimicrobials. It is used for the achievement of local or for systemic absorption.

The vaginal wall is very well suited for the absorption of drugs for systemic use. As it contains a vast network of blood vessels

- This route offers certain advantages, such as avoidance of gut and hepatic first pass metabolism, reduction in gastrointestinal and hepatic side effects, and local targeting of drugs to the reproductive organs.
- Vaginally administered agents and formulations are mainly being developed to provide “dual prophylaxis” for contraception and protection against microbial infections including Acquired Immune Deficiency Syndrome(AIDS) and other sexually transmitted diseases (STDs).
- Drug delivery technologies that have been used for vaginal drug delivery include the intravaginal ring (IVR) and Vaginal Site bio-adhesive technology.

Benefits of Intravaginal Drug Delivery Systems

- Prolonged release,
- Minimal systemic side effects,
- An increase in bioavailability,
- Use of less total drug than an oral dose,
- First-pass metabolism can be avoided,
- Self medication is possible.
- Contact with digestive fluid is avoided and degradation of drug is minimized.
- Nausea, vomiting, emesis induced through oral administration is avoided.
- Quick onset of action.

Limitations of Intravaginal Drug Delivery Systems

- Gender specificity,
- Patient incompliance,
- Only a few drugs are administered by this route,
- Variability in drug absorption related with menstrual cycle, menopause and pregnancy,
- Influence with sexual intercourse.
- Personal hygiene,
- Some drugs are sensitive at vaginal pH.

Factors Affecting Absorption of Drugs

The drug transport across vaginal membrane mainly takes place by three major ways;

- ✓ Transcellularly- via concentration dependent diffusion through the cells,
- ✓ Paracellularly- mediated via tight junctions and
- ✓ Vesicular or receptor mediated transport.

Drug absorption from vaginal delivery system is mainly takes place in two main steps:

- ✓ Drug dissolution in vaginal lumen and
- ✓ Membrane penetration.

The rate and extent of drug absorption after intravaginal administration may vary depending on following factors:

Physiological Factors

- changes in the thickness of epithelium layer,
- cyclic changes,
- changes in the hormones level,
- volume of vaginal fluid,
- alteration of vaginal pH and
- Sexual arousal can potentially affect drug release from any intravaginal delivery system and also alter its rate of absorption.

For example;

1. Vaginal absorption of steroids is affected by the thickness of vaginal epithelium.
2. Vaginal absorption of estrogen shows high in post menopausal women compare to premenopausal women.

The high volume of vaginal fluid may increase the absorption of poorly water soluble drugs; however the same condition again responsible to remove the drug from the vaginal cavity and subsequent reduction of drug absorption.

Physicochemical Factors

- Lipophilicity,
- Ionization,
- Molecular weight,
- Surface charge and
- Chemical nature can influence the vaginal drug absorption.

In consideration to permeability the lipophilic steroids like progesterone and estrone having better permeability than the hydrophilic one like hydrocortisone and testosterone.

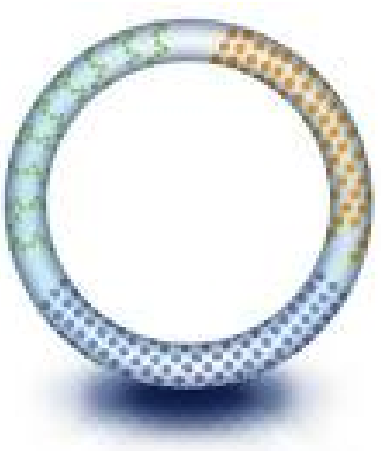
Vaginal Rings

Sustained and controlled-release devices for drug delivery in the vaginal and uterine areas are most often for the delivery of contraceptive steroid hormones.

One such application is the medicated vaginal ring. Medicated vaginal rings fabricated from silastic 382 medical grade elastomer. These are of **‘doughnut-shaped’**. Also known as **intra-vaginal rings** or **V-Rings**.

Vaginal rings provide a means of delivering a drug to the systemic circulation at a controlled release rate.

- **NuvaRing®** is the first-ever marketed vaginal ring; it releases 15 µg ethynyl estradiol and 120 µg etonogestrel, and when used properly, has a failure rate between one and two per 100 woman-years of use.



NuvaRing is inserted into the vagina and left in place for three weeks, after which it is removed for a 'ring-free‘ week to allow menstruation to occur.

Intrauterine Devices

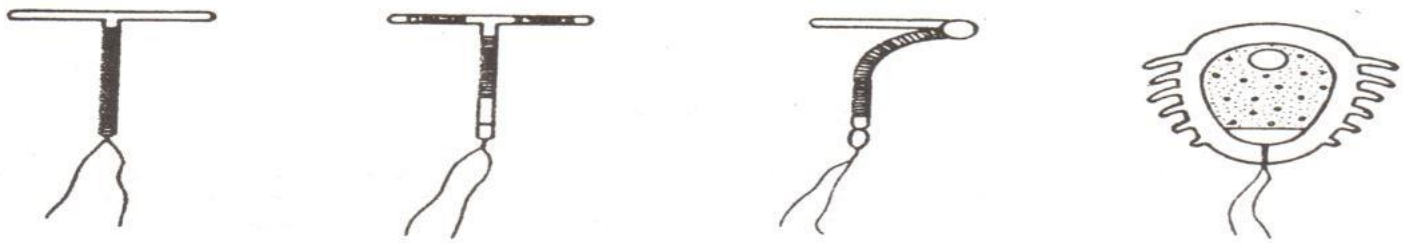
A more common contraceptive device is the intrauterine device (IUD).

Two types of medicated IUD are generally used;

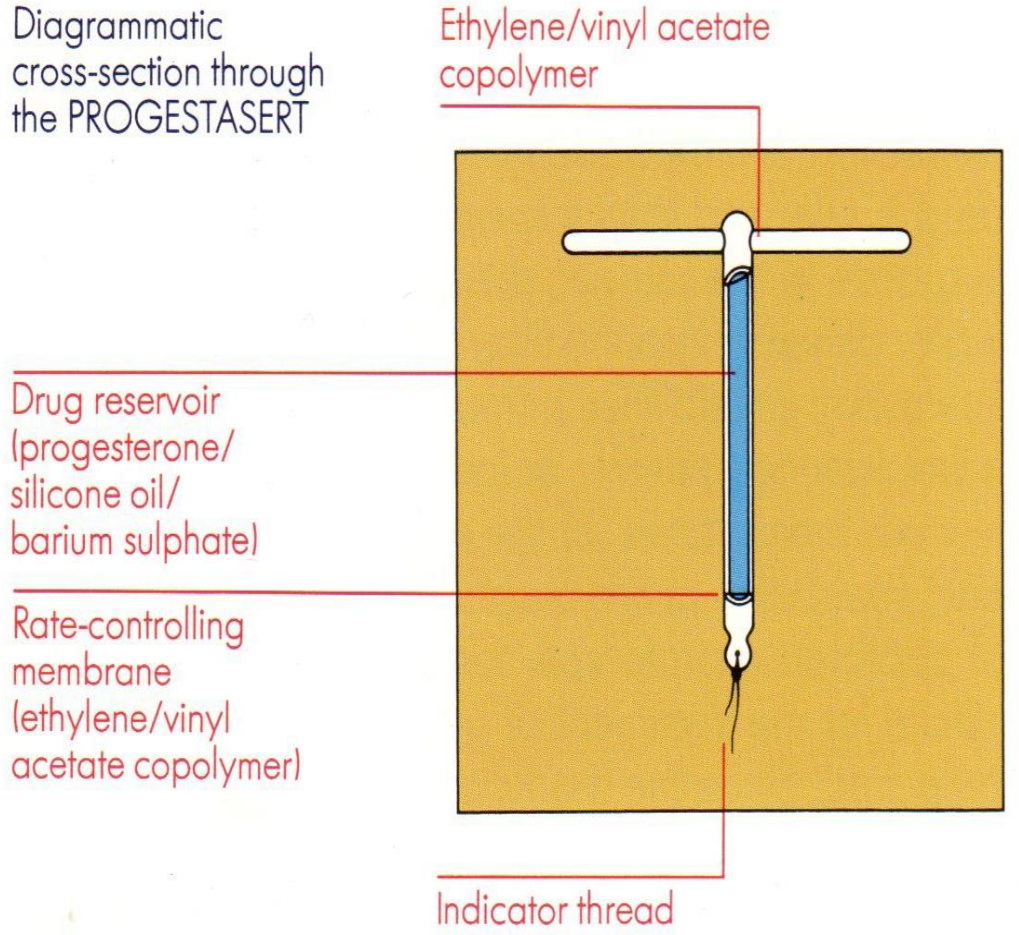
- Contraceptive metals and
- Steroid hormones.

- Efforts to prevent pregnancy have involved inserting objects into the uterus and has been practiced formany years. The first reported use of an intrauterine device (IUD) designed specifically for contraception is 1909.
- However, the first modern use of an IUD was composed of plastic to which barium sulfate was added to make the unit visible under X-rays. While improvements were noted, it was the idea that metals, including copper, could increase the effectiveness of inert, plastic devices.

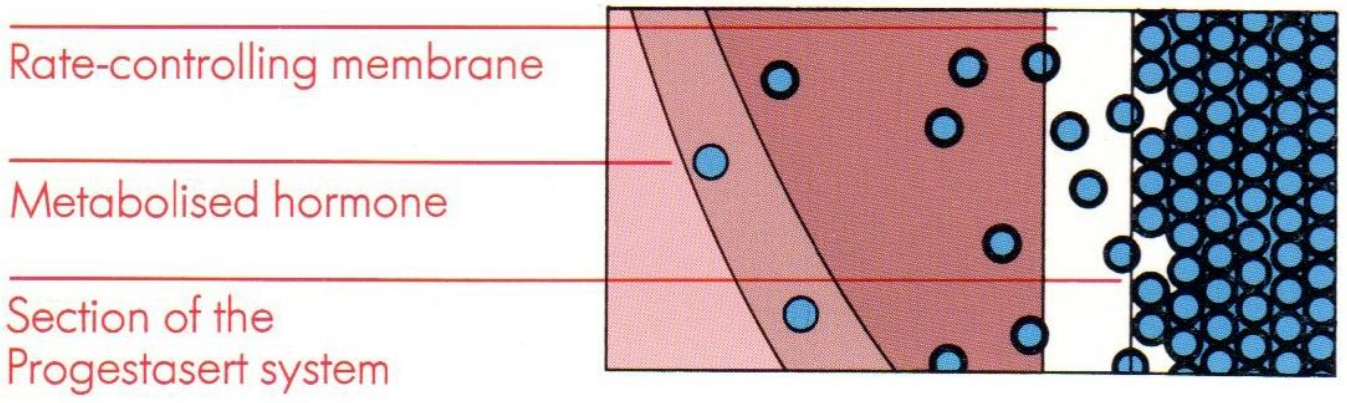
- The first commercial copper-releasing IUD was the Copper T-200 and the Copper 7.



- **Progestasert®** is the steroid releasing intrauterine device (IUD). The principal example is a T-shaped device composed of a rate-controlling membrane of ethylenevinyl acetate copolymer. Inside this membrane is contained a three-day supply of the amount of progesterone normally taken orally.



- However, since the device delivers progesterone to its target locally at a rate of approximately 65 pg/day, the system lasts for over 1 year. Marketed by ALZA under the trade name Progestasert ®, the system showed comparable pregnancy and expulsion rates to conventional IUDs, often with less menstrual bleeding.



NASAL CONTROLLED RELEASE SYSTEMS

Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents.

In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration.

- It is a useful delivery route for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides.
- One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism.
- The nasal route circumvents hepatic first pass elimination associated with the oral delivery:

  -it is easily accessible, and

  -suitable for self-medication.

BENEFITS OF NASAL DELIVERY

1) Drug degradation that is observed in the gastrointestinal tract is absent.

2) Hepatic first pass metabolism is avoided.

3) Rapid drug absorption and quick onset of action can be achieved.

4) The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

5) The nasal bioavailability for smaller drug molecules is good.

6) Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.

7) Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.

8) Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

9) Drugs possessing poor stability in gastrointestinal fluids are given by nasal route.

10) Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.

LIMITATIONS OF NASAL DELIVERY

1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.

2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.

3) Nasal cavity provides smaller absorption surface area when compared to gastrointestinal tract.

4) There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.

5) Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.

6) There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

7) Nasal absorption can be affected by the physicochemical characteristics of the administered drug such as Mw, solubility, dissolution rate, partition coefficient, charge, pKa, particle size and polymorphism.

8) Generally, polar and low molecular weights drugs show low bioavailability of about 10 and 1 %, respectively. The most important factor limiting nasal absorption of polar and large molecular weight drugs is low membrane permeability and this can be overcome by incorporating absorption enhancers in the formulation.

MECHANISIM OF NASAL DRUG ABSORPTION

1. First Mechanism

It involves an aqueous route of transport, which is also known as the paracellular route but this is a slow and passive route. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability.

2. Second Mechanism

It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions.

- The mechanism of nasal drug absorption is affected by several factors. For systemic drug delivery, the anatomically most important region in the nose is the respiratory region between the three distinct functional regions identified as vestibular, respiratory, and olfactory.
- Physicochemical properties of the drugs such as ionization, lipophilicity, surface charge and hydrophobicity of molecules are the other important factors besides the molecular weight.

- Briefly, properties desired for nasal bioadhesive formulations can be summarized as,

(a) good adherence to nasal mucous membrane, and ability to absorb mucus;

(b) form a viscous layer or show a slow clearance; and

(c) protect active agent/drug or release it slowly.

NASAL DRUG DELIVERY STRATEGIES

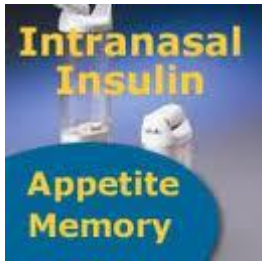
- Bioadhesive powders
- Micro- and nano- particulate systems
- Hydrogels
- Inserts

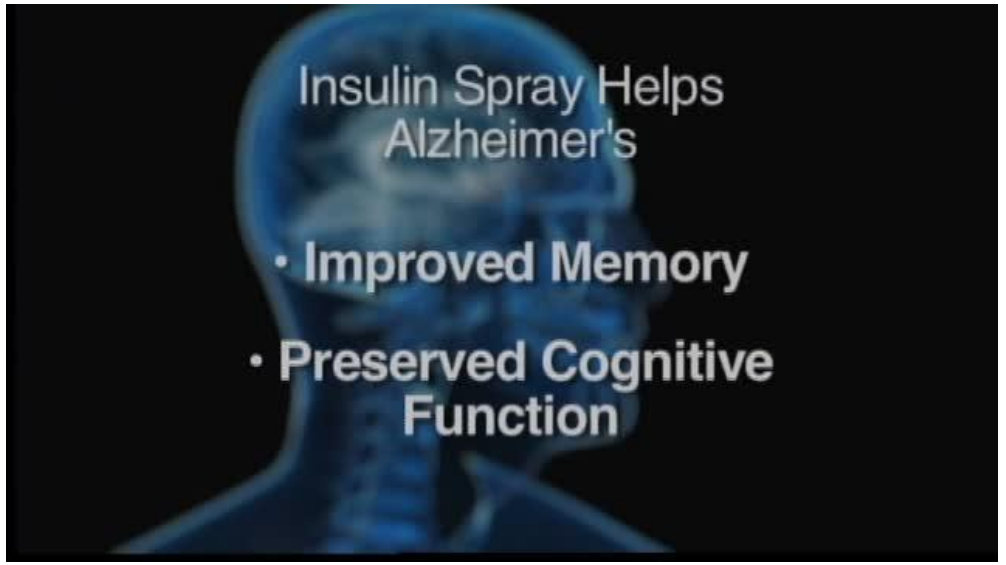
❖ Bioadhesive Powders

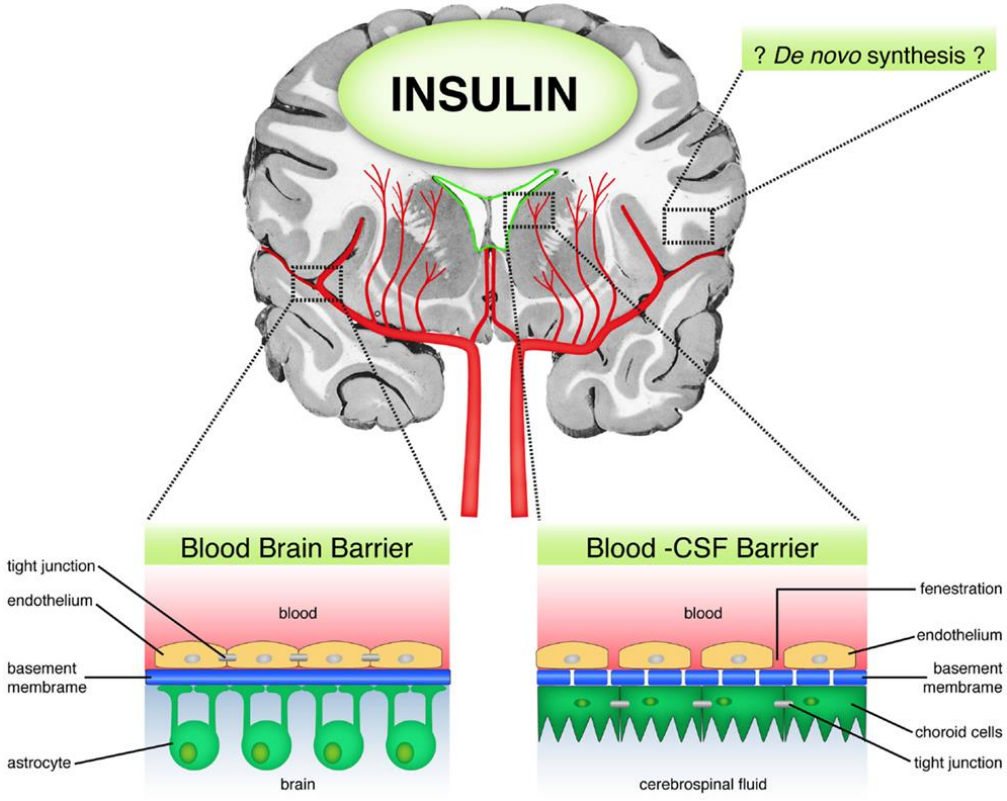
First patented system is **Rhinocort®** which contains Beklometasone Dipropionate

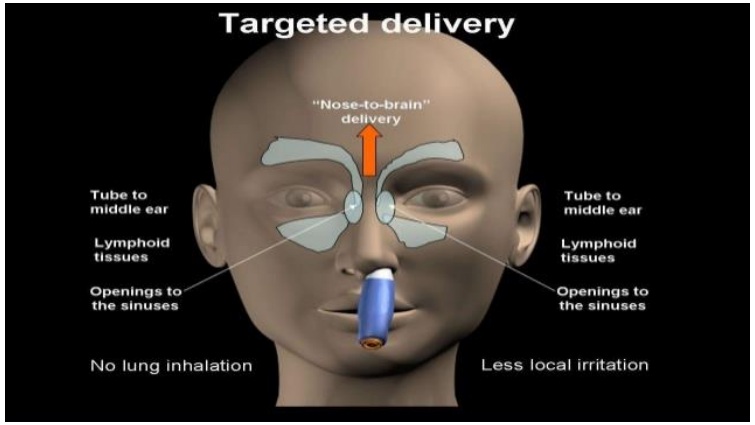
SYSTEMIC EFFECT NASAL PREPARATIONS (NASAL SPRAY)

SALMON CALCITONIN	MIACALCIC	OSTEOPOROSIS
TRIAMCINOLONE ACETONIDE	NASOCORT SPRAY	ALLERGIC RHINITIS
ZOLMITRAPINE	ZOMIG	MIGRAINE
CYANOBALAMIN	NASCOBAL JEL	VITAMIN B12 DEFICIENCY
ESTRADIOL	AERODIAL ESTRADIOL	OSTEOPOROSIS
INSULIN		TYPE 2 DIABETES


Intranasal
Insulin
Appetite
Memory


Insulin Spray Helps
Alzheimer's
• Improved Memory
• Preserved Cognitive
Function


INSULIN
? De novo synthesis ?
Blood Brain Barrier
Blood -CSF Barrier
tight junction
endothelium
basement
membrame
astrocyte
blood
brain
blood
fenestration
endothelium
basement
membrame
choroid cells
tight junction
cerebrospinal fluid


Targeted delivery
"Nose-to-brain"
delivery
Tube to
middle ear
Lymphoid
tissues
Openings to
the sinuses
Tube to
middle ear
Lymphoid
tissues
Openings to
the sinuses
No lung inhalation
Less local irritation

- **Chronic Sinusitis,**
- **Rhinitis,**
- **Migraine,**
- **Diabetes,**