Ocular Drug Delivery System

The eye is a unique and precious organ. It is considered as the window of the soul. There are many eye ailments which affect this organ and one can loss the eye sight also. Therefore many ophthalmic drug delivery systems are available.

Ocular Drug Delivery System: Pharmaceutical preparation that are applied topically to the eye for the treatment of surface and intra ocular dysfunction are called ocular drug delivery system.

These are classified as conventional and newer drug delivery systems. Most commonly available ophthalmic preparations are eye drops and ointments, used topically rather systemically.

These dosage forms are easy to instill but suffer from the inherent drawback that the majority of the medication is immediately diluted in the tear film as soon as the eye drop solution is instilled and is rapidly drained away from the precorneal cavity by constant tear flow and lacrimo-nasal drainage.

Therefore, the target tissue absorbs a very small fraction of the instilled dose.

Limitations of topical and intravitreal route of administration have challenged scientists to find alternative mode of administration like periocular routes. Transporter targeted drug delivery has generated a great deal of interest in the field because of its potential to overcome many barriers associated with current therapy.

Application of nanotechnology or several ocular drug delivery systems like - microemulsions, nanosuspensions, nanoparticles, liposomes, niosomes, dendrimers, implants, and hydrogels are emerged as novel drug delivery systems for the eye.

Advantages of Ocular Drug Delivery Systems

1. Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.

2. To provide sustained and controlled drug delivery.

3. To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.

4. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.

5. To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.

6. To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.

7. To provide better housing of delivery system.

Limitations of Ophthalmic Drug Delivery:

1. Dosage form cannot be terminated during emergency.

2. Interference with vision.

3. Difficulty in placement and removal.

4. Occasional loss during sleep or while rubbing eyes.

Despite these limitations, significant improvements in ocular drug delivery have been made. The improvements have been with objective of maintaining the drug in the bio-phase for an extended period.

The anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances.

Anatomy and Routes of Delivery of the eye

Drug delivery to the eye can be broadly classified into anterior and posterior segments:

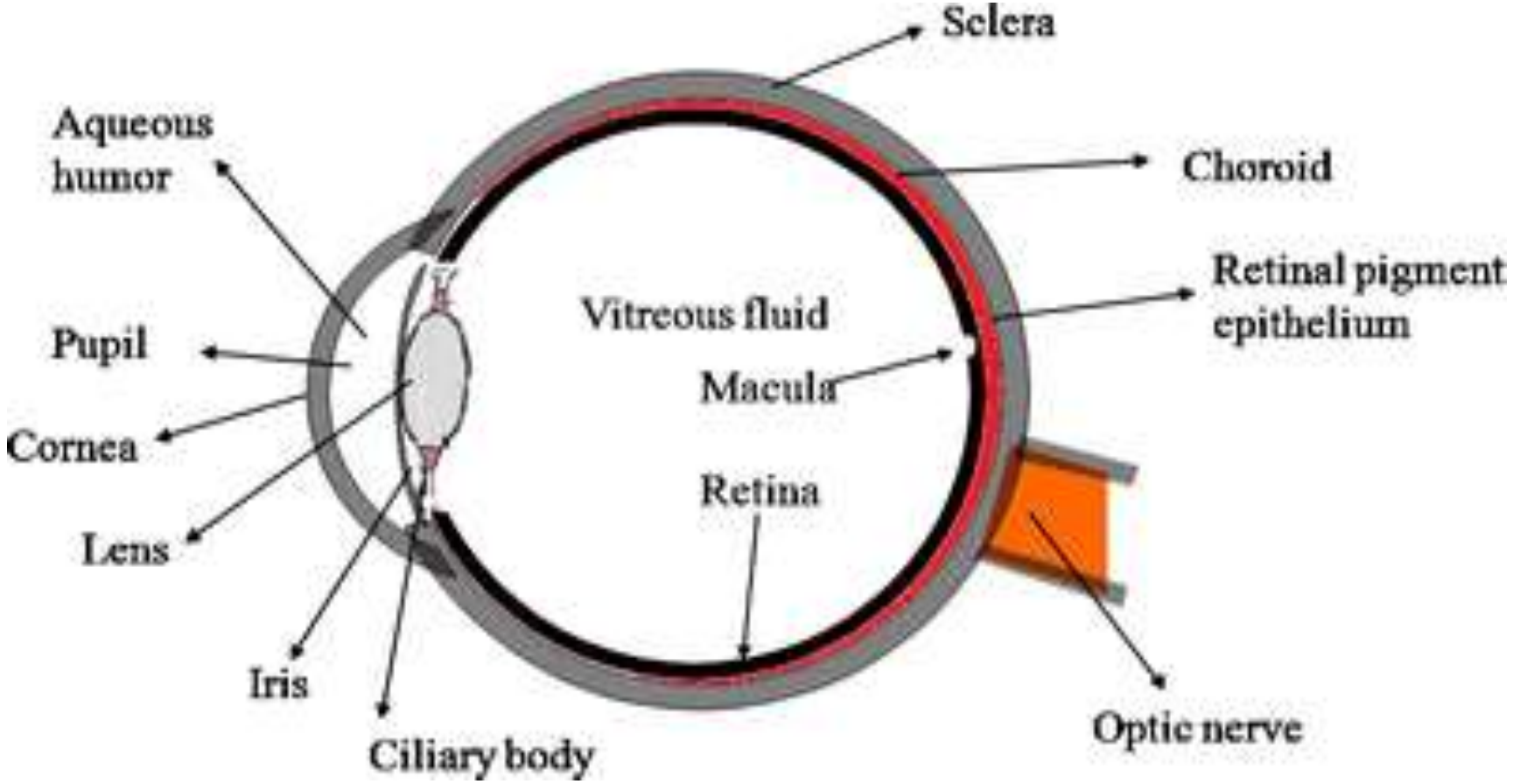


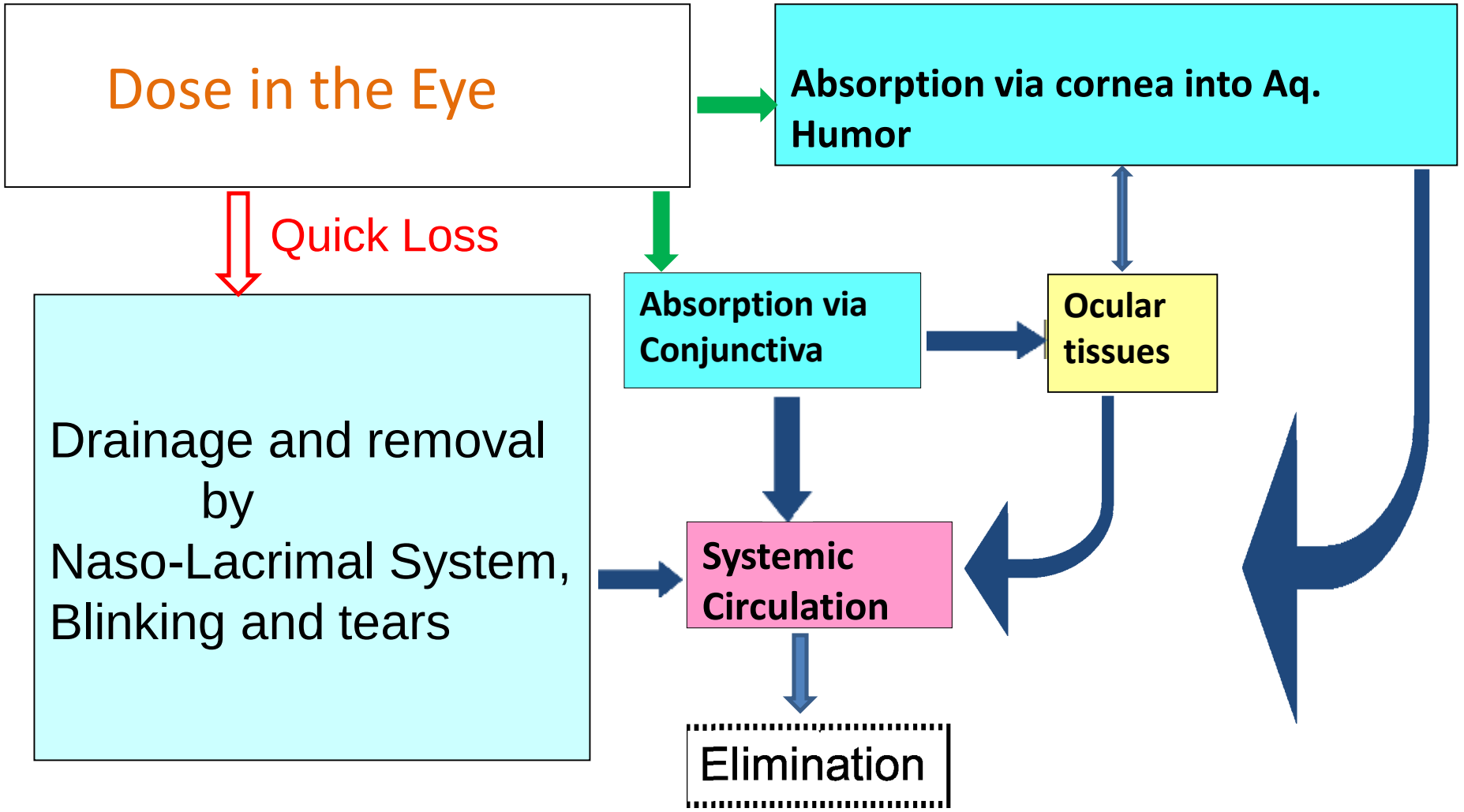
Figure 1 : **Structure of the eye**

Anterior segment consists of front one third of eye that mainly includes pupil, cornea, iris, ciliary body, aqueous humor, and lens (Fig 1).

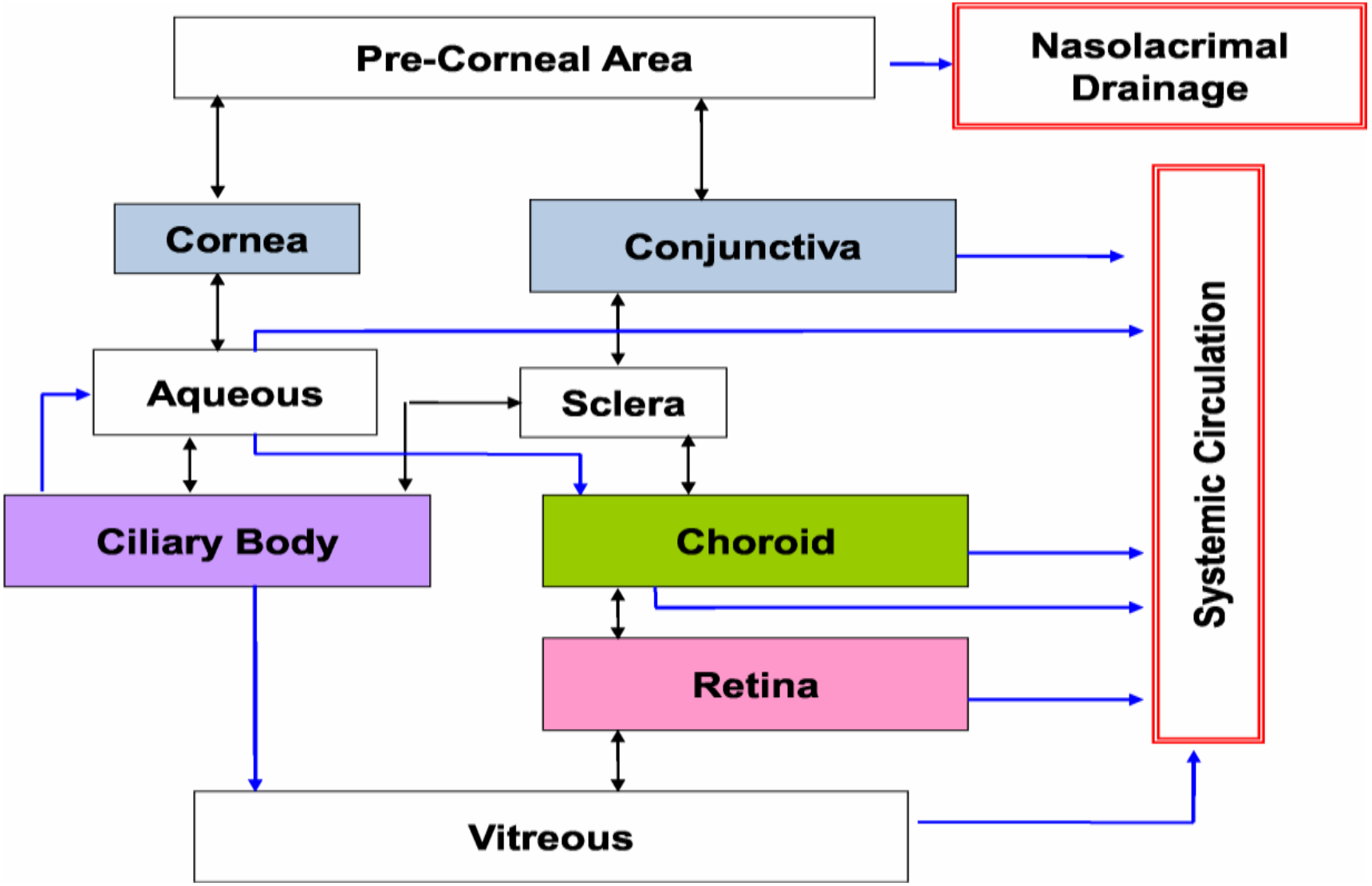
The posterior segment consists of the back two thirds of the eye that includes vitreous humor, retina, choroid, macula, and optic nerve (Fig 1).

Anterior Segments:	Posterior Segments:
Cornea	**Vitreous**
Pupil	**Retina**
Aqueous Humor	**Macula**
Irish	**Choroid**
Lens	**Sclera**
Ciliary body	**Optical Nerve.**

Drug Delivery to the Front of the Eye (Topical)



Drug Delivery to Front and Back of the Eye



Ocular Drug Design and Delivery: Challenges

For the therapeutic treatment of most ocular problems, topical administration is the preferred route. But it needs frequent dosing. For systemically administered drugs, only a very small fraction of the total dose reach the eye from the general circulatory system.

Problems with Delivery of Drugs:

- Rapid drain out of the drug from the precorneal cavity by constant tear flow and lacrimo-nasal drainage.

- Blood-retinal barrier (BRB) prevents high concentrations of drugs passage from the blood stream.
- Most agents injected into the vitreous are cleared rapidly and are therefore ineffective.
- Effective dose often toxic.
- Subconjunctival and intravitreal injections carry a risk of infection.

Enhancement in Bioavailability

Topical bioavailability can be improved by maximizing precorneal drug absorption and minimizing precorneal drug loss.

1. Viscosity improver:

In order to prolong precorneal residence time and to improve bioavailability, attempts were made to increase the viscosity of the formulation.

The viscosity enhancers used were hydrophilic polymers such as cellulose, polyalcohol and polyacrylic acid, Sodium carboxy methyl cellulose etc.

2. Gels :

Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers. So the dosing frequency can be decreased to once a day.

Cellulose acetate phthalate dispersion constituted a micro-reservoir system of high viscosity.

3. Penetration enhancers:

They act by increasing corneal uptake by modifying the integrity of comeal epithelium.

Chelating agents, preservatives, surfactants and bile salts were studied as possible penetration enhancers. But the effort was diminished due to the local toxicity associated with enhancers.

4. Prodrugs:

Prodrugs enhance corneal drug permeability through modification of the hydrophilic or lipophilicity of the drug. The method includes modification of chemical structure of the drug molecule, thus making it selective, site specific and a safe ocular drug delivery system.

Drugs with increased penetrability through prodrug formulations are - epinehrine, phenylephrine, timolol, pilocarpine and albuterol.

5. Cyclodextrins:

Cyclodextrins act as carriers by keeping the hydrophobic drug molecules in solution and delivering them to the surface of the biological membrane, where the relatively lipophilic membrane has a much lower affinity for the hydrophilic cyclodextrin molecules.

Optimum bioavailability can be achieved when just enough cyclodextrin (<15%) is added to the aqueous eye.

6. Bioadhesive polymers:

The bioadhesive polymers adhere to the mucin coat covering the conjunctiva and the corneal surfaces of the eye, thus prolonging the residence time of a drug in the conjunctival sac. These polymers can be neutral, synthetic or semi synthetic.

Polyacrylic acid, polycarbophil and hyaluronic acid are commonly used synthetic polymers.

NOVEL OCULAR DRUG DELIVERY SYSTEMS

One has to understand the physiological and biochemical factors involved in normal and pathological conditions for designing a successful ocular drug delivery system.

An ideal therapy requires selectively targeting of active agent to various diseases like CNV (cytomegalovirus), diabetic retinopathy and solid tumors in the eye.

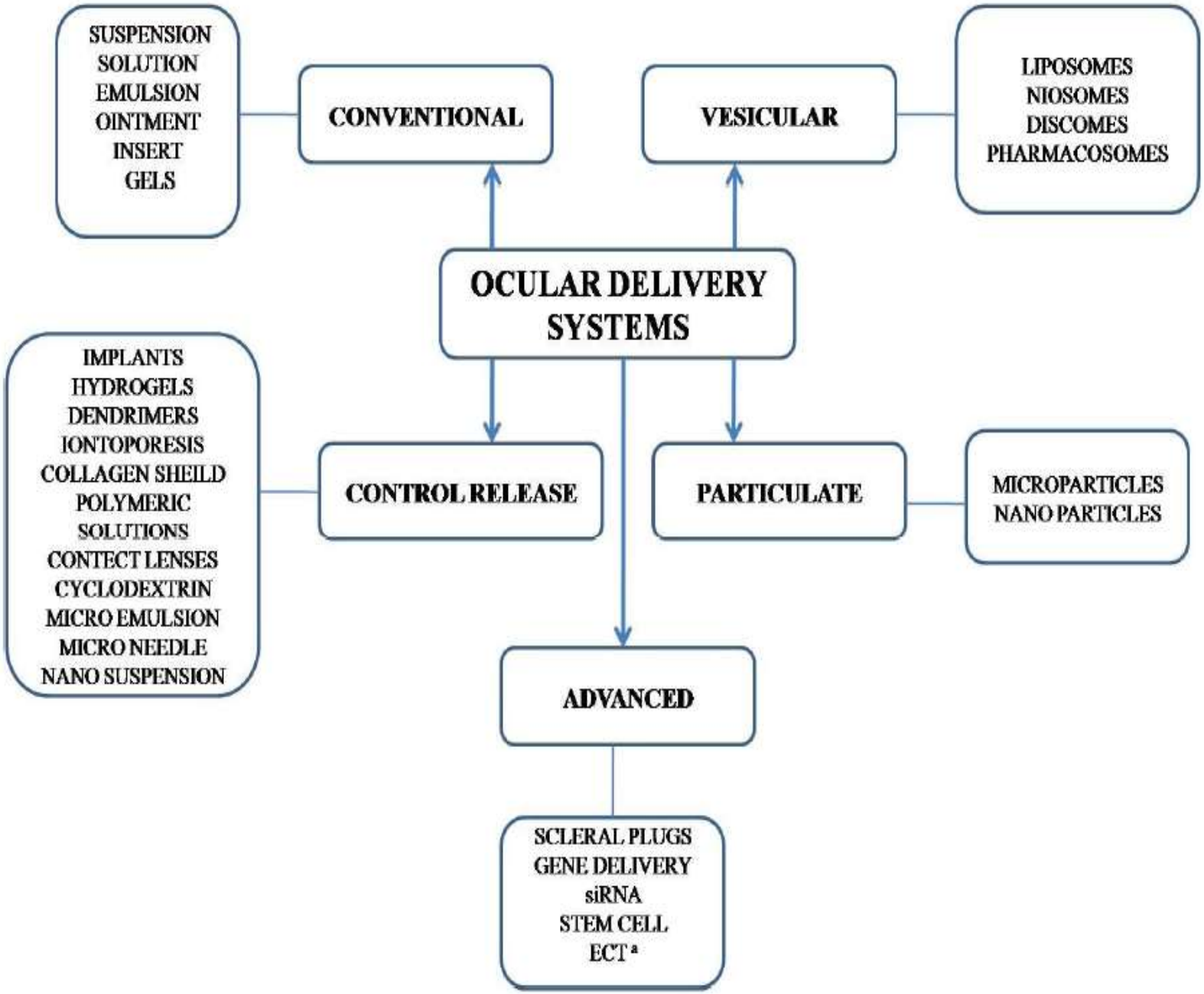


Fig: Types of Ocular Drug Delivery System

CONVENTIONAL DELIVERY SYSTEMS

Eye Drops:

Drugs which are **active** at eye or eye surface are widely administered.

Form : ***Solutions, Emulsion and Suspension***.

Used for: **Anterior Segment Disorders**

Influence on Retention on Eye:

Hydrogen ion concentration,
Osmolality,
Viscosity and Instilled Volume.

Absorbed to the systemic blood:

via the conjunctival and nasal blood vessels.

Ocular absorption: **by the corneal epithelium (limited)**

Less than 5 Percent of the dose is absorbed after topical administration. Maximal attainable ocular absorption is only about 10 Percent of the dose.

CONVENTIONAL ...

Ointment and Gels:

Ointment Advantage:
Prolongation of drug contact time using ophthalmic ointment vehicle.
Drawback: blurring of vision and matting of eyelids can limits its use.

Gel Advantage:
Provide sustain action over a period of 24 hours. Ex-Pilopine HS.

Reported: ointments and gels vehicles can prolong the corneal contact time of many drugs administered by topical ocular route, thus prolonging duration of action and enhancing ocular bioavailability of drugs.

CONVENTIONAL ...

Insert:

Inserts are available in different varieties depending upon their composition and applications.

Ocusert:

Ocular insert are sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage.

Lacrisert :

Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca, act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea.

VESICULAR DELIVERY SYSTEM

Liposomes:

Biocompatible and Biodegradable lipid vesicles made up of natural lipids.
Diameter: 25–10 000 nm.

Mechanism: Having an **intimate contact** with the **corneal and conjunctival** surfaces and thus **increases the probability** of ocular drug **absorption**.
Used mainly for:
Drugs that are **poorly absorbed**,
Drugs with **low partition coefficient**,
poor solubility or those with **medium to high molecular weights.**

The corneal epithelium is thinly coated with negatively charged mucin to which the positive charged surface of the liposomes may bind.

VESICULAR …

Niosomes and Discomes:

Major limitations of Liposomes:
Chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids.

Properties of Niosomes:
1. **Chemically stable** as compared to liposomes and
2. Can **entrap both** hydrophobic and hydrophilic drugs.
3. They are **non toxic** and
4. Do **not** require **special handling** techniques.
5. Niosomes are **nonionic surfactant** vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs.

Reported: There was about **2.49 times** increase in the ocular bioavailability of **timolol maleate encapsulated in niosome** as compared to **timolol maleate solution.**

VESICULAR …

Non-ionic

Surface active agents based **discoidal vesicles** known as **(discomes)** loaded with **timolol maleate** were formulated and characterized for their in vivo parameters.

In vivo studies showed that **discomes released** the contents in a **biphasic profile** if the drug was loaded using a pH gradient technique.

Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the **ocular site.**

Pharmacosomes:

Pure drug vesicles formed by the amphiphilic drugs.

Any drug possessing a **free carboxyl group** or an **active hydrogen atom** can be **esterified** (with or without a spacer group) to the **hydroxyl group** of a lipid molecule, thus generating an **amphiphilic prodrug.**

The **amphiphilic prodrug is converted to pharmacosomes** on dilution with water.
The pharmacosomes show **greater shelf stability**, **facilitated transport across the cornea**, and **a controlled release profile**.

CONTROL DELIVERY SYSTEMS

Implants:

Implants are effective against:

Chronic ocular diseases like cytomegalovirus (CMV) retinitis.

Advantage:

Earlier non biodegradable polymers were used but they needed surgical procedures for insertion and removal.

Presently biodegradable polymers such as **Poly Lactic Acid (PLA)** are ***safe and effective*** to deliver drugs in the vitreous cavity and ***show no toxic signs***.

Intravitreal implants of ***fluocinolone acetonide*** were developed for the treatment of ***posterior segment*** and reported to ***control the ocular inflammation*** of retina.

CONTROL ...

Iontophoresis:

In Iontophoresis **direct current drivesions** into cells or tissues.

For iontophoresis the ions of importance **should be charged molecules** of the drug.Positively chargedof drug are driven into the tissues at the anode and vice versa.

Advantage:
Ocular iontophoresis delivery is not only **fast, painless and safe** but it can also deliver high concentration of the drug to a **specific site**. Iontophoretic application of antibiotics in eye not only increases their **bactericidal activity** but also **reduce the severity of disease**. Similarly application of anti-inflammatory agents can **reduce vision threatening side effects.**

CONTROL ...

Dendrimer:

Dendrimers can successfully used for **different routes of drug administration** and have **better water-solubility, bioavailability and biocompatibility.**

Report:

Vandamme and co workers have developed and evaluated poly (amidoamine) dendrimers containing fluorescein for controlled ocular drug delivery. They determined **the influence of size, molecular weight and number of amine, carboxylate and hydroxyl surface groups** in several series of dendrimers.

The **residence time was longer** for the solutions containing dendrimers with **carboxylic and hydroxyl surface groups.**

CONTROL ...

Cyclodextrin:

Cyclodextrins (CDs) are cyclic **oligosaccharides** capable of **forming inclusion complexes with many guest molecules**.

CD complexes are reported to **increase corneal permeation** of drugs like **dexamethasone, dexamethasone acetate, cyclosporine and pilocarpine** resulted in **higher bioavailability** than the conventional eye drops.

This complexation of CD **does not interrupt the biological membrane** compared to conventional **permeation enhancer** like **benzalkonium chloride**.

Due to inclusion, the **free drug is not available**, so drugs with inherent irritant properties can be successfully delivered by this approach.

CD molecules are inert in nature and were found to be **non irritant** to the human and animal eye.

CONTROL …

Contact lenses:

Water soluble drugs soaked in drug solutions **can be absorbed** through Contact lenses.

The drug saturated contact lenses are placed in the eye which releases the drug in eye for **a long period of time**.

For prolongation of ocular residence time of the drugs, **hydrophilic contact lenses** can be used.

Greater penetration of **fluorescein** has been reported by ***Bionite lens*** made from **hydrophilic polymer (2-hydroxy ethyl methacrylate)** in human.

CONTROL ...

Collagen Shield:

Consist of –

Cross linked collagen,

fabricated with foetal-calf skin tissue and

developed as a corneal bandage to promote wound healing

Topically applied **antibiotic conjugated with the shield** is used to promote **healing of corneal ulcers.**

Because of its **structural stability, good biocompatibility and biological inertness**, collagen film proved as **a potential carrier** for ophthalmic drug delivery system.

Collagen ophthalmic inserts are available for delivery of **pilocarpine** to the eye.

CONTROL ...

Microemulsion:

Microemulsion is **dispersion of water and oil** stabilized using **surfactant and co-surfactant** to **reduce interfacial tension** and usually characterized by small droplet size (100 nm), **higher thermodynamic stability** and **clear appearance.**

Selection of aqueous phase, organic phase and surfactant/co-surfactant systems are critical parameters which can affect stability of the system.

Optimization of these components results in significant **improvement in solubility** of the drug molecule **e.g. indomethacin, chloramphenicol** for eye diseases.

CONTROL ...

Nanosuspensions:

Nanosuspensions have emerged as a promising strategy for the **efficient delivery of hydrophobic drugs** because they **enhanced** not only the **rate and extent of ophthalmic drug absorption** but also the **intensity of drug action** with significant **extended duration of drug effect**.

For commercial preparation of nanosuspensions, techniques like ***media milling and high-pressure homogenization*** have been used.

Report:
The higher drug level in the aqueous humour was reported using **Eudragit RS100 nanosuspensions** for the ophthalmic controlled delivery of **ibuprofen.**

CONTROL ...

Microneedle:

As an **alternative to topical route** Researchers have developed microneedle to deliver drug to posterior segment.

Report:
The extent **of lateral and transverse diffusion of sulforhodamine** was reported to be **similar** across human cadaver sclera.

Microneedle had shown prominent **in vitro penetration into sclera** and **rapid dissolution of coating solution** after insertion while in vivo drug level was found to be significantly higher than the level observed following topical drug administration like **pilocarpine.**

CONTROL ...

Prodrugs:

Ideal Prodrugs for ocular therapy:

- **Increased lipophilicity** and a **high partition coefficient**,
- **High enzyme susceptibility** to such an extent that after corneal penetration or within the cornea,
- Chemically or enzymatically **metabolized to the active** parent compound.

Example:

The partition coefficient of **ganciclovir** found to be increased using an **acyl ester prodrug**, with substantially increased the amount of drug penetration to the cornea which is due to increased susceptibility of the ganciclovir esters to undergo hydrolysis by esterases in the cornea.

CONTROL ...

Penetration Enhancers:

Transport of drug across the cornea is increased **by increasing the permeability** through **corneal epithelial membranes**.

Examples –
Actin filament inhibitors, Surfactants, Bile salts, Chelators, and Organic compounds.

Selection of enhancer is critical due to unique characteristics and great sensitivity of the corneal conjunctival tissues.

Limitations:
Penetration enhancers themselves **can penetrate the eye and may lead to unknown toxicological complications** e.g., **benzalkonium chloride (BAC)** was found to accumulate in the cornea for days.

CONTROL ...

Mucoadhesive Polymers:

They are ***basically*** **macromolecular hydrocolloids** with **plentiful hydrophilic functional groups**, such as **hydroxyl, carboxyl, amide and sulphate** having capability for establishing electrostatic interactions.

A mucoadhesive drug formulation for the **treatment of glaucoma** was developed using a highly potent **beta blocker drug, levobetaxolol (LB) hydrochloride** and **partially neutralized poly acrylic acid (PAA).**

CONTROL ...

Phase Transition Systems/ In situ gel system:

Phase transition of the formulation from the **liquid form to the gel or solid** phase occurs when these systems **instilled into the cul-de-sac of eye** lead to **increase the viscosity** of a drug formulation in the **precorneal region** results in **increased bioavailability**, due to **slower drainage** from the cornea.

Systems can be influenced by-

pH,

temperature or

by ion activation.

CONTROL ...

pH: In this method gelling of the solution is triggered by a change in the pH. CAP latex cross linked polyacrylic acid and derivatives such as carbomers are used. They are low viscosity polymeric dispersion in water which undergoes spontaneous coagulation and gelation after instillation in the conjunctival cul-de-sac.

Temperature: In this method gelling of the solution is triggered by change in the temperature. Sustained drug delivery can be achieved by the use of a polymer that changes from solution to gel at the temperature of the eye.

Ionic strength: In this method gelling of the solution instilled is triggered by the change in the ionic strength.

Example: *Gelrite* is a polysaccharide, low acetyl gellan gum, which forms a clear gel in the presence of mono or divalent cations. The concentration of sodium in human tears is 2.6 g/l is particularly suitable to cause gelation of the material when topically installed into the conjunctival sac.

PARTICULATES
(NANOPARTICLES AND MICROPARTICLES)

Maximum size limit : **about 5-10 mm**
(which a scratching feeling in the eye can result upon ocular instillation)
So, **microspheres and nanoparticles** are promising **drug carriers** for ophthalmic application.

Nanoparticles are prepared using **bioadhesive polymers** to provide **sustained effect** to the entrapped drugs.

Example:
Poly butyl cyanoacrylate nanoparticles, containing **pilocarpine into collagen shields**, showed **greater retention and activity** characteristics with respect to the controls.

Made up of-
Poly lactic acid (PLA) coated with Poly Ethylene Glycol(PEG) shown better efficacy compared to conventional dosage form of Acyclovir for the treatment of ocular ***viral infections.***

ADVANCED DELIVERY SYSTEM

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). Which enables the ***controlled, continuous, and long-term delivery*** of therapeutic proteins directly to the **posterior regions** of the eye.

ECT can potentially serve as a delivery system for chronic ***ophthalmic diseases*** like **neuroprotection in glaucoma**, **anti-angiogenesis in choroidal neovascularization**, and **anti-inflammatory factors for uveitis.**

ADVANCED ...

Gene Therapy:

Gene therapy approaches stand on the **front line** of advanced biomedical research to treat blindness arising from corneal.

Several kinds of viruses including **adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus,** have been manipulated for use in gene transfer and gene therapy applications.

Topical delivery to the eye is the most expedient way of ocular gene delivery.

However, the challenge of obtaining substantial gene expression following topical administration has led to the **prevalence of invasive ocular administration.**

Retroviral vectors have been **widely used** due to their **high efficacy**; however, they do not have the ability to transduce nondividing cells, leads to restrict their clinical use. The advanced delivery systems that **prolong the contact time** of the vector with the surface of the eye **may enhance transgene expression**, thereby **facilitate non-invasive administration.**

ADVANCED …

Stem cell Therapy:

Emerging cell therapies for the restoration of sight have focused on ***two areas*** of the eye that are critical for visual function, the **cornea** and the **retina**.

Most successful ocular application:

Use of ***limbal stem cells***, 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 (recently) **cells grown in culture**.

Stem-cell Therapy has demonstrated **great success** for certain ***maladies of the anterior segment.***

ADVANCED ...

Protein and Peptide therapy:

Delivery of therapeutic proteins/ peptides has **received a great attention** over the last few years.
The intravitreous injection of ranibizumab is one such example.

The **designing** of optimized methods for the sustained delivery of proteins and to **predict the clinical effects** of new compounds to be administered in the eye, the **basic knowledge of Protein and Peptide** is required.

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.**

Immunoglobulin G has been effectively delivered to **retina by transscleral route** with **insignificant systemic absorption**.

ADVANCED ...

Scleral Plug therapy:

Implantation Area: **pars plana region of eye** (simple procedure)

Made of-

Biodegradable polymers and drugs.

Meachanism:
Gradually releases effective 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.

Effective Against:
Vitreoretinal diseases such as proliferative vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections, for vitreoretinal disorders that require vitrectomy.

ADVANCED ...

siRNA therapy:

Promising approach-

For various angiogenesis-related diseases.

Treatment:

1.Choroidal neovascularization

(siRNA directed against vascular endothelial growth factor (VEGF) or VEGF receptor 1 (VEGFR1), and both)

2.siRNA has potential role of ***various genes in ocular disease.***

3.siRNAs may be valuable in the **pathogenesis and development** of new treatments for **several ocular diseases.**

4.Use in unresolved difficulties in **targeting delivery** of the siRNA to the **tumor cells.**

New encapsulated siRNA have been developed using liposomes, coupled-antibodies or others polymer vesicles.

ADVANCED …

Oligonucliotide therapy:

Principle:

Blocking the synthesis of cellular proteins by interfering with either the **transcription of DNA to mRNA** or the **translation of mRNA** to proteins.

Among several mechanisms by which antisense molecules disrupt gene expression and inhibit protein synthesis, the ribo-nuclease H mechanisms are the most important.

Factors:

1. Length of the ON species. *Lengths of 17–25 bases have been shown to be optimal.*
2. Biological stability is the major barrier when delivering both DNA and RNA oligonucleotides to cells.

Protection from nuclease action has been achieved by modification of phosphate backbones, sugar moiety, and bases

ADVANCED ...

Aptamer:

Aptamers are **oligonucleotide ligands.**

Used for-
High-affinity binding to molecular targets.

Mechanism:
They are isolated from complex libraries of synthetic nucleic acid by an iterative process of **adsorption**, **recovery**, and **reamplification.**
They ***bind*** with the target molecules at a ***very low level*** with ***high specificity.***

Example:
One of the earliest aptamers studied structurally was the **15 mer DNA aptamer** against **thrombin, d(GGTTGGTGTGGTTGG).**

ADVANCED ...

Ribozyme therapy:

RNA enzymes or ribozymes are capable of assuming three dimensional conformations and **exhibiting catalytic activity** that induces **site-specific cleavage**, **ligation**, and **polymerization** of nucleotides involving RNA or DNA.

Function:
By binding to the **target RNA** moiety through **Watson-Crick base pairing** and **inactivate** it by **cleaving the phosphodiester backbone** at a specific cutting site.

Ribozyme therapy is promising in **autosomal dominant eye diseases**, including ***glaucoma***.


Thank You!