Unit-5

Novel Drug Delivery Systems

B.Pharma 7 Sem Notes

Unit: 5

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

OCULAR DRUG DELIVERY SYSTEMS

Introduction to Ocular Drug Delivery

Ocular drug delivery refers to the administration of therapeutic agents to the eye for the treatment of various anterior and posterior segment disorders. The eye is a unique and highly specialized organ, physiologically isolated from the rest of the body by several protective barriers. These barriers, while essential for maintaining intraocular homeostasis, significantly restrict the bioavailability of topically applied drugs.

📌 **Key Point:** Only < 5% of a topically applied eye drop reaches intraocular tissues. The remaining > 95% is lost through nasolacrimal drainage, systemic absorption through conjunctival vessels, and lacrimation — resulting in poor bioavailability and systemic side effects.

The Human Eye — Anatomy Relevant to Drug Delivery

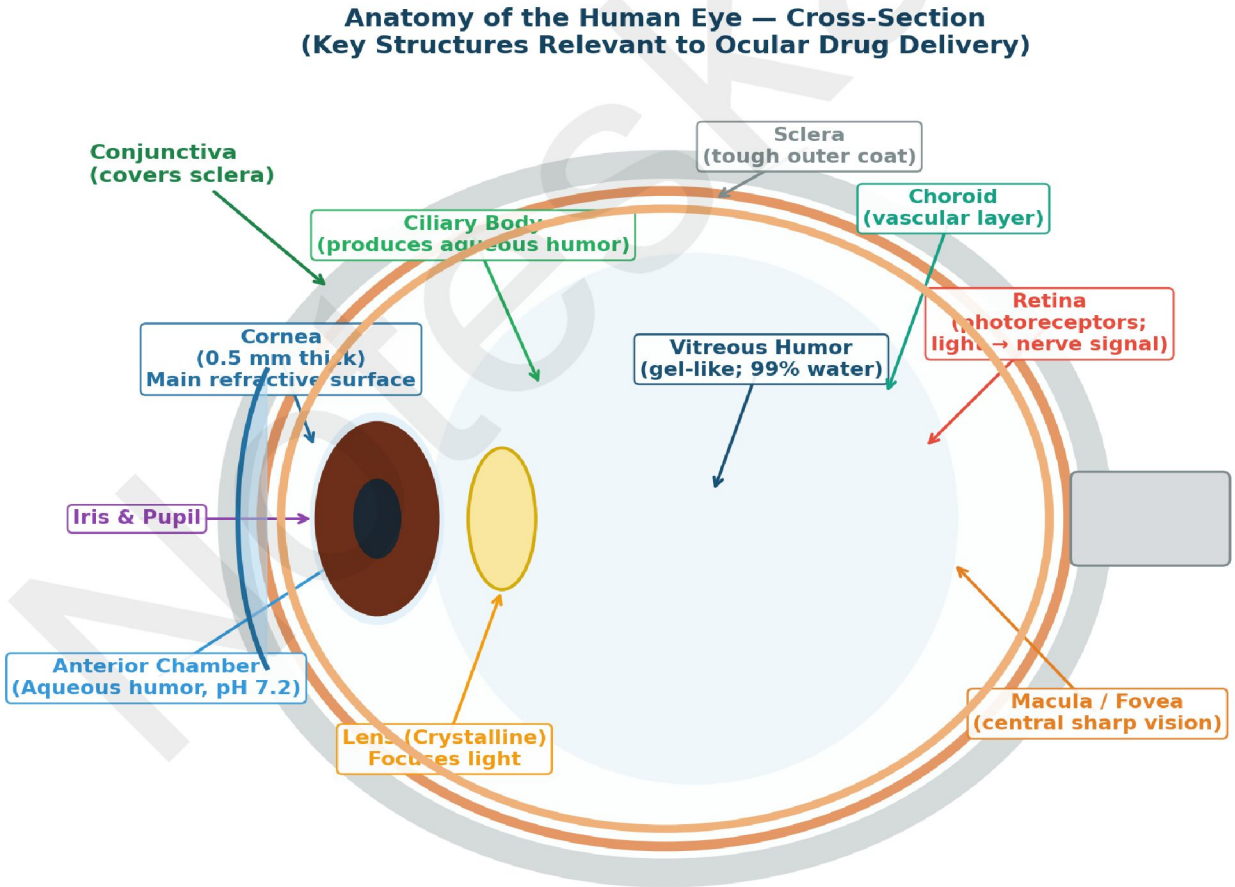

Figure 1: Detailed Anatomy of the Human Eye — Structures and Their Roles in Drug Delivery

Structure	Description	Relevance to Drug Delivery
Cornea	Transparent avascular 5-layered structure (Ep–Bowman–Stroma–Descemet–Endothelium); 0.5 mm thick; 11 mm diameter	Primary route for topical drug absorption; stratified squamous epithelium = lipophilic barrier; stroma = hydrophilic barrier
Conjunctiva	Mucous membrane covering sclera and inner eyelids; 17× more permeable than cornea	Drug absorption route — especially for hydrophilic drugs; causes systemic absorption via blood vessels
Sclera	Tough outer coat; 0.5–1.0 mm thick; collagen fiber matrix	Trans-scleral route for large molecules; basis for periocular injections
Anterior Chamber	Aqueous humor-filled space (pH 7.2, volume 250 µL); between cornea and lens	Drug distributes here after corneal absorption; aqueous outflow = drug clearance mechanism
Iris / Ciliary Body	Pigmented structures; contain blood vessels, muscles	Blood-aqueous barrier location; melanin binds lipophilic drugs (depot effect)
Lens	Crystalline biconvex lens; avascular	Drug accumulation → cataract risk; not a major drug delivery target
Vitreous Humor	Gel-like material filling posterior segment; 4 mL; pH 7.4; 99% water	Large reservoir; intravitreal injections deposit drug here; slow drug clearance
Retina	Innermost sensory layer; photoreceptors (rods and cones); 10 layers	Target for AMD, DR, retinitis; blood-retinal barrier prevents drug access
Choroid	Vascular layer between retina and sclera; rich blood supply	Rapid drug clearance from posterior segment; transscleral drug access route

Routes of Ocular Drug Delivery

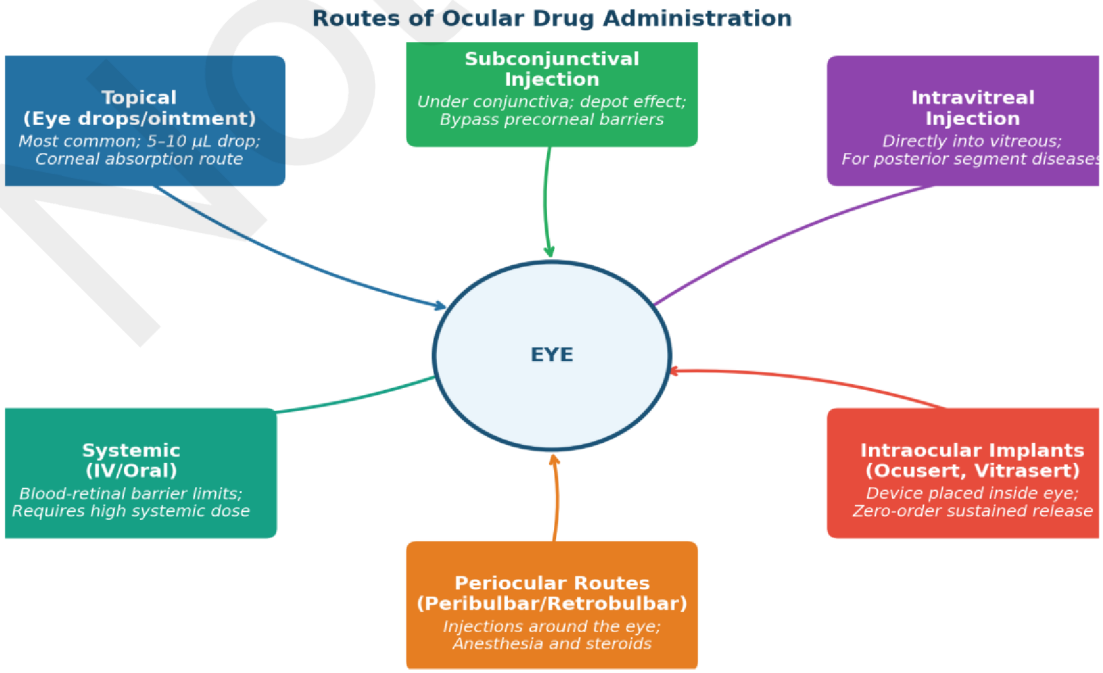

Figure 2: Routes of Ocular Drug Administration — from Topical to Intravitreal

Route	Method	Target Region	Advantages / Disadvantages
Topical	Eye drops, ointments, gels, inserts	Anterior segment (cornea, conjunctiva, anterior chamber)	Easiest; patient-friendly — but < 5% bioavailability; frequent dosing needed
Subconjunctival	Injection under bulbar conjunctiva (0.3–1.0 mL)	Anterior and limited posterior segment	Higher drug levels; avoids precorneal barriers — but painful; risk of haemorrhage
Intravitreal (IVT)	Direct injection into vitreous cavity (0.05–0.1 mL)	Posterior segment (vitreous, retina, choroid)	Highest posterior segment drug levels — but invasive; risk of endophthalmitis, retinal detachment
Periocular (Peribulbar/Retrobulbar)	Injections around the eye orbit	Posterior segment via transscleral diffusion	Good distribution; used for anesthesia and steroids — but variable absorption
Intraocular implant	Device surgically placed in anterior or posterior chamber	Site-dependent (anterior/posterior)	Sustained zero-order release (weeks–years); avoids barriers — requires surgery
Systemic (IV/Oral)	Intravenous infusion or oral tablets	All ocular tissues (limited by BRB)	Can reach posterior segment — but very high doses needed; systemic toxicity risk
Subretinal	Direct injection under retina	Subretinal space	Precise targeting for RPE disorders; gene therapy delivery — highly specialized
Intracameral	Injection into anterior chamber	Anterior chamber	High drug levels; used for antibiotics post-cataract surgery

Intraocular Barriers to Drug Delivery

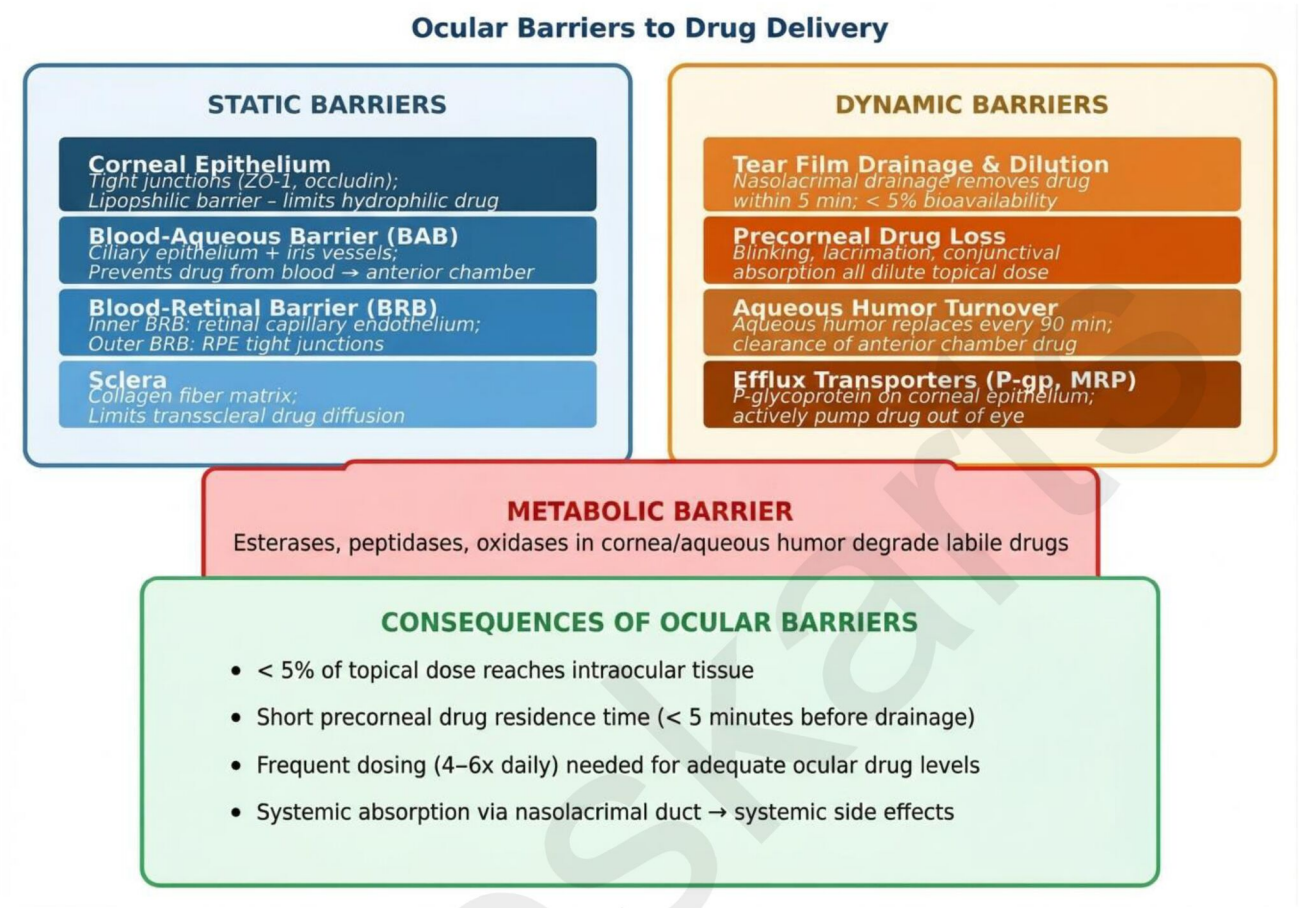

Figure 3: Static, Dynamic, and Metabolic Barriers to Ocular Drug Delivery

The eye possesses multiple highly effective barriers that protect it from foreign substances — making drug delivery uniquely challenging. These barriers are classified as static, dynamic, and metabolic.

Static Barriers

Corneal Epithelium

The corneal epithelium is the primary rate-limiting barrier for topically applied drugs. It is a five-to-seven cell layer thick stratified squamous epithelium with tight junctions (Zonula occludens).

- Tight junctions (TJ) — ZO-1, occludin, claudin proteins seal the paracellular space between epithelial cells.
- Highly lipophilic — prevents passive permeation of hydrophilic drugs.
- Three-layer model: Epithelium (lipophilic) → Stroma (hydrophilic) → Endothelium (lipophilic) = amphiphilic drug required for transcorneal absorption.
- **Optimal drug Log P for corneal absorption:** Between 1 and 3 (intermediate lipophilicity).

Blood-Aqueous Barrier (BAB)

- Located at ciliary body epithelium and iris blood vessel endothelium.
- Composed of non-pigmented ciliary epithelium — tight junctions prevent passage of large molecules from blood to aqueous humor.
- Restricts entry of systemically administered drugs into anterior chamber.
- Disrupted in inflammation (uveitis) — BAB breakdown allows drug entry but also causes damage.

Blood-Retinal Barrier (BRB)

- Most critical barrier for posterior segment drug delivery.
- Inner BRB: Tight junctions between retinal capillary endothelial cells (similar to BBB).
- Outer BRB: Tight junctions of the Retinal Pigment Epithelium (RPE) — between photoreceptors and choroid.
- Prevents passage of most drugs from systemic circulation to retina.
- Target for drug delivery in AMD, Diabetic Retinopathy, CMV retinitis.
- Disruption occurs in: Diabetes, inflammation, retinal vein occlusion.

Scleral Barrier

- Sclera is composed of densely packed collagen fibers — acts as a physical barrier to transscleral drug diffusion.
- Scleral permeability inversely related to molecular weight and lipophilicity.
- Relatively more permeable than cornea for large hydrophilic molecules → basis for trans-scleral drug delivery.
- Permeability: Sclera > Cornea for large molecules; Cornea > Sclera for small lipophilic drugs.

Dynamic Barriers

Tear Film Drainage and Lacrimation

- Normal tear volume: 7–10 µL; maximum corneal instillation volume: 30 µL.
- Standard eye drop volume: 50–70 µL — but ~80% immediately drained via nasolacrimal duct within 15–30 seconds.
- Blinking frequency: 10–15 times/minute → mechanically wipes drug from corneal surface.
- Result: Drug contact time with cornea < 2–5 minutes → < 5% absorbed; rest systemically absorbed through nasal mucosa.
- **Clinical implication:** Systemic absorption via nasolacrimal duct → timolol eye drops cause bronchospasm in asthma patients.

Precorneal Drug Loss Mechanisms

- Solution drainage via nasolacrimal duct (main loss pathway).
- Conjunctival absorption: Conjunctival surface area (17 cm^2) > Cornea (1.3 cm^2) — more drug absorbed by conjunctiva (non-specific) than cornea (specific). Most conjunctival drug enters blood vessels → systemic side effects.
- Dilution by tears (baseline tear volume 7 µL; turnover rate 16%/min).
- Drug-protein binding in tear film (lactoferrin, lysozyme bind drugs).

Aqueous Humor Turnover

- Aqueous humor produced by ciliary body at 2.5 µL/min.
- Total volume replaced every ~90 minutes.
- Drugs absorbed into anterior chamber diluted and eliminated via aqueous outflow (trabecular meshwork → Schlemm's canal → episcleral veins).

Efflux Transporters

- P-glycoprotein (P-gp/MDR1): Located in corneal epithelium, ciliary body, retina — actively pumps drugs OUT of ocular tissues.
- MRP-2 (Multidrug Resistance-associated Protein): Transports organic anions; reduces drug accumulation.
- Breast Cancer Resistance Protein (BCRP): Additional efflux pump on retinal pigment epithelium.
- These efflux pumps significantly reduce intracellular drug concentrations in ocular tissues.

Metabolic Barrier

- Corneal epithelium contains: Esterases, Oxidoreductases, Cytochrome P450 enzymes (CYP1A2, CYP1B1), Peptidases.
- Aqueous humor contains: Peptidases, Proteases that degrade peptide/protein drugs.
- Vitreous humor: Enzymatic activity lower — more favorable for macromolecule delivery.
- **Prodrug strategy:** Drugs can be designed as ester prodrugs → corneal esterases cleave ester → active drug released inside eye. Example: Latanoprost (PGF2α isopropyl ester prodrug) → corneal esterases → free latanoprost acid (active).

Methods to Overcome Ocular Barriers

Formulation-Based Approaches

Viscosity Enhancement

- Increasing formulation viscosity reduces drainage rate and prolongs precorneal residence time.
- Polymers used: HPMC, HPC, MC, PVA, Carbopol, Sodium hyaluronate, Guar gum, Xanthan gum.
- Optimal viscosity: 15–50 cps (too high → uncomfortable; too low → insufficient retention).

Viscosity Enhancer	Concentration	Properties
HPMC (Hydroxypropyl methylcellulose)	0.3–1.0%	Most widely used; lubricant; compatible; pseudoplastic
Carbopol (Polyacrylic acid)	0.1–0.3%	High viscosity at low conc.; mucoadhesive; pH-sensitive
Sodium Hyaluronate (HA)	0.1–0.4%	Natural vitreous component; viscoelastic; excellent biocompatibility

Polyvinyl Alcohol (PVA)	1.0–1.5%	Good film-forming; non-irritating; artificial tear formulations
Carboxymethylcellulose (CMC)	0.5–1.5%	Mucoadhesive; popular in artificial tears (Refresh Tears)

pH Adjustment

- Optimal formulation pH: 6.0–8.0 (tear fluid pH = 7.4; lacrimal secretion slightly alkaline at pH 7.4–8.0).
- pH affects: Drug ionization → permeability; drug stability; patient comfort.
- Phosphate buffers and borate buffers commonly used.
- **Example:** Pilocarpine HCl (pKa 6.8) — at pH 6.8, 50% unionized → better corneal penetration than at lower pH.

Mucoadhesive Polymers

- Mucoadhesive polymers bind to conjunctival mucin layer → resist nasolacrimal drainage → prolonged contact.
- Polymers: Chitosan (cationic; excellent mucoadhesion), Carbopol (anionic PAA), HPMC, HPC, Polycarbophil, Hyaluronic acid.
- **Chitosan advantage:** Cationic at physiological pH; binds anionic mucin strongly; also opens tight junctions (paracellular transport enhancer).

Penetration Enhancers

Enhancer Type	Examples	Mechanism
Surfactants	Benzalkonium chloride (BAK), EDTA, Brij series	Disrupt epithelial membrane; open tight junctions — but BAK toxic at high concentrations
Cyclodextrins	HP-β-CD, dimethyl-β-CD	Solubilize lipophilic drugs; increase corneal permeability; reduce drug-protein binding
Bile salts	Sodium deoxycholate, taurocholate	Disrupt cell membranes; increase paracellular transport
Fatty acids	Oleic acid, capric acid	Fluidize lipid bilayers of corneal epithelium
EDTA (Chelating agent)	Disodium EDTA 0.05–0.5%	Binds Ca^{2+} → opens tight junctions → increased paracellular flux

pH-Responsive / Ion-Activated Systems

- **Gelrite (Gellan gum):** Low viscosity liquid at pH 7; forms rigid gel on contact with cation-rich tear fluid. Commercial product: Timoptic-XE (timolol maleate 0.5% — once daily, replacing twice-daily drops).
- **Alginate-based:** Aqueous solution forms gel in presence of Ca^{2+} ions in tears. Alginic acid + Calcium gluconate → cross-linked gel at corneal surface.
- **Temperature-sensitive:** Poloxamer 407 (Pluronic F127) — sol at room temperature, gel at body temperature (34°C at corneal surface).

Drug Design Approaches

Prodrug Approach

- Drug converted to inactive ester or amide prodrug → better corneal penetration (lipophilic prodrug).
- Corneal esterases activate prodrug → release active drug inside eye.

Prodrug	Active Drug	Indication	Benefit
Latanoprost (isopropyl ester)	Latanoprost acid (PGF2α)	Glaucoma	Better corneal penetration than free acid
Dipivefrin (dipivalyl ester)	Epinephrine	Glaucoma	600× better corneal penetration than epinephrine
Acyclovir triacetate	Acyclovir	Herpetic keratitis	Enhanced corneal absorption
Chloramphenicol esters	Chloramphenicol	Bacterial conjunctivitis	Improved solubility and absorption

Sustained Release Approaches

- Nanoparticles (PLGA, albumin, chitosan) — phagocytosed by corneal epithelium; sustained intracellular drug release.
- Liposomes — encapsulate drug; interact with corneal epithelium; prolong drug contact.
- Microemulsions — thermodynamically stable; enhance drug solubility and corneal penetration.
- Cyclodextrin complexes — improve solubility of insoluble ophthalmic drugs.

Physical Methods

- **Iontophoresis:** Low electric current (1–10 mA/cm²) drives ionized drug through ocular tissues. Transscleral iontophoresis for posterior segment. Used for: Gentamicin, Dexamethasone, Foscarnet, Anti-VEGF delivery.
- **Microneedles:** Hollow microneedles placed on sclera — create microchannels for drug diffusion into posterior chamber. Painless; research stage.
- **Ultrasound:** Sonophoresis enhances transscleral drug delivery — low-frequency US increases permeability.
- **Laser-facilitated delivery:** Laser creates transient micropores in cornea — allows large molecules to permeate.

📌 **Key Point:** Key Strategy to Overcome Barriers: Combine (1) Viscosity enhancement for prolonged contact + (2) Mucoadhesion to prevent drainage + (3) Penetration enhancers or nanocarriers for improved transcorneal flux + (4) Prodrug activation inside eye.

Ocular Formulations — Preliminary Study

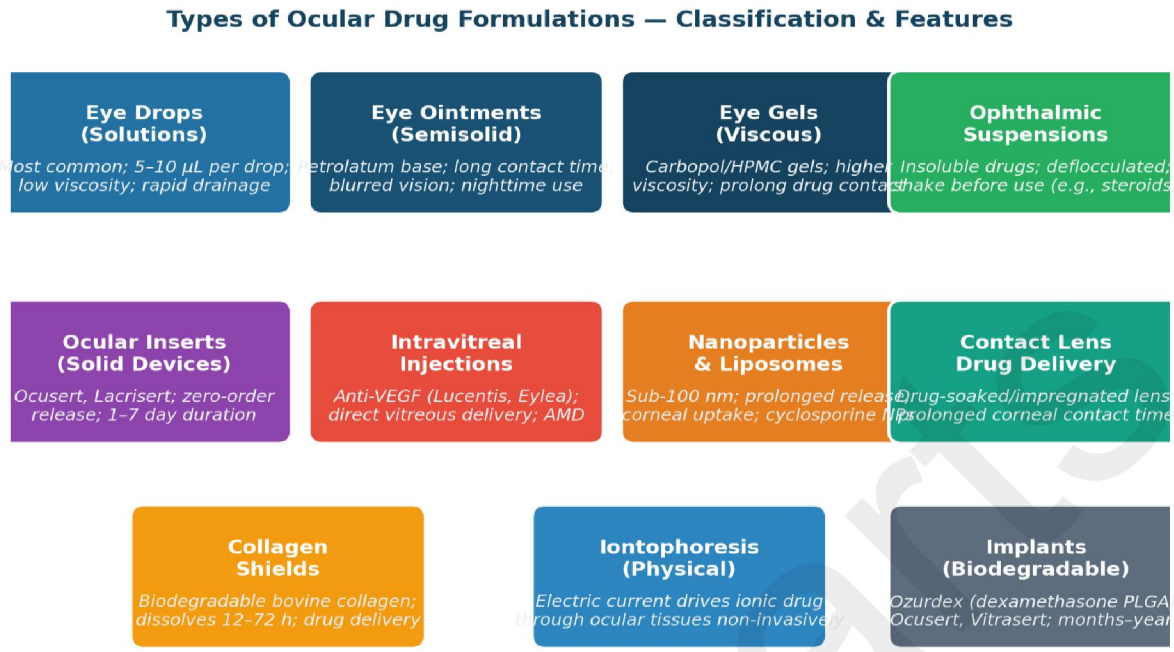

Figure 4: Classification of Ocular Drug Delivery Formulations

Ophthalmic Solutions (Eye Drops)

Sterile aqueous or non-aqueous solutions of drugs instilled into the lower conjunctival sac. Most widely used ophthalmic dosage form despite low bioavailability.

Formulation Requirements

Parameter	Requirement	Rationale
Sterility	Must be sterile (USP/BP standards)	Prevents intraocular infection; eye lacks immune defense
Isotonicity	270–310 mOsm/L (equivalent to 0.9% NaCl)	Prevents ocular irritation; NaCl or mannitol used for tonicity adjustment
pH	6.0–8.0 (ideal 7.4)	Match tear pH; minimize irritation; affect drug ionization and stability
Buffering	Phosphate or borate buffer systems	Maintain pH against lacrimal buffer; pH 6.5–7.5 most comfortable
Viscosity	4–10 cps (water = 1 cps)	Slight viscosity increase prolonged residence time
Preservatives	BAK 0.01%; Benzalkonium Cl; PHMB; Thimerosal (no longer used); Purite	Antimicrobial in multi-dose containers; can cause toxicity in long-term use
Antioxidants	Sodium metabisulfite (0.1%), EDTA, ascorbic acid	Prevent oxidative drug degradation

Drug concentration	As low as therapeutically effective	Minimize systemic absorption and local toxicity

Commonly Used Ophthalmic Solutions

Drug	Brand	Category	Dosing
Timolol maleate 0.25/0.5%	Timoptic	β-blocker; glaucoma	Twice daily (BID)
Latanoprost 0.005%	Xalatan	PGF2α analog; glaucoma	Once daily (QD)
Ciprofloxacin 0.3%	Ciloxan	Fluoroquinolone antibiotic	Every 2h → QID
Dexamethasone 0.1%	Maxidex	Corticosteroid; inflammation	QID
Cyclosporine 0.05%	Restasis	Immunomodulator; dry eye	BID
Brimonidine 0.1/0.15/0.2%	Alphagan	α2-agonist; glaucoma	TID
Dorzolamide 2%	Trusopt	Carbonic anhydrase inhibitor; glaucoma	TID
Artificial tears (CMC 0.5%)	Refresh Tears	Lubricant; dry eye	PRN (as needed)

Ophthalmic Ointments and Gels

- **Ointments:** Semisolid preparations with petrolatum/liquid paraffin/mineral oil base. High drug retention in cul-de-sac. Prolonged drug contact (4–8 hours vs. <5 min for drops). Disadvantages: Blurred vision; sticky feeling; not for contact lens wearers. Used at bedtime. Example: Erythromycin, Bacitracin, Chloramphenicol ointments.
- **Gels (Ophthalmic gels):** Aqueous polymer gels — Carbopol, HPMC, HA. More comfortable than ointments; less blurring. Pilocarpine 4% gel (Pilopine HS) — once-nightly dosing vs. 4× daily drops. Artificial tear gels: Genteal Gel (CMC + glycerin).
- **In-situ gelling systems:** Low viscosity at room temperature → high viscosity gel on contact with tear fluid (pH, temperature, or ion change). Timoptic-XE (Gelrite — timolol 0.5% once daily), Besifloxacin 0.6% (Besivance).

Ophthalmic Suspensions

- Insoluble drugs formulated as fine particle suspensions.
- Particle size: < 10 µm to avoid corneal irritation; typically 2–5 µm.
- Must be resuspendable on shaking — controlled flocculation to prevent caking.
- Advantages: Higher drug loading than solutions for poorly soluble drugs; longer contact.

Product	Drug	Type	Indication
Pred Forte	Prednisolone acetate 1%	Corticosteroid suspension	Ocular inflammation post-surgery
FML	Fluorometholone 0.1/0.25%	Corticosteroid suspension	Mild-moderate inflammation
Lotemax	Loteprednol etabonate 0.5%	Soft steroid suspension	Inflammation; dry eye

Tobradex	Tobramycin + Dexamethasone	Antibiotic-steroid combo	Bacterial blepharoconjunctivitis
Azasite	Azithromycin 1%	Antibiotic suspension in DuraSite gel	Conjunctivitis — once or twice daily

Advanced Ocular Formulations

Ophthalmic Nanoparticles

- Polymeric NPs (PLGA, albumin, chitosan), SLN, nanocapsules — 100–500 nm.
- Corneal epithelium uptake via endocytosis → intracellular sustained drug release.
- Advantages: Prolonged drug levels; avoid frequent dosing; suitable for peptides.
- **Example:** Cyclosporine PLGA NPs for dry eye; Timolol SLN for glaucoma.

Liposomal Ophthalmic Formulations

- Liposomes interact with corneal epithelial cell membranes → fuse and release drug.
- Can be surface-modified with mucoadhesive polymers for prolonged precorneal residence.
- **Example:** Liposomal Cyclosporine (Ikervis 0.1% — EU approved for dry eye); Liposomal Ciprofloxacin.

Microemulsions

- Thermodynamically stable, optically transparent, isotropic mixtures of oil, water, surfactant.
- Nano-droplet size (< 100 nm) → excellent corneal wetting; enhanced drug penetration.
- **Example:** Cyclosporine 0.09% microemulsion (Cequa) — for dry eye disease.

Contact Lens Drug Delivery

- Drug-soaked, vitamin E-loaded, or molecularly imprinted contact lenses — prolonged drug release to corneal surface.
- Advantages: Lens maintains drug at corneal surface throughout wearing hours.
- Research area: Smart contact lenses with drug-impregnated polymers.

Intravitreal Injections

- Direct injection of drug (30–100 µL) into vitreous cavity with 30G needle.
- Bypasses all ocular barriers → highest posterior segment drug concentration.
- Frequency: Every 1–3 months for anti-VEGF agents (Ranibizumab, Aflibercept, Bevacizumab).

Drug	Brand	Target	Indication
Ranibizumab	Lucentis	Anti-VEGF (Fab fragment)	Wet AMD, DME, RVO
Aflibercept	Eylea	Anti-VEGF (fusion protein)	Wet AMD, DME, RVO

Brolucizumab	Beovu	Anti-VEGF (scFv)	Wet AMD — every 12 weeks after loading
Faricimab	Vabysmo	Anti-VEGF + anti-Ang2	Wet AMD + DME
Dexamethasone implant	Ozurdex	Steroid (biodegradable PLGA)	DME, uveitis, RVO
Fluocinolone acetonide	Iluvien	Steroid (non-biodegradable)	Diabetic macular edema — 3-year release
Ganciclovir implant	Vitrasert	Antiviral (non-biodegradable)	CMV retinitis — 8-month release

Ocusert Ocular Therapeutic System

The Ocusert Ocular Therapeutic System is a controlled release, flexible, elliptical ocular insert designed to be placed in the lower conjunctival cul-de-sac. It continuously releases pilocarpine at a precise, constant (zero-order) rate for 7 days, replacing the conventional regimen of 4 pilocarpine eye drops per day. Developed by the ALZA Corporation and approved by the FDA in 1974.

📌 **Key Point:** Ocusert is the FIRST commercially successful controlled-release ocular insert. It achieves zero-order pilocarpine delivery for 7 days — dramatically improving glaucoma management compared to 4× daily eye drops.

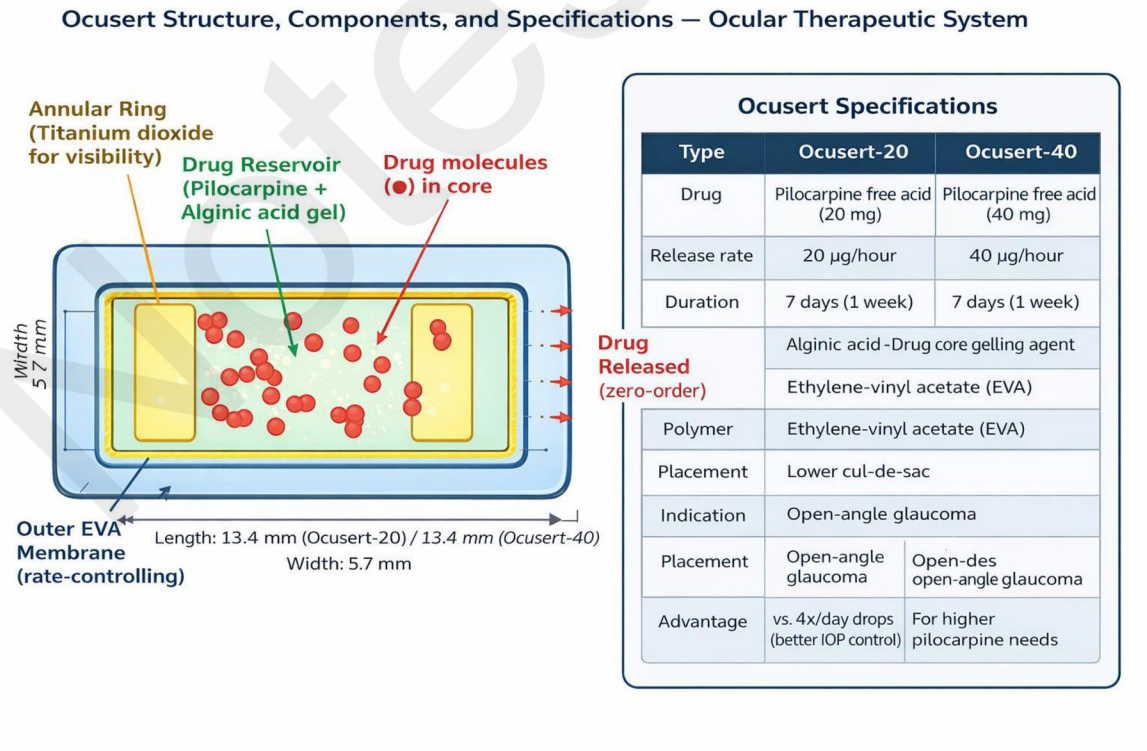

Figure 5: Ocusert Structure, Components, and Specifications — Ocular Therapeutic System

Structure and Components of Ocusert

Component	Material	Function
Drug Core	Pilocarpine free acid + Alginic acid gel + Di-2-ethylhexyl phthalate (plasticizer)	Drug reservoir; alginic acid immobilizes pilocarpine for zero-order release
Rate-Controlling Membrane	Ethylene-Vinyl Acetate copolymer (EVA)	Controls drug diffusion rate; membrane thickness determines pilocarpine flux
Annular Ring	Titanium dioxide-impregnated white EVA ring	Frames the oval insert for visibility; aids insertion/removal; renders insert white
Overall shape	Oval/elliptical disc	Fits comfortably in lower conjunctival cul-de-sac (fornix)
Dimensions	13.4 mm (long axis) × 5.7 mm (short axis) × 0.3–0.5 mm (thickness)	Designed to fit human lower cul-de-sac without interfering with vision

Types of Ocusert

Parameter	Ocusert Pilo-20	Ocusert Pilo-40
Pilocarpine release rate	20 µg/hour	40 µg/hour
Weekly pilocarpine dose	3.4 mg/week	6.7 mg/week
Equivalent drop therapy	~0.5–1% Pilocarpine drops	~2–4% Pilocarpine drops
Drug content	5 mg (total)	11 mg (total)
Suitable for	Mild to moderate glaucoma	Moderate to severe glaucoma
Duration	7 days (replaced weekly)	7 days (replaced weekly)
Membrane thickness	~0.15 mm	~0.3 mm (thicker → slower diffusion)

Mechanism of Drug Release from Ocusert

- Drug (Pilocarpine) partitions from the alginic acid gel core into the EVA membrane.
- Drug diffuses through the EVA membrane driven by concentration gradient (Fick's Law).
- Rate of release: $J = D \times Km \times \Delta C / h$ (D = diffusion coeff., Km = partition coeff., h = membrane thickness).
- Zero-order release achieved because: Saturated drug concentration in core maintained → constant ΔC → constant flux.
- Drug released from both flat faces of the insert into tear film → absorbed through cornea.
- After 7 days: Drug core depleted → insert removed and replaced with new one.

Placement of Ocusert

- Patient washes hands; pulls down lower eyelid.
- Insert placed in lower conjunctival cul-de-sac (fornix) using fingertip or provided inserter.
- Once placed, held in position by capillary forces and eye movements.

- White annular ring makes insert visible for checking.
- Weekly removal: Gentle downward pull on lower eyelid → slide insert out.
- Position checked daily — can migrate to upper fornix during sleep (patient instructed to reposition).

Advantages of Ocusert Over Pilocarpine Eye Drops

Advantage	Comparison with Eye Drops
Constant intraocular pressure (IOP) control	Eye drops give peak-trough IOP fluctuations; Ocusert maintains steady IOP throughout the day
Reduced dosing frequency	4× daily drops → 1 weekly insert replacement (improved compliance)
Lower total drug exposure	Weekly Ocusert dose (3.4 mg) < equivalent drops dose (~28 mg/week) — 8× less total drug
Fewer side effects	Less miosis, accommodation spasm, night blindness vs. drops (drops cause peak pilocarpine surges)
Improved patient compliance	Weekly system more convenient than 4× daily drops — especially for elderly
Reduced systemic absorption	Controlled slow release → no peak plasma levels; less cardiac, GI side effects
Night vision improvement	Constant low-level miosis vs. intermittent high-level miosis with drops

Disadvantages of Ocusert

- Patient training required — technique for insertion and removal.
- Can accidentally fall out during sleep or vigorous activity (swimming, sports).
- Initial discomfort as foreign body in eye.
- May migrate — requires daily visual inspection and repositioning.
- Expensive — higher cost than conventional eye drops.
- Requires refrigeration for storage (2–8°C).
- Only one drug available (pilocarpine) — cannot be used for other drugs yet.
- Some patients report persistent foreign body sensation.

Other Ocular Inserts and Implants

Device	Drug	Type	Duration / Details
Lacrisert	Hydroxypropyl cellulose (HPC 5 mg)	Soluble rod-shaped insert	Dissolves in 24 hours; lubricates dry eye; lower cul-de-sac
Vitrasert	Ganciclovir 4.5 mg	Non-biodegradable EVA/PVA implant (intravitreal)	8 months; CMV retinitis in AIDS

Ozurdex	Dexamethasone 0.7 mg	Biodegradable PLGA implant (intravitreal)	6 months; DME, uveitis, RVO
Iluvien	Fluocinolone acetonide 0.19 mg	Non-biodegradable polyimide implant (intravitreal)	3 years; diabetic macular edema
Yutiq	Fluocinolone acetonide 0.18 mg	Non-biodegradable implant (intravitreal)	3 years; non-infectious posterior uveitis
Dexycu	Dexamethasone 342 µg in extended-release vehicle	Intracameral injection	Single dose post-cataract surgery; 30-day release
Surodex	Dexamethasone 60 µg PLGA disc	Biodegradable intracameral implant	30 days; cataract surgery
Muro 128	NaCl 2/5% ophthalmic ointment	Hyperosmotic; reduces corneal edema	PRN; daily

INTRAUTERINE DRUG DELIVERY SYSTEMS (IUDS)

Introduction to Intrauterine Drug Delivery Systems

Intrauterine Drug Delivery Systems (IUDDS) are devices placed inside the uterine cavity to deliver drugs locally for contraception, treatment of gynecological conditions, or emergency contraception. These systems exploit the unique physiology of the uterine cavity — small enclosed space, rich blood supply, direct access to target tissue — to achieve prolonged, controlled drug delivery with minimal systemic exposure.

📌 **Key Point:** Intrauterine Device (IUD) = Small, T-shaped or other shaped device inserted into the uterine cavity by a trained healthcare provider. Provides contraception for 3–10 years (depending on type). World's most effective reversible contraceptive (> 99% effectiveness).

Anatomy of Uterus Relevant to IUD Delivery

Structure	Description	Relevance
Uterine body (corpus)	Muscular organ; cavity volume ~3–4 mL; endometrium lines cavity	IUD resides in cavity; drug acts on endometrium
Endometrium	Inner mucosal lining; cyclically shed (menstruation)	Target tissue for hormonal IUD effects; foreign body reaction for Cu-IUD
Myometrium	Thick muscular wall	Uterine contractions may expel IUD
Cervix	Narrow lower opening; cervical os	Route of IUD insertion; cervical mucus barrier affected by LNG-IUD
Cornua (uterine angles)	Upper lateral angles where fallopian tubes join	IUD arms extend to cornua; drug released here prevents fertilization
Blood supply	Uterine arteries from internal iliac; dense endometrial capillaries	Rapid local drug absorption; minimal systemic exposure for some drugs

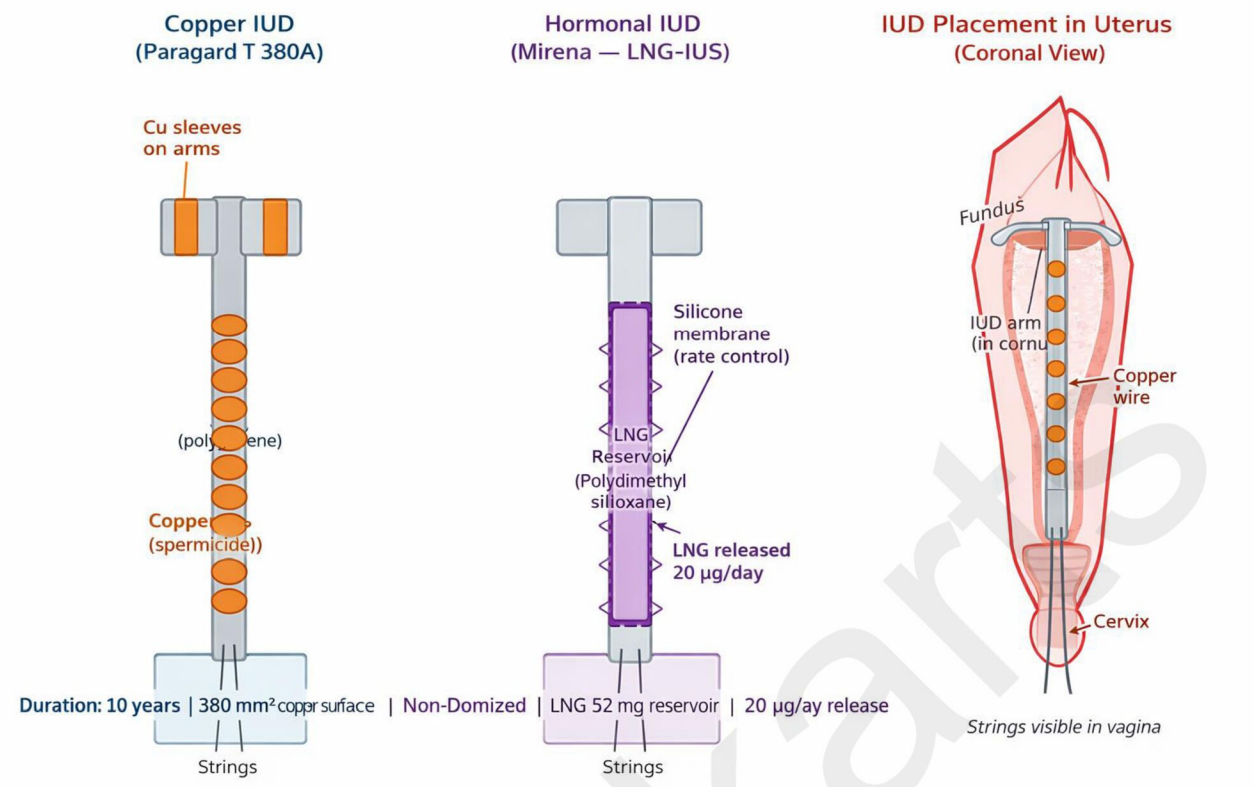

Figure 6: Types of IUDs — Copper IUD (Paragard T380A), Hormonal IUD (Mirena LNG-IUS), and Uterine Placement

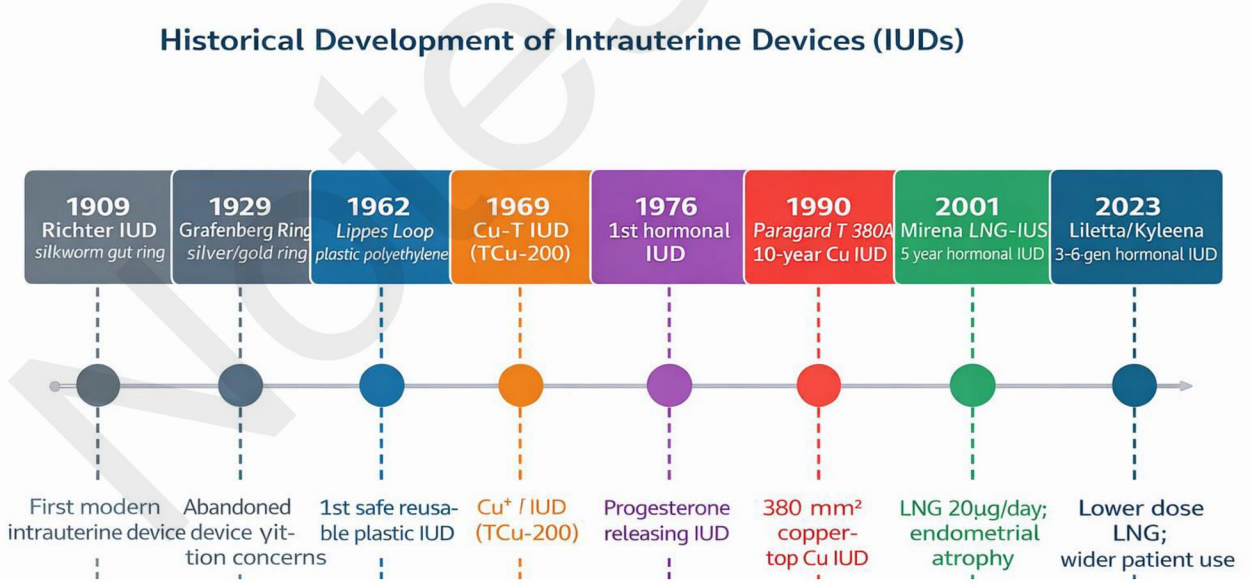

Figure 7: Historical Development Timeline of Intrauterine Devices (1909–2023)

Advantages and Disadvantages of IUDs

Advantages

Advantage	Explanation
Highly effective contraception	> 99% contraceptive effectiveness — among the most effective reversible methods (failure rate < 1%)
Long-acting	Copper IUDs: 10 years; Hormonal IUDs (Mirena): 5–8 years; reduced need for daily compliance
Reversible	Fertility returns rapidly after removal (within 1 month for most women)
No daily dosing	Unlike oral contraceptive pills — once inserted, no patient action required for years
Local drug delivery	LNG-IUD delivers progestin locally in uterus — systemic side effects far less than oral pills
Emergency contraception	Copper IUD most effective emergency contraceptive (> 99% effective within 5 days of unprotected sex)
Non-hormonal option	Cu-IUD: copper provides contraception without hormones — suitable for women who cannot take hormones
Reduced menstrual blood loss	LNG-IUD: dramatically reduces menstrual flow (80–90% reduction) — used for heavy menstrual bleeding treatment
Cost-effective	High upfront cost offset by 5–10 years of use — extremely cost-effective long-term
Suitable post-partum	Copper IUD can be inserted immediately post-delivery or post-abortion
Breastfeeding compatible	LNG-IUD: very small systemic LNG levels; compatible with breastfeeding (unlike combined oral pills)
Therapeutic applications	LNG-IUD treats: Heavy menstrual bleeding, dysmenorrhea, endometriosis, endometrial hyperplasia

Disadvantages

Disadvantage	Explanation
Requires trained insertion	Must be inserted by a trained healthcare provider — cannot self-insert
Insertion discomfort	Cramping and pain during insertion; cervical dilation may be needed in nulliparous women
Expulsion risk	2–10% IUDs spontaneously expelled, especially in the first year; more common in younger women
Infection risk (PID)	Risk of pelvic inflammatory disease (PID) mainly within first 3 weeks of insertion; screen for STIs beforehand

Ectopic pregnancy risk	If contraceptive fails, ectopic pregnancy risk higher (though absolute ectopic risk is very low)
Uterine perforation	Rare (1 in 1000 insertions) but serious complication during insertion
Changed menstrual pattern	Cu-IUD: heavier, longer, more painful periods (especially first 3–6 months)
Hormonal side effects (LNG-IUD)	Irregular spotting (first 3–6 months), acne, mood changes, headache in some women
Amenorrhea (LNG-IUD)	LNG-IUD may cause absence of periods — though medically safe, distressing to some women
STI non-protection	IUD does not protect against sexually transmitted infections
String complications	IUD strings may cause partner discomfort during intercourse; strings may not be visible at follow-up
Not suitable for all	Contraindicated in: Unexplained vaginal bleeding, uterine abnormalities, current STI/PID, pregnancy, uterine fibroids distorting cavity

Development of Intrauterine Devices — History and Types

First Generation IUDs (1960s) — Inert Plastic

- First widely used IUDs were made of inert plastic (polyethylene) with no pharmacological action.
- **Lippes Loop:** Invented by Jack Lippes (1962). Double-S shaped polyethylene device. Available in 4 sizes (A, B, C, D). Mechanical distortion of uterine cavity → inhibits implantation. Now largely replaced by copper IUDs.
- **Saf-T-Coil (Margulies Spiral):** Early 1960s; inert plastic. Moderate efficacy; replaced by later generations.
- Limitations: Moderate efficacy; heavy bleeding; painful periods; high expulsion rate compared to modern IUDs.

Second Generation IUDs (1970s) — Copper-Bearing

- Addition of copper wire/copper sleeves dramatically improved contraceptive efficacy and allowed smaller device sizes.
- **T-Cu 200 (1969):** First copper IUD by Zipper and Tatum. Copper wire on T-stem (200 mm² surface area). 4–5 year duration.
- **T-Cu 380A (Paragard — 1988 US approval):** T-shaped polyethylene with 314 mm² copper wire on stem + 33 mm² copper sleeves on each arm = 380 mm² total copper. Most studied copper IUD. 10-year approved duration (can last 12+ years). Non-hormonal. Also most effective post-coital contraceptive.
- **Multiload (MLCu-375):** Anchor-shaped; 375 mm² copper; used in Europe and Asia.
- **Nova T Cu 200Ag:** Silver-core copper wire (prevents fragmentation of copper over time).

Third Generation IUDs (1976–present) — Hormonal / Progestin-Releasing

Progestasert (1976)

- **Drug:** Natural progesterone (38 mg).
- **Release rate:** 65 µg/day.
- **Duration:** 1 year only (short due to rapid progesterone depletion).
- **Device:** T-shaped; silicone oil + progesterone core in ethylene/vinyl acetate tube.
- **Significance:** First hormonal IUD; proved feasibility of sustained uterine drug release.
- **Withdrawal:** Discontinued due to short duration and higher ectopic pregnancy rates.

Mirena (LNG-IUS — Levonorgestrel Intrauterine System)

Mirena (Bayer) is the most successful hormonal IUD globally. It delivers levonorgestrel (LNG) — a synthetic progestogen — directly to the uterine cavity at a precisely controlled rate.

Parameter	Details
Drug	Levonorgestrel (LNG) — synthetic progestogen
Total drug load	52 mg LNG in polydimethylsiloxane (PDMS) reservoir cylinder
Release membrane	Polydimethylsiloxane membrane on cylinder surface — rate-controlling
Initial release rate	20 µg/day (first year); declines to ~10 µg/day by year 5
Duration of action	5 years (FDA approved); 8 years in some guidelines
Systemic LNG levels	Very low — ~150 pg/mL plasma LNG (vs 1500–2500 pg/mL with oral LNG pills)
Contraceptive effectiveness	99.8% (Pearl Index 0.1–0.2)
FDA-approved indications	Contraception + treatment of heavy menstrual bleeding (menorrhagia) — US (2009)
Device material	Polyethylene T-frame; radiopaque barium sulfate core for X-ray visibility
Insertion	By trained provider; cervical local anesthetic may be used; takes < 5 minutes

Other Hormonal IUDs

Device	Drug	Dose/Day	Duration	Feature
Kyleena	LNG	17.5 mg (initial 9 µg/day → 5 µg/day)	5 years	Smaller frame — better for nulliparous; lower LNG dose

Liletta	LNG	52 mg (initial 18.6 µg/day)	8 years	Lower cost; approved for extended 8-year use
Skyla	LNG	13.5 mg (initial 14 µg/day)	3 years	Smallest LNG-IUD; designed for young/nulliparous women
Jaydess (EU)	LNG	13.5 mg	3 years	European equivalent of Skyla
Progestasert (hist.)	Progesterone	38 mg (65 µg/day)	1 year	First hormonal IUD; withdrawn

Mechanisms of Action of IUDs

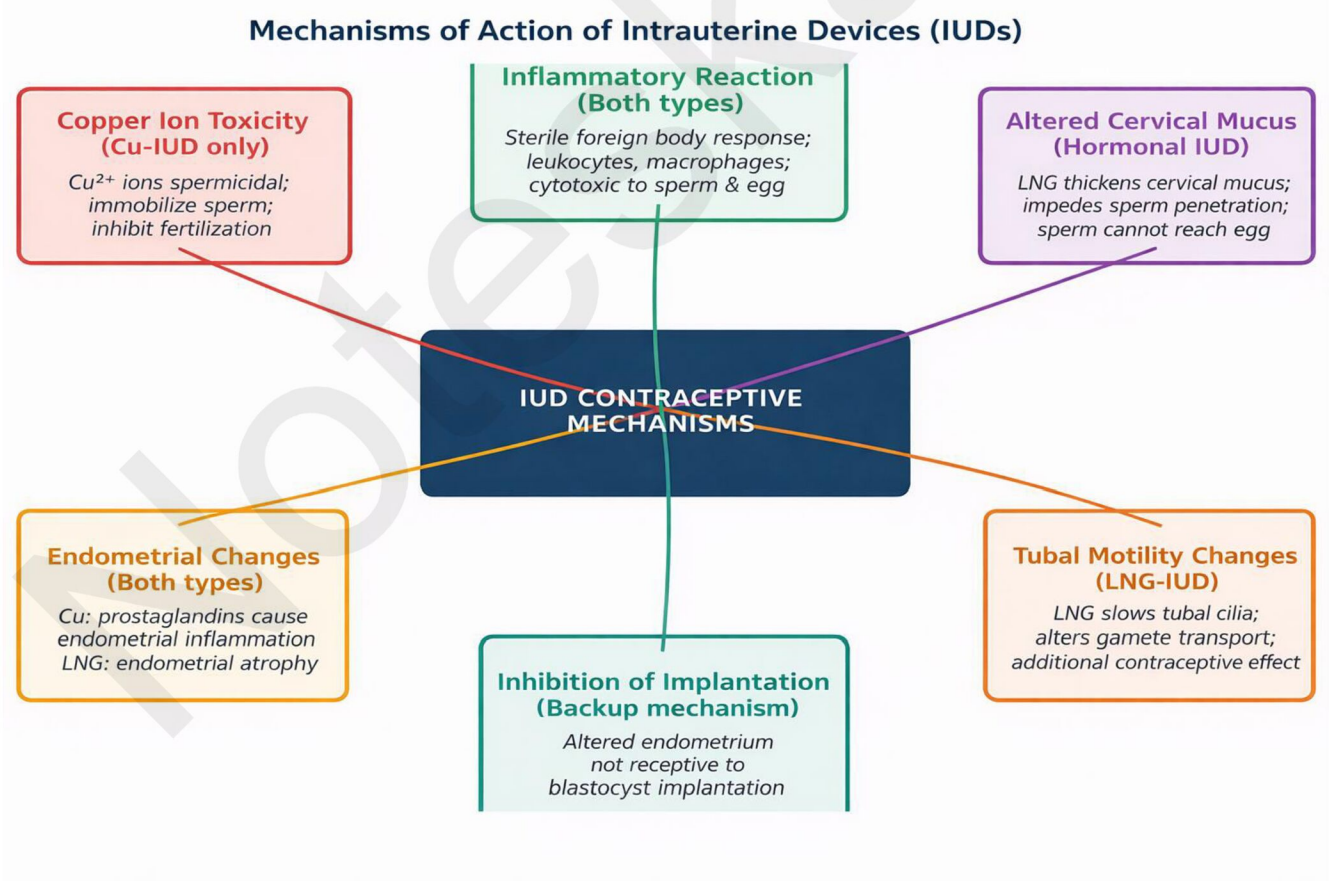

Figure 8: Six Mechanisms of Contraceptive Action of Intrauterine Devices (IUDs)

Copper IUD (T-Cu 380A) Mechanisms

- **Copper ion (Cu^{2+}) spermicidal action (Primary):** Cu^{2+} ions released into uterine fluid → toxic to sperm. Cu^{2+} immobilizes sperm (impairs motility), alters acrosome reaction, and inhibits enzymes needed for fertilization. Primary contraceptive mechanism.
- **Sterile foreign body inflammatory reaction:** IUD presence triggers local leukocyte infiltration → phagocytosis of sperm and ova. Prostaglandins released → altered endometrial environment hostile to implantation.
- **Altered endometrium:** Endometrial inflammation → prostaglandin release → altered endometrial receptivity → even if fertilization occurs, implantation is prevented (backup mechanism).
- **As emergency contraceptive:** Copper IUD inserted within 5 days of unprotected intercourse → Cu^{2+} + endometrial effects prevent fertilization or implantation. Most effective emergency contraceptive (failure rate < 0.1%).

Hormonal IUD (Mirena/LNG-IUS) Mechanisms

- **Thickening of cervical mucus (Primary — LNG specific):** LNG suppresses estrogen-dependent cervical mucus production → thick, impenetrable cervical mucus → sperm cannot enter uterine cavity.
- **Endometrial atrophy:** LNG causes progressive endometrial thinning (atrophy) → decidualization → endometrium not receptive to implantation → reduced menstrual bleeding (basis for HMB treatment).
- **Suppression of ovulation (partial):** Not reliable ovulation suppression — systemic LNG levels too low for consistent ovulatory inhibition (unlike oral pills). Approximately 50% of cycles are ovulatory.
- **Altered tubal motility:** LNG affects ciliary movement in fallopian tubes → altered gamete transport.
- **Sperm function:** Local LNG may impair sperm capacitation within uterine cavity.

Applications of Intrauterine Drug Delivery Systems

Contraception

IUD Type	Device	Effectiveness	Duration
Copper IUD	Paragard T380A	99.2% (Pearl Index 0.6–0.8)	10 years (most effective EC)
Hormonal IUD (High dose)	Mirena, Liletta	99.8% (Pearl Index 0.1–0.2)	5–8 years
Hormonal IUD (Low dose)	Kyleena, Skyla	99.7%	3–5 years
Post-coital (Emergency)	Cu-IUD T380A	> 99.9% if inserted ≤ 5 days	Also provides long-term contraception after

Treatment of Heavy Menstrual Bleeding (HMB / Menorrhagia)

- Mirena (LNG 20 µg/day) FDA-approved for HMB (2009) — reduces menstrual blood loss by 80–97%.

- Mechanism: LNG causes endometrial atrophy → fewer blood vessels → lighter periods.
- Alternative to: Oral tranexamic acid, NSAIDs, combined oral contraceptives, and even hysterectomy.
- Clinical evidence: Mirena as effective as endometrial ablation for HMB at 5-year follow-up.
- **NICE Guideline:** LNG-IUS recommended as first-line medical treatment for HMB before surgical options.

Dysmenorrhea (Painful Menstruation)

- LNG-IUD reduces endometrial prostaglandins → reduced uterine contractions → less primary dysmenorrhea.
- Significant reduction in menstrual pain scores reported in clinical trials.

Endometriosis

- LNG-IUS used as off-label treatment for endometriosis-associated pain.
- Local high LNG concentration causes endometrial atrophy → reduces ectopic endometrial tissue activity.
- Reduces dyspareunia, pelvic pain, and dysmenorrhea in endometriosis patients.

Endometrial Hyperplasia and Prevention

- LNG-IUS treats non-atypical endometrial hyperplasia (precancerous condition) — regression rate > 90%.
- Used in: Women on estrogen therapy (HRT) for endometrial protection.
- WHO-recommended: LNG-IUS for endometrial protection in women receiving systemic estrogen.

Non-Contraceptive Medical Uses Summary

Indication	Device	Evidence Level
Heavy menstrual bleeding (HMB)	Mirena LNG 52 mg	FDA-approved (2009); Level 1 evidence
Endometriosis pain	LNG-IUD (Mirena)	Off-label; clinical evidence Level 2
Primary dysmenorrhea	LNG-IUD	Clinical evidence; not formally approved
Endometrial hyperplasia (non-atypical)	LNG-IUD	WHO/RCOG recommended; Level 2
Endometrial protection during HRT	LNG-IUD	Alternative to oral progestogen; Level 1
Postmenopausal hormone therapy	Mirena + estrogen patch	Off-label; evidence-based in practice
Uterine fibroids (small)	LNG-IUD	Reduces associated bleeding; not curative
Adenomyosis	LNG-IUD	Reduces pain and bleeding; off-label

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