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OCULAR DRUG DELIVERY SYSTEM

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BP704T-UNIT-V

Ocular Drug Delivery Systems: Introduction, intra ocular barriers and methods to overcome – Preliminary study, ocular formulations and ocuserts

Intrauterine Drug Delivery Systems: Introduction, advantages and disadvantages, development of intra uterine devices (IUDs) and applications

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Introduction

The novel approach in which drug can instilled on the cull de sac cavity of eye is known as ODDS. Ophthalmic preparations are specialized sterile preparation 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 conjuction 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, and the relative impermeability of the corneal epithelial membrane are the major challenges. Various strategies [2] for ocular drug delivery are considered; from basic formulation techniques for improving availability of drugs. ODDS can be mainly prepared as gels, ointments, microspheres, ocular inserts and nanoparticles etc.

Advantages of ODDS [3]

1. It increases accurate dosing.
2. It provides sustained and controlled drug delivery system.
3. It increases the ocular bioavailability of drug by increasing the corneal contact time.
4. It provides targeting within the ocular globe so as to prevent the loss to other ocular tissues.
5. It provides comfort, better compliance to the patient and to improve therapeutic performance of drug.
6. It provides better housing of delivery system.

Disadvantages of ODDS [4]

1. Dosage form cannot be terminated during emergency.
2. It Interfere with vision.
3. It is difficult in placement and removal.
4. Three is occasional loss during sleep or while rubbing eyes.

Anatomy of eye

The eye is a spherical structure [5] with a wall consisting of three layers the outer sclera, the middle choroid layer and the inner retina. The sclera is a tough fibrous coating that protects the inner layers. It is white except for the transparent area at the front, the cornea which allows light to enter the eye. The choroid layer situated inside the sclera contains many blood vessels and is modified at the front of the eye as the pigmented iris. The biconvex lens is situated just behind the pupil. The chamber behind the lens is filled with vitreous humor a gelatinous substance occupying 80% of the eye ball. The anterior and posterior chambers are situated between the cornea and iris and lens respectively and filled with aqueous humor. At the back of the eye is light detecting retina.

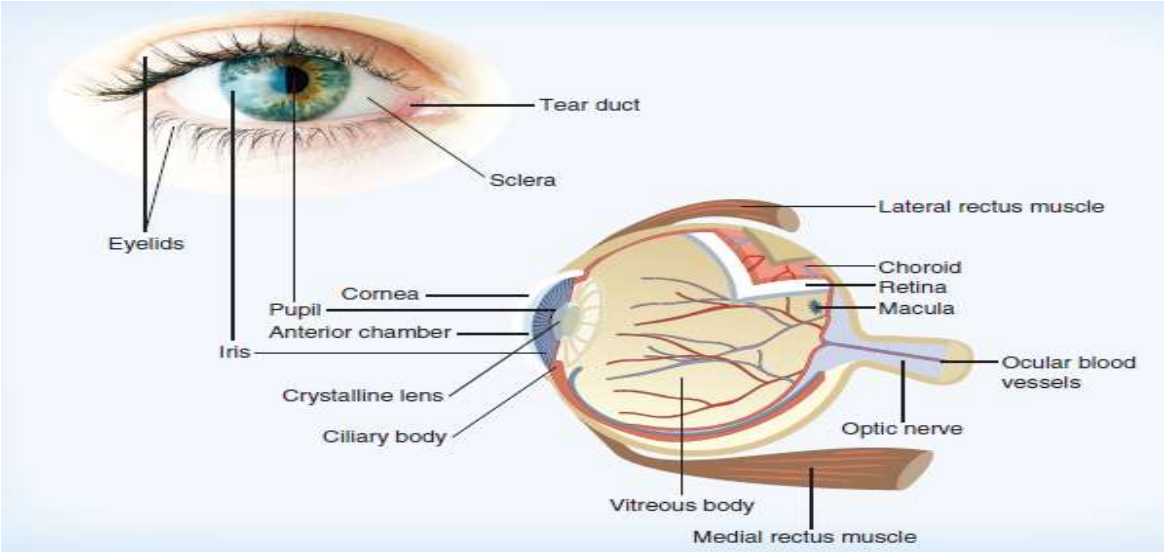

Fig. 1: Anatomy of eye

Intra ocular barriers [6]

1. Tear

The precorneal barrier is tear film which reduces the effective concentration of the administrated drugs due to dilution by the tear turn over (1µl/min), 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 on the cheek or exit through the naso lacrimal duct.

2. Cornea

The cornea consists of three layers [7] such as epithelium, stroma and endothelium and a mechanichal barrier to inhibit transport of exogenous substances into the eye. Each layer possesses a different polarity and a rate limiting structure for drug permeation. The corneal epithelium is lipophilic nature and tight junctions are formed to restrict paracellular drug permeation from the tear film. The 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. The endothelial junctions are leaky and facilitate the passage of macromolecules between aqueous humor and stroma.

3. Conjunctiva

Conjuctiva 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 lympatics. Hence administered drugs in the conjunctival space may be cleared through blood and lymph. The conjuctival 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 and it decreases roughly expontially with molecular radius. The posterior sclera is composed of a looser weave of collagen fibres than the anterior sclera and the human sclera is relatively thick near the limbus (0.53 ± 0.14 mm), thin at the equator (0.39 ± 0.17 mm) and much thicker near the optic nerve (0.9-1.0mm). The increase of hydrophobic/lipophilic character 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. Positively charged drugs may exhibit poor permeability due to their binding to the negatively charged proteoglycan matrix.

5. Choroid/Bruch's membrane

Choroid is one of the most highly vascularized tissues of the body to supply the blood to retina. The choroidal capillary endothelial cells are fenestrated and in humans are relatively large in diameter (20-40 μm). Bruch's membrane (BM) causes thickening with age. These changes cause increased calcification of elastic fibres increased cross linkage of collagen fibres and increased turn over glycosaminoglycans. The advanced glycation end products and lipofuscin accumulate in BM. Thickness changes of choroid and BM might affect drug permeability from sub conjunctiva space into the retina and vitreous.

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. The driving forces of outward transport of molecules from the subretinal spaces are hydrostatic and osmotic and small molecules may transport through the paracellular inter RPE cellular clefts and by active transport through the transcellular route.

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 called iBRB for the inner and oBRB for outer BRB respectively. The function of iBRB is supported by Muller cells and astrocytes. The retinal capillary endothelial cells are not fenestrated and have apaucity of vesicles. The function of these endothelial vesicles are reported as endocytosis or transcytosis that may be receptor mediated or fluid phase requiring adenosine triphosphate. Muller cells support neuronal activity and maintain the proper functioning of iBRB under normal conditions. Therefore oBRB (RPE) restricts entry of drugs from the choroid into the retina.RPE is a monolayer of highly specialized hexagonal shaped cells located between sensory retina and the choroid. The tight junctions of the RPE efficiently restrict intercellular permeation into sensory retina.

Methods to overcome barriers [8]

I. Physical methods

1. Iontophoresis,
2. Sonophoresis

3. Microneedles

I. Physical methods

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

1. 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 the drug molecule. Electrorepulsion primarily applies to the movement of ionic drugs, while electro-osmosis can enhance the transport of both neutral and charged molecules by convective solvent flow. The relative contribution of electrorepulsion and electro-osmosis depends on both the physicochemical characteristics of the drug (e.g. size, charge and charge to molecular-weight ratio) and the electrical properties of the biological membrane. Ocular iontophoresis offers a drug delivery system that is fast, painless, safe and in most cases result in the delivery of high concentration of drug at specific site.

2. 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 (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. Cavitation is generally considered the predominant factor for enhanced drug delivery and is defined as the formation of microbubbles due to an acoustic pressure gradient within the coupling medium. Corneal permeability enhancement is generally a result of stable cavitation at low ultrasound intensities, whereas both stable and inertial cavitation play important roles at higher ultrasound strengths.

3. 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. To date, numerous ML

fabrication approaches have been utilized, resulting in a variety of shapes, sizes, materials and configurations. Enhanced drug delivery into the cornea and anterior segment of the eye can be achieved by insertion of MLs across the corneal epithelium. Various polymeric MLs have found great use in intrascleral drug delivery. According to their delivery mechanism, ocular MLs can be categorized into four types such as solid microneedles, drug-coated microneedles, dissolving microneedles and hollow microneedles.

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 metabolic activity of ocular tissues provides an opportunity of utilization of chemically modified drugs that have a predictable metabolic bioconversion in the eye.

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 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[9]

1. Eye-Drops

Drugs which are active at eye or eye surface are widely administered in the form of solutions, emulsion and euspension. 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. Eye drop forms hydrogen

bonding with the mucus and corneal and conjuctival epitheliums which are all negatively charged to extend the effects of drug to several hours. Azithromycin ophthalmic solution is formulated with Durasite (Inspire Pharmaceuticals Inc.) can be used for the treatment of bacterial conjunctivitis.

2. Opthalmic Inserts

Ophthalmic inserts are sterile preparations with a solid or a semisolid consistency, and whose size and shape are especially designed for ophthalmic application. The inserts are placed in the lower fornix and less frequently, in the upper fornix or on the cornea.

Classification of ocular inserts

Based upon their solubility behaviour

I. Insoluble inserts
II. Soluble inserts
III. Bioerodible inserts

I. Insoluble ocuserts [10]

Insoluble ocuserts can be classified into two categories such as reservoir system and matrix system.

a. Reservoir system

In this system the drug released either by diffusion or by an osmotic process. It contains respectively, a liquid, a gel, a colloid, a semisolid, a solid matrix, or a carrier containing drug.

- ✓ **Diffusional insert or ocuserts**

Based on porous membrane ocuserts system is a novel ocular drug delivery system. From diffusional inserts/Ocusert drug release is based on a diffusional release mechanism.The diffusional systems are composed of a central reservoir of drug enclosed in specially designed semipermeable or microporous membranes which allow the drug to diffuse through the reservoir at a precisely determined rate. The drug release from such a system is controlled by the lacrimal fluid permeating through the membrane until a sufficient internal pressure is reached to drive the drug out of the reservoir. The drug delivery rate is controlled by diffusion through the membrane, which one can be controlled. For example in ocusert device there is uniform controlled release (20 or 40μg/hr for 7 days of pilocarpine as an ocular hypotensive drug. It consists of two outer layers of ethylene vinyl acetate co polymer(EVA) and an inner layer of pilocarpine in alginate gel within di(ethylhexyl) phthalate for a release enhancer, sandwiched

between EVA layers. Ocusert has certain demerits such as difficult of inserting the device,ejection of device from eye and irritation during insertion.

- ✓ **Osmotic inserts**

The osmotic inserts are usually composed of a central part bounded by a peripheral part and are of two types:

Type 1

The central part is composed of a single reservoir of a drug surrounded by the polymer as discrete small deposits with or without an additional osmotic solute dispersed throughout a polymeric matrix. An insoluble semipermeable polymer film comprised the second peripheral part of these inserts. In the form of apertures, the osmotic pressure against the polymer matrix causes its rupture. Near the surface of the device drug is then released through these apertures from the deposits.

Type 2

The central part is composed of two different compartments. In two separate compartments the drug and osmotic solutes are placed, the drug reservoir being surrounded by an elastic impermeable membrane and by a semi-permeable membrane the osmotic solute reservoir surrounded. The second peripheral part of this type is similar to type 1. The tear fluid diffuses into the peripheral deposits through the semipermeable polymeric membrane, wets them and induces their dissolution. The solubilized deposits generate a hydrostatic pressure against the polymer matrix causing its rupture under the form of apertures. Drug is then released through these apertures from the deposits near the surface of the device which is against the eye, by the sole hydrostatic pressure.

b. Matrix systems

The second category matrix system is mainly represented by contact lenses and particular group of insoluble ophthalmic devices. It forms a three dimensional network or matrix capable of retaining water, aqueous drug solution or solid components and consist of covalent cross-linked hydrophilic or hydrophobic polymer.

- ✓ **Contact lenses**

Contact lenses are initially used for vision correction. These are shaped structure made up of a covalently cross linked hydrophilic or hydrophobic polymer that forms a three-dimensional network or matrix capable of retaining water, aqueous solution or solid components. When a

hydrophilic contact lens is soaked in a drug solution, it absorbs the drug, but does not give a delivery as precise as that provided by other non-soluble ophthalmic systems. The drug release from such a system is generally very fast at the beginning and then declines exponentially with time. The release rate can be decreased by incorporating the homogenous mixture of drug during the manufacture or by adding a hydrophobic component. Contact lenses are divided into 5 parts such as rigid, semi-rigid, elastomeric, soft hydrophilic and bio-polymeric

II. Soluble Ophthalmic inserts

Soluble inserts correspond to the oldest class of ophthalmic inserts. Soluble inserts normally defined as erodible, monolithic polymeric devices that releasing the drug and do not need removal while undergo gradual dissolution. Through polymer swelling true dissolution occurs mainly, while to a chemical or enzymatic hydrolytic process erosion corresponds. In swelling-controlled devices in a glassy polymer, the active agent is homogeneously dispersed. Water from the tear fluid begins to penetrate the matrix when the insert is placed in the eye, then by releasing their drug content, swelling and consequently polymer chain relaxation and drug diffusion take place.

Types of soluble ophthalmic inserts

a. Based on natural polymers e.g. collagen.

b.Based on synthetic or semi synthetic polymers

a. Natural polymers

Natural polymer used to produce soluble ophthalmic inserts is preferably collagen. The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying, and re-hydrating it before use on the eye. The amount of drug loaded will depend on the amount of binding agent present, the concentration of the drug solution into which the composite is soaked as well as the duration of the soaking. As the collagen dissolves, the drug is gradually released from the interstics between the collagen molecules.

b. Synthetic and semi-synthetic polymer

This is based upon use of polymers i.e. semi-synthetic polymers (e.g., cellulose derivatives) and synthetic polymers i.e. polyvinyl alcohol. By using Eudragit, a polymer usually used for enteric coating or as a coating agent of the insert, a decreased release rate can be obtained. Ethyl cellulose, a hydrophobic polymer, can be used to decrease the deformation of the insert and thus to prevent blurred vision.

III. Bio-erodible ocular inserts

These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants. Some important ocular inserts which are available commercially (SODI) or in advanced states of development (collagen shields, Ocufit and Minidisc) **.**

- ✓ **Soluble ophthalmic drug insert**

Soluble ophthalmic drug insert (SODI) is a small oval wafer, which was developed by soviet scientists for cosmonauts who could not use eye drops in weightless conditions. A SODI is a soluble copolymer of acrylamide, N-vinyl pyrrolidone, and ethyl acrylate. It is in the form of sterile thin films or wafers of oval shape, weighing 15 to 16 mg. After introduction into the upper conjunctival sac, the SODI softens in 10 to 15 sec, conforming to the shape of the eyeball; in the next 10 to 15 min the film turns into a polymeric clot, which gradually dissolves within 1 h while releasing the drug.

- ✓ **Collagen shields**

Collagen is the structural protein of bones, tendons, ligaments, and skin and comprises more than 25% of the total body protein in mammals. Collagen shields are currently manufactured from porcine scleral tissue or bovine corium (dermis) collagen and contain mainly type I collagen and some type III collagen. They are shaped like a contact lens and are supplied in a dehydrated form, requiring rehydration prior to insertion. Variations in collagen crosslinking induced with ultraviolet light (UV) during manufacture dictate lens duration before dissolution. Three different collagen shields are currently available with dissolution times of 12, 24, and 72 hours. Corneal collagen shields have a diameter of 14.5–16.0 mm, a base curve of 9 mm, and a central thickness of 0.15–0.19 mm.

- ✓ **Ocufit**

The Ocufit is a sustained release, rod shaped device made of silicone elastomer, patented in 1992 and currently developed by Escalon Ophthalmics Inc. (Skillman, NJ). It was designed to fit the shape and size of the human conjunctival fornix. Accordingly, it does not exceed 1.9 mm in diameter and 25-30 mm in length, although smaller sizes for children and newborn babies are planned.

✓ **The Minidisc ocular therapeutic system**

This monolytic polymeric device, originally described by Bawa et al. (Bausch and Lomb, Rochester, New York) and referred to as Minidisc ocular therapeutic system (OTS), is shaped like a miniature (diameter 4-5 mm) contact lens, with a convex and a concave face, the latter conforming substantially to the sclera of the eye. The particular size and shape reportedly allow an easy placement of the device under the upper or lower lid without compromising comfort, vision or oxygen permeability. The ocular inserts devices are given in table 1.

Table 1: Ocular inserts devices

Name	**Description**
Soluble ocular drug Insert	Small oval wafer, composed of soluble copolymers consisting of actylamide, N-venyl pyrrolidone and ethyl acetate, soften on insertion
New ophthalmic drug delivery system	Medicated solid polyvinyl alcohol flag that is attached to a paper- covered with handle. On application, the flag detaches and gradually dissolves, releasing the drugs
Collagen shields	Erodible disc consist of cross-link porcine scleral collagen
Ocusert	Flat, flexible elliptical insoluble device consisting of two layers, enclosing a reservoir, use commercially to deliver Pilocarpine for 7 days
Minidisc or ocular therapeutic	system 4-5 mm diameter contoured either hydrophilic or hydrophobic disc
Lacrisert	Rose-shape device made from Hydroxy propyl cellulose use for the eye syndrome as an alternative to tears
Gelfoam	Slabs of Gelfoam impregnated with a mixture of drug and cetyl ester wax in chloroform
Dry drops	A preservative free of hydrophilic polymer solution that is freeze dried on the tip of a soft hydrophobic carrier strip, immediately hydrate in tear strip

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 pancta is a

long standing approach.Efficacy of an ocular hypotensitive agent in eye drops in conjuction with punctual occlusion by punctual plug is reported.

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 release profiles vary with the kind of polymers used their molecular weights and the amount of drug in the plug. LX201(Lux Biosciences, USA) is a silicone matrix episcleral implant designed to deliver cyclosporine A to the eye surface for one year. 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. Ointment breaks up into small droplet and remains as a depot of drug in the cul de sac for extended periods. But blurring of vision and matting of eyelids can limits those use.

II. Drug delivery systems to posterior segment of the eye [11]

1. Intravitreal Implants

- ✓ **Durasert™ Technology System**

Durasert™ technology system (pSivida Crop.,US) 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 Durasert™ technology system ganciclovir loaded implant can be used for the treatment of cytomegalo virus retinitis.This implant is made of ethylene vinyl acetate copolymer(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.

- ✓ **Novadur™ Technology**

Ozurdex® (Allergan Inc.,US) is an intravitreal implant containing 0.7mg of dexamethasone composed of PLGA(length 6.5mm,diameter 0.45mm) approved by FDA.It is used for the treatment of macular edema due to branch retinal vein occlusion(BRVO) and central retinal vein occlusion(CRVO). Ozurdex® is administered by specially designed injector with a 22 gauge needle into vitreous cavity.

- ✓ **I-vation™ TA**

I-vation™ technology(Sur Modics Inc.,US)is used to deliver triamcinolone acetonide(TA) into the vitreous of the eye. I-vation™ intravitral implant is atitanium helical coil (length 0.5mm,width 0.21mm) coated with TA(925µg) and non biodegradable polymers poly(methylmethacrylate) and EVA.This implant can sustain in vivo minimum for two years.

- ✓ **NT-501**

Encapsulated cell technology (Neurotech Pharmaceuticals Inc.,US) provides extracellular delivery of ciliary neutropic factor(CNTF) through long term and stable intraocular release at constant doses through a device implanted in the vitreous. It contains human RPE cells genetically modified to secrete recombinant human CNTF. The device consists of a sealed semi permeable membrane capsule surrounding of six strands of polyethylene terephthalate yarn which is loaded with cells. The device is surgically implanted in the vitreous through a tiny sclera incision and is anchored by a single suture through a titanium loop at one end of the device. The semi permeable membrane allows the outward diffusion of CNTF and other cellular metabolites and the inward diffusion of nutrients necessary to support the cell survival in the vitreous cavity while protecting the contents from host cellular immunologic attack.

2. Injectable particulate systems

- ✓ **IBI-20089**

IBI-20089 contains triamcinolone acetonide(TA) using Verisome™ drug delivery platform technology which is developed by Icon Bioscience Inc..When the IBI-20089 comes contact with saline the solution becomes milky,slightly opaque color and forms gel.IBI-20089 is a solution of TA in biodegradable benzyl benzoate.It is designed to deliver drug upto one year with a single intra vitreal injection.

- ✓ **RETAAC**

RETAAC can be injected intra vitreously into patients with diabetic macular edema (DME) and their efficacy compared to naked TA injections. RETAAC treated eyes showed decrease of retinal thickness as well as improved visual acuity for 1 year.It is safe and well tolerated by the retina.

- ✓ **Cortiject®**

Cortiject® (Novagali Pharma S.A.) is a preservative free emulsion composed of oily carrier and phospholipid as surfactant, encapsulating a target tissue activated corticosteroid prodrug.

- ✓ **Visudyne®**

Visudyne® (QLT Ophthalmics Inc.,USA) is an intravenous liposomal formulation containing photosensitizer.Verteporfin in photodynamic therapy for predominantly classic subfoveal choroidal neovascularization due to AMD,pathologic myopia or presumed ocular histoplasmosis.Plasma lipoproteins such as low density lipoprotein(LDL) are reported to enhance the delivery of hydrophobic verteprofin to malignant tissue since tumour cells have shown to increase numbers of LDL receptors.Verteporfin released in blood from liposome is associated with LDL and uptakes in neovascular tissues and undissociated verteporfin still encapsulated in liposome is accumulated in vascular endothelial cells via LDL receptor mediated endocytosis since phosphatidyl glycerol is a major constitute of Visudyne® formulation.

III. Advanced delivery system[12]

1. Cell encapsulation

The entrapment of immunologically isolated cells with hollow fibres or microcapsules before their administration into the eye is called encapsulated cell technology (ECT).It enables the controlled, continuous and long term delivery of therapeutic proteins directly to the posterior regions of the eye. The polymer implant containing genetically modified human RPE cells secretes ciliary neuotrophic factor into the vitreous humour of patient's eye.ECT is used as a delivery system for chronic ophthalmic diseases like neuroprotection in glaucoma, antiangiogenesis in choroidal neovascularization,anti inflammatory factors for uveitis.

2. Gene therapy

Along with tissue engineering gene therapy approaches are used to treat blindness arising from corneal diseases, cataract, glaucoma etc. Many viruses including adenovirus, retrovirus, adeno-associated virus and herpes simplex virus are manipulated for use in gene transfer and gene therapy applications. Topical delivery to the eye is the most expedient way of ocular gene delivery. Retroviral vectors are used due to their high efficacy and lead to restrict their clinical use. The advanced delivery systems prolong the contact time of vector with the surface of the eye may enhance transgene expression thereby facilitate non invasive administration.

3. Stem cell Therapy:

Cell therapies are used for the restoration of sight that are critical for visual function, the cornea and the retina. The current method for management of ocular conditions consists of eliminating the injurious agent or attempting to minimize its effects. The limbal stem cells are

used the most successful ocular application transplanted from a source other than the patient for the renewal of corneal epithelium. The sources of limbal cells include donors, autografts, cadaver eyes and cells grown in culture.

4. Protein and peptide therapy

The delivery of therapeutic proteins and peptides to eye plays a vital role for drug delivery. But several limitations such as membrane permeability, large size, metabolism and solubility restrict their efficient delivery. Poor membrane permeability of hydrophilic peptides may be improved by structurally modifying the compound thus increasing their membrane permeability. Ocular route is not preferred route for systemic delivery of such large molecules.Immunoglobulin G is effectively delivered to retina by transscleral route with insignificant systemic absorption.

5. Scleral plug therapy

Scleral plug can be implanted using a simple procedure at pars plana region of eye, made of biodegradable polymers and drugs. It releases effective doses of drugs for several months upon biodegradation. The release profiles vary with the kind of polymers used, their molecular weight and the amount of drug in the plug. The plugs are effective for treating vitreoretinal diseases such as proliferative vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require virectomy.

6. siRNA therapy

The siRNA therapy is used for the treatment of choroidal neovascularization. The siRNA is directed against vascular endothelial growth factor (VEGF) or VEGF receptor 1(VEGFR1) and these approaches are used in clinical trials. Topical delivery of siRNA is directed against VEGF or its receptors are reported to suppress corneal neovascularisation. The si RNA therapy is also used for delivery of genes in ocular disease processes. It is reported that siRNA may be use in the pathogenesis and development of new treatments of ocular diseases based on in vivo and in vitro studies. New encapsulated siRNA are developed using liposomes coupled antibodies or polymer vesicles.

7. Oligonucliotide therapy

Oligonucleotide (ON) therapy is based on the principle of blocking the synthesis of cellular proteins by interfering with either the transcription of DNA to mRNA or the translation of mRNA to proteins.The antisense molecules disrupt gene expression and inhibit protein synthesis.

A number of factors are determined to contribute to the efficacy of antisense oligonucliotide.The primary consideration is the length of the ON species.Lengths of 17-25 bases have reported to be optimal as longer ONs have the potential to partially hybridize with non target RNA species.Biological stability is the major barrier to consider when delivering both DNA and RNA oligonucleotides to cells.Protection from nuclease action can be achieved by modification of phosphate backbones,sugar moiety and bases.

8. Aptamer

Aptamers are oligonucleotide ligands that are used for high affinity binding to molecular targets.It is isolated from synthetic nucleic acid by an iterative process of adsorption,recovery and reamplification.It binds with the target molecules at a very low level with high specificity.Pegaptanib sodium(Pfizer) is an RNA aptamer directed against VEGF where VEGF isoform primarily responsible for pathological ocular neovascularization and vascular permeability.

9. Ribozyme therapy

RNA enzymes or ribozymes are single stranded RNA molecules capable of assuming three dimensional conformations and exhibiting catalytic activity that induces site specific cleavage, ligation and polymerization of nucleotides involving RNA or DNA. It binds to the target RNA moiety and inactivates it by cleaving the phosphodiester backbone at a specific cutting site.The delivery of ribozymes in autosomal dominated retinitis pigmentosa (ADRP) shows positive action for controlling disease.ADRP is caused by mutations in genes that produce mutated proteins leading to the apoptotic death of photoreceptor cells.

IV. Vesicular system [13]

1. Liposomes

Liposomes are vesicles composed of lipid membrane enclosing an aqueous volume.Lipophilic drugs can be delivered to the ocular system by liposomal drug delivery system. They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed,the drugs with low partition coefficient, poor solubility. Hence it increases the ocular drug absorption.

2. Niosomes

Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. They are more stable than liposomes.Hence they can target drug to eye very easily.

3. Pharmacosomes

Pharmacosomes are efficient tool to achieve desired therapeutic goals such as drug targeting and controlled release. Any drug possessing an active hydrogen atom (-COOH,-OH,-NH_2, etc.) can be esterified to the lipid with or without spacer chain that strongly result in an amphiphilic compound which will facilitate membrane, tissue or cell wall transfer in the organism. These are defined as colloidal dispersions of drugs covalently bound to lipids and may exist as ultrafine vesicular, micellar or hexagonal aggregates, depending on the chemical structure of drug-lipid complex. The pharmacosomes show greater stability,facilitated transport across the cornea and a controlled release profile.

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INTRAUTERINE DRUG DELIVERY SYSTEMS

Introduction

There is a need for the development of new, improved birth control methods that are easy to use, have few side effects, and do not require consistent daily attention or application prior to every act of intercourse. Long-acting contraceptive methods [1] which eliminate the need for such daily activity and for some specific action at the time of coitus are designed to meet this need. However, developing a new contraceptive is a major challenge. 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. There is no doubt that the acceptability and popularity of the method could be enhanced by giving attention to the patient's physical and psychological comfort during insertion [2]. 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.

Advantages of IUDDS [3]

1. They are more than 99 per cent effective in preventing pregnancy.
2. They last for a long time
3. They are safe to use if you are breastfeeding.
4. No medications stop them from working.
5. It provides another contraceptive choice if there is difficulty taking the hormone oestrogen.
6. There is no vaginal bleeding at all or a light regular period after use.

Disadvantages of IUDDS [4]

1. It does not protect against sexually transmitted infections (STIs).
2. IUDDS is not useful if a uterus that is not the usual shape and pelvic infection.
3. It is not suitable in case of heavy periods, low iron levels, and endometriosis.
4. It may increase the likelihood of ectopic pregnancy.
5. There are risks during insertion and removal.

6. 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.

Anatomy of Uterus

The uterus or womb [5] is shaped like an inverted pear. It is a hollow muscular organ with thick walls, and it has a glandular lining called the endometrium. The uterus measures about 7.5 cm in length, 5 cm in breadth, at its upper part, and nearly 2.5 cm in thickness; it weighs from 30 to 40 gm. The part of the body which lies above a plane passing through the points of entrance of the uterine tubes is known as the fundus; the part below is termed the body. The body narrows toward the cervix, and a slight external constriction marks the juncture between the body and the cervix is known as the isthmus. It is the short narrowed portion of the uterus located inferior to the body and superior to the cervix. Uterus consists of mainly 3 parts such as fundus, body and cervix.

Fundus

The fundus is convex in all directions, and covered by peritoneum continuous with that on the vesical and intestinal surfaces. The lateral margins are slightly convex. At the upper end of each the uterine tube pierces the uterine wall. Below and in front of this point the round ligament of the uterus is fixed, while behind it is the attachment of the ligament of the ovary. These three structures lie within a fold of peritoneum which is reflected from the margin of the uterus to the wall of the pelvis, and is named the broad ligament.

Body

The body gradually narrows from the fundus to the isthmus. The vesical or anterior surface is flattened and covered by peritoneum, which is reflected on to the bladder to form the vesicouterine excavation. The surface lies in apposition with the bladder. The intestinal or posterior surface is convex transversely and is covered by peritoneum, which is continued down on to the cervix and vagina.

Cervix

The cervix is the lower constricted segment of the uterus. It is somewhat conical in shape, with its truncated apex directed downward and backward, but is slightly wider in the middle than either above or below. The cervix is made of fibrous connective tissue and is of a firmer

consistency than the body of the uterus. It is less freely movable than the body. The cervix projects through the anterior wall of the vagina, which divides it into an upper, supravaginal portion, and a lower, vaginal portion.

Structure:

The uterus is composed of three coats [6] like an external or serous, a middle or muscular, and an internal or mucous.

1. The serous coat / Peritoneum: The serous coat is derived from the peritoneum; it invests the fundus and the whole of the intestinal surface of the uterus; but covers the vesical surface only as far as the junction of the body and cervix.

2. The muscular coat / Myometrium: The muscular coat forms the chief bulk of the substance of the uterus. The middle layer of tissue (myometrium) is muscular and comprises the greater part of the bulk of the organ. It is very firm and consists of densely packed, unstriped, smooth muscle fibres. Cells of this layer undergo hypertrophy and hyperplasia during pregnancy in preparation to expel the fetus at birth.

3. The mucous membrane/ Endometrium: The mucous membrane is smooth, and closely adherent to the subjacent tissue. The innermost layer of tissue in the uterus is the mucous membrane, or endometrium. It lines the uterine cavity as far as the isthmus of the uterus, where it becomes continuous with the lining of the cervical canal. Endometrium can be further subdivided into 2 parts:

- ✓ **Deep stratum basalis**: Changes little throughout the menstrual cycle and is not shed at menstruation.
- ✓ **Superficial stratum functionalis**: Proliferates in response to oestrogens, and becomes secretory in response to progesterone. It is shed during menstruation and regenerates from cells in the stratum basalis layer.

Vessels and Nerves:

The arteries of the uterus are the uterine, from the hypogastric; and the ovarian, from the abdominal aorta. They are remarkable for their tortuous course in the substance of the organ, and for their frequent anastomoses. The termination of the ovarian artery meets that of the uterine artery, and forms an anastomotic trunk from which branches are given off to supply the uterus, their disposition being circular. The veins are of large size, and correspond with the arteries. They end in the uterine plexuses. In the impregnated uterus the arteries carry the blood to, and

the veins convey it away from, the intervillous space of the placenta. The nerves are derived from the hypogastric and ovarian plexuses, and from the third and fourth sacral nerves.

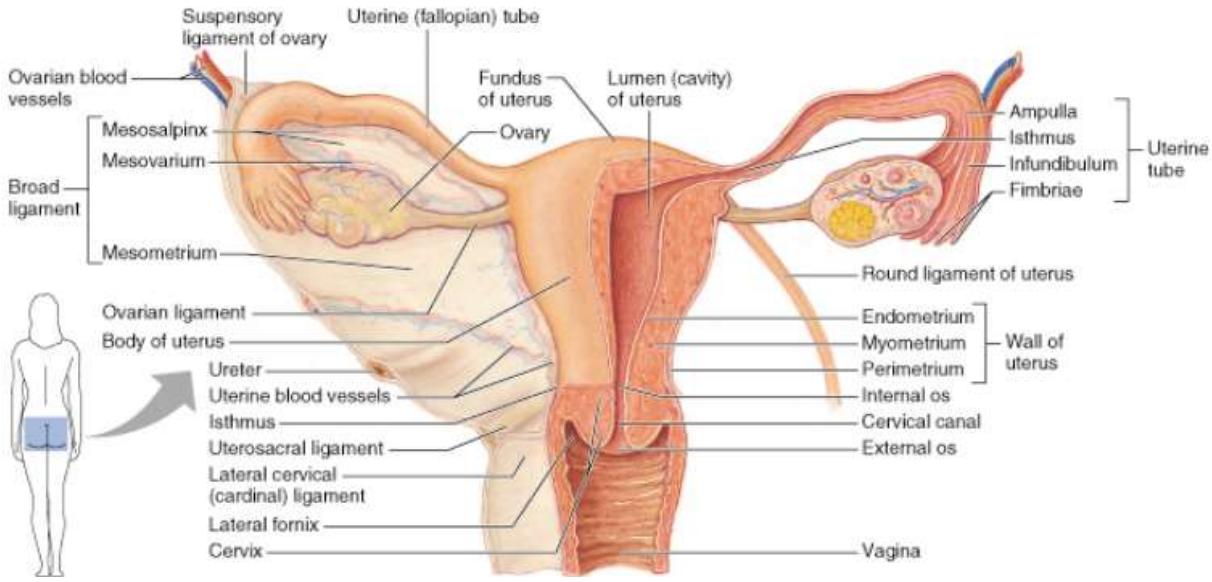

Fig.1: Anatomy of Uterus

Development of Intrauterine Device (IUD)

Intrauterine Device (IUD) is a small object [7] 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 of IUDs [8]

1. It is highly effective in preventing pregnancy.
2. It is inexpensive.
3. It does not interrupt sex.
4. It does not require partner's involvement.
5. It can be used for a long period of time.
6. It can be used as an emergency method of birth control.
7. An IUD provides long-term contraception for 3 to 5 years and is cost-effective.

Disadvantages of IUDs [9]

1. It does not protect against sexually transmitted infections (STIs).
2. It may increase the likelihood of ectopic pregnancy (pregnancy outside the uterus).
3. It can cause heavier and more painful periods.
4. Cramping and discomfort occurs during and 24-48 hours after insertion
5. There are risks during insertion and removal

Time of using an IUD

An IUD is usually inserted [10] during a menstrual period, when the cervix is slightly open and pregnancy is least likely. There is however a greater chance of expulsion if a device is introduced early in the cycle because the uterus can squeeze the device back out. Therefore, the best time for insertion is just after a period. However, an IUD may be inserted at any time. The best timing for IUD insertion for women in different situations is given in Table 1.

Table 1: Time of IUD insertion

Woman's situation	**When to start**
Having menstrual cycles	Any time within the first 12 days after the start of menstrual bleeding, preferably after bleeding has stopped, at the woman's convenience.
After childbirth	The IUD is best inserted within ten minutes of delivery of the placenta. It can be inserted at any time within 48 h after childbirth. If not immediately after childbirth, then as early as four weeks after childbirth.
After miscarriage or abortion	Immediately, if no infection is present.
Lactating mothers with lactational amenorrhea (LAM)	Any time, providing the mother is not pregnant.
When stopping another method	Immediately.

Types of intrauterine systems [11]

The type now most widely used is

1. Copper-bearing IUDs: These are made of plastic with copper sleeves and copper wire on the plastic, such as TCu-380A and MLCu-375

2. Hormone-releasing IUDs: These are made of plastic and steadily release small amounts of progesterone or other progestin hormones, such as LNG-20 and Progestasert.

3. Inert or unmedicated IUDs: These are made of plastic or stainless steel only, such as Lippes Loop and Chinese stainless steel rings.

1. Copper IUDs

Copper wire or copper [12] sleeves are put on the plastic frame (polyethylene frame). Examples include Copper T, CuT380 A, Multiload 375 etc. The various types of Copper IUDs differ from each other by the amount of copper. The initial Copper IUDs were wound with 200-250 mm^2 wire (CopperT 200). The modern copper containing devices contain more copper and a part of copper in the form of solid tubal sleeves rather than wire. This increases the efficacy and lifespan (Cu T-380 A).

- ✓ ***CuT 380A*** **-** It is a T shaped device with a polyethylene frame holding 380 mm2 of exposed surface area of copper. The IUD frame contains barium sulfate thus making it radio-opaque.
- ✓ ***CuT-380Ag*** **-** It is identical to 380 A except that the copper wire on the stem has a silver core to prevent fragmentation and extend the life span of the copper.
- ✓ ***CuT 380 slimline*** **-** It has copper sleeves flushed at the ends of horizontal arms to facilitate easier loading and insertion. The performance of CuT-380 Ag and the CuT-380 slimline is equal to that of CuT-380 A.
- ✓ ***Multiload 375*** **-** It has 375 mm^2 of copper wire wound around its stem. The flexible arms are designed to minimize expulsions. The multiload 375 and T cu-380 A are similar in their efficacy and performance.
- ✓ ***Nova T*** **-** It is similar to the CuT-200, containing 200 mm^2 of copper. However, the Nova T has a silver core to the copper wire, flexible arms, and a large flexible loop at the bottom to prevent cervical perforation.

Copper T 380A

Copper T 380A (ParaGard; Teva Pharmaceutical Industries Ltd., Sellersville, PA, USA) is one of the most commonly available and widely used in many countries. It contains 380 mm^2 copper surface area supplied by a sleeve of solid copper on each of the arms (together 32 cm in width) and wrapped by a copper wire along the 36 mm vertical stem. Monofilament polyethylene thread is tied through the base creating two white tail strings measuring 10.5 cm in length to facilitate detection and removal of the device. The CuT-380A IUD is designed to be used in women whose uterine cavities sound to a depth of 6–9 cm.

The CuT-380A IUD is placed into the uterus using a two-handed technique. The IUD arms are loaded manually pointing downward into the insertion tubing after uterine sounding has verified that the woman's uterus is in the appropriate depth (6–9 cm). The loaded IUD tubing should be advanced directly in one step to the uterine fundus, and then the arms are to be released.

Mechanisms of action

The copper IUD functions as a contraceptive (inhibiting fertilization). CuT-380A IUD inhibits sperm motility and block activation of acrosomal enzymes in the sperm head needed for the sperm to penetrate through the zona pellucida to enable union of the gametes. The copper slows down the movement of sperm within the woman's uterus and so prevents them from reaching the fallopian tubes and fertilizing the egg. The device also stimulates a strong reaction in the wall of the uterus, which prevents implantation of the egg (even if it is fertilized).

Advantages of the Copper T 380A IUD

1. IUDs are a highly effective, safe, long-acting contraceptive method.
2. Women need to make only a single decision to use it, whereas the pill requires daily decisions, and condoms and spermicides require decisions with each act of intercourse.
3. There are no hormonal side effects with copper-bearing or inert IUDs.
4. It does not interact with any medicine the client may be taking, so it is ideal for those who are taking antiepileptic or antituberculosis medications.
5. The IUD is best used by those wanting a long-acting and prompt reversible method.
6. The Copper T 380A IUD also helps prevent ectopic pregnancies.
7. Copper T 380A IUD does not affect the quantity and quality of breast milk, it can be used by lactating women.

Disadvantages of the Copper T 380A IUD

IUDs are not suitable for all women. Using them carries the following risks:

1. ***Pelvic inflammatory disease (PID):*** One of the main concerns about using IUDs is the possibility of developing PID. The greatest risk of pelvic infection associated with the use of IUDs occurs at insertion.
2. ***Menstrual problems:*** Increased menstrual pain (dysmenorrhoea) may accompany IUD use. Between 10%–15% of IUD users have their IUD removed because of symptoms or signs

associated with bleeding or spotting. However, the amount of blood is usually minor and of little consequence.

3. ***Expulsions:*** An IUD may come out of the uterus, possibly without the woman knowing. This is more common when the IUD is inserted soon after child birth, or when there are abnormal amounts of menstrual flow or severe dysmenorrhoea (painful cramps during menstruation).
4. ***Pregnancy:*** Half of intrauterine pregnancies that occur with the IUD in place end in spontaneous abortion. If the IUD is removed early in pregnancy, the spontaneous abortion rate drops to about 25%.

MLCu

These devices are predominately used in Europe and Asia and are available in short versions for nulliparous women. The MLCu-375 provides 5 years of contraceptive protection while the MLCu250 lasts for 3 years. The UNFPA & IPPF provide these IUDs to partner countries.

2. Hormone-Releasing IUDs

Hormonal [13] IUDs (brand names Mirena, Skyla, and Liletta; referred to as intrauterine systems in) work by releasing a small amount of levonorgestrel (LNG), a progestin. The primary mechanism of action is making the inside of the uterus fatal to sperm. They can thin the endometrial lining and potentially impair implantation but this is not their usual function. Because they thin the endometrial lining, they reduce or even prevent menstrual bleeding, and can be used to treat menorrhagia (heavy menses), once pathologic causes of menorrhagia (such as uterine polyps) have been ruled out. The progestin released by hormonal IUDs primarily acts locally; use of Mirena results in much lower systemic progestin levels than other very-low-dose progestogen only contraceptives.

Progestasert

It is a T shaped IUD made of ethylene and vinyl acetate copolymer containing titanium dioxide. The vertical stem contains a reservoir of 38 mg progesterone together with barium sulfate dispersed in silicone fluid. The progesterone is released at the rate of 65 µg per day.

LNG-releasing IUDs

There are three branded LNG-releasing IUDs currently available. There are two similarly size IUDs with 52 mg LNG and one is smaller with 13.5 mg LNG. The release rates of LNG were

measured at different times following the placement, which initially lead to some confusion in naming conventions.

LNG-releasing IUDs (20 µg/24 h) (Mirena®, Liletta/Levosert®)

Each of these IUDs is composed of a T-shaped polyethylene radiopaque frame measuring 32 mm×32 mm. Encircling the stem is a hormone cylinder composed of a mixture of 52 mg levonorgestrel and silicone (polydimethylsiloxane). Controlling the rate of release of LNG from this reservoir is a semiopaque silicone (polydimethylsiloxane) membrane. A monofilament polyethylene thread is attached to a hook at the end of the vertical stem creating two tail strings that are useful to reassure the woman of the IUD's continued presence and to facilitate removal. LNG is released during the first year at a rate of 20 µg/d. After early equilibration, plasma levels average 150–200 pg/mL. The average levels over the first 3 years were 218 ng/L.

The first LNG-IUD 20 that was widely adopted (Mirena) is approved by health authorities in more than 140 countries, for 5 years, for contraception. It is approved for the treatment of heavy or prolonged menstrual bleeding and to serve as a source of progestin for postmenopausal estrogen therapy in women with an intact uterus. Extended use of the original LNG-IUD for up to 7 years has been suggested for women who are at least 25 years of age at the time of placement.

Currently, the newer version (Liletta/Levosert; Allergan, Inc., Irvine, CA, USA) has only been tested for a limited number of years, so approval is for only 3 years. However, clinical trials are continuing; if the efficacy [14] is maintained, the approval will undoubtedly be expanded in duration. Because the IUD portion of these two products is virtually identical, it is expected that ultimately the clinical impacts will both be the same. However, in the US, Liletta® is approved for contraception only, but in Europe, Levosert® (Uteron Pharma, Liege, Belgium) is also approved for the treatment of heavy menstrual bleeding.

Mechanisms of action

The mechanism is thickening of the cervical mucus to blocking the entry of sperm into the upper genital tracts; ovulation is suppressed in only ~50% of cycles in the first year of use and in significantly fewer cycles in later years. Sperm can penetrate through the cervix mucus by only 2–3 mm in LNG-IUD users at the time of ovulation and that this impact persists throughout the life of the IUD.

LNG-IUD 8 (Skyla/Jaydess®)

The LNG-IUS 8 (Bayer Healthcare Pharmaceuticals) has the same basic structure as higher-dose LNG-IUSs, but is smaller in both vertical and horizontal dimensions. The arms measure 28 mm, and the stem is 30 mm long. The T-shaped frame is made of polyethylene. The reservoir has only 13.5 mg LNG wrapped around the stem. The monofilament tail strings are identical to Mirena. The LNG-IUD 8 is introduced into the uterine cavity in tubing with a smaller outer diameter of 3.8 mm. To distinguish this lower-dose IUD on imaging from its higher-dose versions, a ring of 99.95% pure silver was placed at the top of the vertical stem close to the horizontal arms. Even with the small ring, it is safe. Marketed in the US as Skyla and worldwide as Jaydess, this lower-dose, 3-year IUD with 13.5 mg LNG releases an average of 8 µg/d over the first year.

Table 2: Comparison between copper and hormonal IUDs

Comparison	**Copper IUD**	**Hormonal IUDs**			
		Mirena	**Skyla**	**Liletta**	**Kyleena**
Hormone in total device	Nil	52 mg LNG	13.5 mg LNG	52 mg LNG	19.5 mg LNG
Initial amount released	Nil	20 µg/d	14 µg/d	18.6 µg/d	16 µg/d
Approved effectiveness	10 years	10 years	10 years	10 years	10 years
Mechanism of action	-Copper is toxic to sperm	-LNG thickens cervical mucus to prevent sperm from reaching egg. -Prevents ovulation at times			
Advantages	-No hormones -Emergency contraception	- Various level of hormone options -Lighter periods after 3 months			
Disadvantages	-Heavier menstrual flow and cramps	-Ovarian cysts			

3. Inert or unmedicated IUDs:

IUD does not have a bioactive component. It is made of inert [14,15] materials like stainless steel (such as the stainless steel ring (SSR), a flexible ring of steel coils that can deform to be

inserted through the cervix) or plastic (such as the Lippes Loop, which can be inserted through the cervix in a cannula and takes a trapezoidal shape within the uterus). It is less effective than copper or hormonal IUD, with a side effect profile similar to copper IUD. The mechanism of action is inducing a local foreign body reaction, which makes the uterine environment hostile both to sperm [14] and to implantation of an embryo. These IUDs have higher rates of preventing pregnancy after fertilization, instead of before fertilization, compared to copper or hormonal IUDs. Inert IUDs are not approved for use in the United States, UK, or Canada. But in China, these IUDs are the most common form of contraception.

Applications of IUD

1. IUD is effectively useful in contraception [16] 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.
2. For people with severe health conditions that make pregnancy dangerous, an IUD can be life-saving. IUD protects against pregnancy-related health issues.
3. 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.
4. 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.
5. IUDs include the treatment of menorrhagia, anemia, dysmenorrhea and pelvic pain associated to endometriosis, and endometrial protection during hormone replacement.

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