CHAPTER-1

Introduction
INTRODUCTION

1.1 ANATOMY AND PHYSIOLOGY OF THE EYE\textsuperscript{1,2,3,4,5,6}:

Eyes are most marvelous of the sense organs as they make us aware of various objects all around us, nearly and far away. Eyes are nearly spherical in shape except that its front portion i.e., transparent cornea bulges a bit forward. The eye is protected by the eyelashes, eyelids, tears and blinking. The eyelashes catch foreign materials as the blink reflex prevents injury by closing the lids, blinking occurs frequently during waking hours to keep the corneal surface free of mucous and moistened by the tears secreted by the lacrimal glands. Tears wash away irritating agents and are bactericidal, preventing infections. The protective operations of the eyelids and lacrimal system is such that, there is a rapid removal of material instilled in to the eye, unless the material is suitably small in volume, chemically and physiologically compatible with surface tissues. The eye is one of the most delicate and yet most valuable of the sense organs and is a challenging subject for topical administration of drugs.

Eyelids:

Eyelids are located infront of the eye and they serve two purposes:

- Mechanical protection of the globe i.e., eyelids serve very well to protect the front surface of the eyes from excessive wind, small particles in the air and from minor mechanical injury.
- Creation of an optimum milieu for the cornea. The eyelids are lubricated and kept fluid filled by secretions of the lacrimal glands and specialized cells residing in the bulbar conjunctiva. The antechamber has the shape of a narrow cleft directly over the front of the eyeball,
with pockets like extensions upward and downward. The pockets are called superior and inferior fornices (vaults) and the entire space, the cul-de-sac. The elliptical opening between the eyelids is called palpebral fissure.

Eyeball:

The eyeball measures about 2.5 cm in diameter, only a small portion (about 1/6th part) of the globular eye is exposed in front, the rest is hidden in bony socket of the orbit on a cushion of fat and connective tissue. The globe of the eye or the wall of the human eyeball consists essentially of three layers:

- The outermost, protective tunic is made up of the sclera, the white portion of the eye and the cornea, the clear transparent layer.
- The middle layer is mainly vascular, consisting of the choroid, ciliary body and iris.
- The innermost layer is the retina, consisting of the essential nervous system responsible for vision.

To identify several ocular tissues for a better understanding of their functions and their involvement in selected ophthalmic disease states as well as to locate specific sites of drug administration and action including –

- Conjunctiva
- Cornea
- Anterior chamber
- Canal of Schlemm
- Trabecular meshwork
- Lens, vitreous chamber, retina, optic disc, optic nerve bundles, central retinal artery and vein.
- Iris
- Ciliary body
- Ciliary muscle
- Posterior chamber
Photograph-1.1: Sagittal Section of the Eye
Conjunctiva:

The conjunctival membrane covers the outer surface of the white portion of the eye and the inner surface of the eyelids. In most places it is loosely attached and thereby permits free movement of the eyeball, this makes possible subconjunctival injection. The conjunctiva forms an inferior and a superior sac except for the cornea, the conjunctiva is the most exposed portion of the eye.

Precorneal film or lacrimal system:

The conjunctival and corneal surfaces are lubricated by a film of fluid, precorneal tear film, secreted by the lacrimal glands. The secretion of the lacrimal gland, the tears, is delivered through a number of fine ducts into the conjunctival fornix. The secretion is a clear, watery fluid containing 0.7% protein and the enzyme lysozyme. The mucin-protein layer of the film is especially important in maintaining the stability of the film. The sebaceous glands of the eyelids secrete an oily fluid that helps to reduce evaporation from the exposed surfaces of the eye by spreading over the tear film. Spontaneous blinking replenishes the fluid film by pushing a thin layer of fluid ahead of the lid margins as they come together.

The tear film is composed of a thin outer lipid layer, a thicker middle aqueous layer and a thin inner mucoid layer. It is renewed during each blink and dry spots are produced when blinking is suppressed. The precorneal tear film maintains the integrity of the cornea in normal conditions and unaffected by the addition of concentration of up to 2% sodium chloride to conjunctival fluid, a pH below 4 or above 9 causes derangement of the film.
Cornea:

Cornea mainly consists of the following structures from the front to back, (i) Epithelium; (ii) Bowman’s membrane; (iii) Stroma; (iv) Descemet’s membrane; (v) endothelium. The cornea is 0.5 to 1mm in thickness and normally it possesses no blood vessels except at the corneoscleral junction. The cornea is transparent to ordinary diffuse light, largely because of a special laminar arrangements of the cells and fibers and the absence of blood vessels. Cloudiness of the cornea may develop due to any one of the several factors including excess pressure in the eyeball as in glaucoma, scar tissue, due to injury or infection.

Corneal Epithelium: The corneal epithelium is 5-6 cell layers thick centrally with 8-10 layers at the periphery and is composed of a basal germinative layer, intermediate wing cells and a surface squamous layer that possesses tight junctions. Mucopolysaccharides bound to the outer membrane provide stability to the tear film.

Corneal Stroma and Bowman’s Membrane: Bowman’s layer is the anterior border of stroma in humans, measuring 8-14μm thick and is composed of clear, randomly oriented collagen films surrounded by mucoprotein ground substance and numerous pores in the inner structure allows the passage of terminal branches of corneal nerves from the stroma into the epithelium. The stroma occupies 90% of the corneal thickness and contains about one-third of the cells of the cornea in the form of keratocytes. The connective tissue of the stroma is composed of multiple layer of closely knit collagen bundles or lamellae, which are arranged evenly to distribute the stress of the intraocular pressure to the limbus, the thickened zone that joins the cornea and sclera.
Corneal endothelium and Descemet's Membrane: The Descemet’s membrane of the endothelium lies between the stroma and the endothelium. The corneal endothelium, a monolayer of polygonal cells about 3μm thick, has unique structure and properties. The endothelial cell layer has a remarkable ability to rapidly pump fluid from the stromal side to the anterior chamber. The concentration of sodium ions is high in the stroma. The intercellular borders form a junction that is open along its full length, which allows a rapid leakage of water and solutes in the reverse direction to the fluid pump. The middle vascular layer of the eyeball consists of choroid, ciliary body and iris. The inner surface of the choroid layer, which is close to retina contains pigment cells, in the front portion of the eyeball the choroid becomes thicker and forms a round ciliary body. The ciliary body is hidden by the muscular ring of colored membranes called iris. The choroid lines the inner surface of the sclera, it is very rich in blood vessels and is a deep chocolate brown in color. Choroid is the metabolic support for the retina.

Ciliary Body: The major function of the ciliary body is the production of aqueous humor. There are many capillaries in the ciliary body, systemic drugs enter the anterior and posterior chambers largely by passing through the ciliary body vasculature and then diffusing into the iris where they can enter the aqueous humor. The ciliary body is one of the major ocular sources of drug-metabolizing enzymes, responsible for drug detoxification and removal from the eye.

Iris: The iris functions primarily to adjust the amount of light reaching the retina. Two groups of muscles, the sphincter and the dilator work in opposite directions to control the light reaching the retina. These muscles are supplied by cholinergic and adrenergic innervation respectively. The pigment granules
of the iris epithelium absorb light as well as lipophilic drugs. This type of binding is characteristically reversible, allowing release of drug overtime. As a result, the iris can serve as a reservoir for some drugs, concentrating and then releasing them for longer than otherwise expected.

**Aqueous Humor:** Aqueous humor is formed by the ciliary body and occupies the posterior and anterior chambers, having a volume of about 0.2ml. The fluid is constantly generated by the pigmented and non-pigmented epithelium of the ciliary body, which is supplied by a rich bed of capillaries. It flows from the posterior chamber through the pupil and then slowly circulates in the anterior chamber, circulated by the thermal differential between the cornea and the deeper ocular tissues. The aqueous humor exits at the angle between the cornea and iris through the sieve-like trabecular meshwork. It then enters the canal of Schlemm, which leads directly into low-pressure episcleral veins and finally into the general circulation.

**Lens:** The normal human lens originates from a double layer of epithelium. It grows to become a thick, flexible tissue composed of cells densely packed with clear proteins known as crystallines. The lens capsule or outer membrane reaches thickness of several micrometers anteriorly and is one-tenth as thick posteriorly. The lens is held in place by the zonules, which run from the ciliary body and fuse into the outer layer of the lens capsule. The lens tends to develop cataracts or opacities with age, interfering with vision.

**Vitreous Chamber:** It is filled with a viscous fluid, vitreous humor, which is a viscoelastic connective tissue composed of small amounts of glycosaminoglycans, including of hyaluronic acid and proteins such as collagen. At birth, the material of the vitreous is gel like in humans.
Retina: The inner nervous tissue layer (retina) is the light sensitive innermost coat of the eye. It is exceedingly thin, transparent and is made up of at least 10 separate layers of cells. The external layer of retina contains the photoreceptor cells, the rods and cones, whereas the deeper layer contains pigment cells. The remaining layers of retina contain nerve cell bodies and processes. The retina is situated between the clear vitreous humor in its inner surface and the choroid on its outer surface. Retina consists of two distinct chambers, anterior and posterior. The anterior chamber is the anterior space between the cornea and the lens and is occupied by a fluid called the 'aqueous humor'. The aqueous humor is formed by the ciliary body to bathe the lens, iris and posterior cornea. The fluid flows forward between the lens and the iris into the anterior chamber and helps to maintain the shape of the anterior eye. The aqueous humor drains from the eye through the canals of Schlemm at the junction of the cornea and sclera, then diffuses into the blood. The balance between production and absorption of aqueous humor helps to maintain proper pressure within the eye. The posterior chamber lies between the lens and retina and is filled with the colorless, transparent, gel like vitreous humor. The vitreous humor presses the retina firmly against the wall of the eye and helps to maintain the shape of the eye.

1.2 COMMON EYE DISORDERS:

A number of disorders can affect the structures of the eye, with outcomes ranging from moderate discomfort to significant loss of vision. The health care provider should be familiar with the signs and symptoms of common eye disorders and understand the decision making process behind treatment. This chapter reviews common eye disorders by anatomic location and by medication classification. The clinical presentations of these disorders,
the principles of treatment, and a review of the mechanisms and profiles of commonly used ophthalmic medications are provided.

**Disorders of the Eyelid and Lacrimal Gland**

The often nonspecific signs of eyelid swelling, diffuse tenderness to palpation, erythema, and increased tearing on presentation should elicit a differential diagnosis of causes ranging from chronic, benign disorders of the lid and lacrimal system to more acute conditions that warrant immediate intervention. The following are common, treatable conditions easily identified in an acute care setting.

**Hordeolum and Chalazion**

An external hordeolum, or stye, is a small abscess resulting from an acute infection of a lash follicle and its associated sebaceous gland (gland of Zeiss) or sweat gland (gland of Moll). Because *Staphylococcus* is the pathogenic organism, such styes can also develop in patients with chronic, underlying staphylococcal blepharitis. A chalazion is a chronic, focal inflammation of the eyelid secondary to obstruction of the ducts of the sebaceous meibomian glands.

**Blepharitis and Meibomitis:**

Blepharitis is a chronic condition marked by red, crusty, thickened eyelids with engorged blood vessels at the margins. Patients often complain of itching, burning, and excessive tearing from foreign body sensation. Infection with *Staphylococcus* at the base of the lashes is believed to have an important role in the genesis of this external eye disorder. Meibomitis or posterior blepharitis is characterized by inspissated oil glands at the eyelid margins. Patients present with symptoms of burning and excessive tearing.
Contact Dermatitis:

In a patient with the sudden onset of a periorbital rash with eyelid swelling and a mild, watery discharge who denies fever and tenderness to palpation, the diagnosis of contact dermatitis should be considered.

Preseptal Cellulitis:

Preseptal cellulitis must be considered in the patient presenting with mild fever, tightness of the eyelid skin, and bogginess (chemosis) of the conjunctiva of the eye, in addition to the signs of eyelid edema, erythema, and tenderness. This infection of the eyelid and periorbital structures anterior to the orbital septum usually is the result of inoculation from a puncture wound or laceration or from an adjacent area of infection, such as the sinuses. In adults, the most likely causative organisms are *Staphylococcus aureus* and streptococci. *Haemophilus influenzae* should be considered in children under 5 years, who typically are affected by bacteremic spread from an otitis media or pneumonia.

Dacryocystitis and Dacryoadenitis:

Dacryocystitis is an acute infection of the lacrimal sac resulting from blockage of the nasolacrimal duct. The obstruction prevents normal drainage of tears from the lacrimal sac into the nose and promotes stasis predisposing the patient to secondary infection with bacteria. The patient presents with pain, redness, and swelling over the most nasal aspect of the lower lid, where the lacrimal sac is located. Dacryoadenitis is an acute infection of the lacrimal glands. Patients present with pain, redness and swelling over the outer one-third of the upper eyelid. The infecting bacteria tend to be *S. aureus*, *Neisseria gonorrhoeae* and *Streptococci*. There may also be a viral cause and mumps; infectious mononucleosis, and herpes zoster should be considered.
Orbital Cellulitis

Orbital cellulitis is one of the few true ocular emergencies necessitating immediate medical attention. Therefore, it is important to be aware of the signs and symptoms of this soft tissue infection, which extends behind the orbital septum. The patient may present with a red eye, blurred vision, fever, purulent discharge, and pain with eye movement. Critical signs include eyelid edema and conjunctival chemosis and injection. The eye may actually be proptotic, with restricted movement in the various directions of gaze. The most common causative organisms are *S. aureus*, *Streptococcus species*, and *H. influenzae*. A fungal cause, such as Mucor mycosis, should be considered in diabetic or immunocompromised patients.

Thyroid Ophthalmopathy:

Thyroid ophthalmopathy is the most common cause of unilateral or bilateral proptosis in adults. Patients typically present with double vision, foreign body sensation, and retraction of the eyelids, especially on downgaze.

Disorders of the conjunctiva and Sclera:

Conjunctivitis is one of the most commonly treated disorders of the eye. Patients typically present with a red eye and discharge, which may range from mild to copious, clearish to mucopurulent. Vision may be affected because of excessive tearing and irritation.

Bacterial Conjunctivitis:

Bacterial conjunctivitis is characterized by the acute onset of redness, foreign body sensation, mucopurulent discharge, and excessive eyelid crusting upon waking. Examination is remarkable for conjunctival hyperemia, mucopurulent discharge, a papillary reaction along the palpebral conjunctiva, and the absence of preauricular lymphadenopathy. The most common
causative organisms of a bacterial conjunctivitis are *S. aureus*, *S.epidermidis*, *Streptococcus pneumoniae*, and *H. influenzae*. Gonococcal conjunctivitis should be high on the differential diagnosis in any patient presenting with a hyperacute (onset within 12 hours), extremely profuse mucopurulent discharge with marked chemosis and papillary reaction.

**Viral Conjunctivitis:**

Viral conjunctivitis usually presents acutely with the onset of a watery mucous discharge, conjunctival hyperemia, and lid edema. Examination often shows a palpebral follicular response, preauricular lymphadenopathy, and, in severe cases, subconjunctival hemorrhages and pseudomembrane formation. Adenovirus is the most common causative organism. In particular, serotypes 8 and 19 are implicated in epidemic keratoconjunctivitis, a severe and highly contagious form of viral conjunctivitis that can cause a concomitant keratitis in up to 80% of cases.

**Chronic Conjunctivitis:**

A chronic conjunctivitis is defined by the duration of symptoms, including discharge, conjunctival hyperemia, and general irritation for more than 4 weeks. Adult inclusion conjunctivitis, or chlamydial conjunctivitis, is a chronic conjunctivitis typically affecting sexually active teenagers and young adults. The patient presents with unilateral, mucopurulent discharge, a prominent palpebral and in some cases bulbar follicular reaction, and preauricular lymphadenopathy.

**Allergic Conjunctivitis:**

Hayfever, or seasonal allergic conjunctivitis, is a type I hypersensitivity immune response in which the binding of antigen immunoglobulin E antibody complexes to mast cells causes the release of histamine and other inflammatory
mediators. The inciting antigen usually is airborne pollen, and the allergic response consists of conjunctivitis marked by a watery discharge, pruritis, eyelid edema, conjunctival chemosis, and a palpebral conjunctival papillary reaction.

Subconjunctival hemorrhage:

A ruptured blood vessel in the subconjunctival layer can cause blood to collect beneath the conjunctiva in a sectoral or diffuse pattern. The patient may first notice the extremely red eye after coughing or straining as during a Valsalva maneuver.

Episcleritis and Scleritis:

Episcleritis is a benign and self-limited disorder that often presents in young adults as an acutely red eye in a sectoral pattern. The patient may complain of mild discomfort in the affected eye, with some tenderness to palpation over the hyperemic area and excessive tearing; however, vision is not affected. Scleritis is a severe inflammatory condition of the scleral layer of the eye that topically presents with a severe boring eye pain, sectoral or diffuse redness, tearing and photophobia.

Corneal Infiltrate and Corneal ulcer:

Contact lens wear is the most common predisposing factor in the development of a corneal infiltrate and its progression to a corneal ulcer. Typically, the patient presents with a red eye, tearing or discharge, a significant degree of ocular pain, photophobia, and foreign body sensation, as well as decreased vision. Anterior chamber inflammation ranging from mild cell and flare to frank hypopyon may also be seen on examination. Bacterial keratitis is the most common form of corneal infection. *Pseudomonas aeruginosa*, in particular, is the most common causative bacterial organism.
Herpes Simplex Virus: Corneal Epithelial Disease and Keratitis:

As in bacterial keratitis, the patient presenting with herpes simplex infection of the cornea has a red, painful eye with photophobia, tearing, and decreased vision. A periorbital skin rash may be present, and the patient often gives a history of previous episodes of “painful red eye”. A dendritic or branching epithelial defect usually is appreciated when the corneal surface is stained with fluorescein.

Anterior Uveitis:

Uveitis is a term used to describe general inflammation of the structures that make up the uveal tract: the iris, ciliary body, and choroid. Anterior uveitis may consist simply of inflammation of the iris (iritis) or of inflammation of both the iris and ciliary body (iridocyclitis). Intermediate posterior, and panuveitis are other categories in the anatomic classification of uveitis. The patient presenting with acute anterior uveitis complains of photophobia, redness, excessive tearing, and perhaps mildly decreased vision. On examination, the hallmark is white blood cells, ranging from scant to too numerous to count, floating in the anterior chamber.

1.3 GLAUCOMA\textsuperscript{9,10,11,12,13}:

Glaucoma is a group of diseases of the eye characterized by damage to the ganglion cells and the optic nerve. If left untreated, these effects may lead to various degrees of loss of vision and blindness. Increased intraocular pressure (IOP) remains the most important risk factor for the development of glaucoma. Glaucoma is typically classified as either open angle or angle closure (closed angle), based upon causes of increased intraocular pressure.
Types of Glaucoma

As can be observed from the following table, glaucoma may be classified in a variety of ways, which describe causative factors, when known. Glaucoma is usually described as either angle closure or open angle glaucoma. These terms are based upon the mechanism of obstruction of outflow of aqueous humor and help clinicians develop treatment strategies. Open angle glaucoma occurs in 80 to 90% of cases. Angle closure glaucoma is usually a more acute form of disease and is seen in 5 to 10% of all patients. A third type is congenital glaucoma, which results from developmental ocular abnormalities and occurs in less than 2% of patients. Finally, glaucoma may be secondary to other ocular disorders, systemic disorders, or trauma, or may be seen with medication usage, or after intraocular surgery. Open angle glaucoma can be further described as either high tension or normal tension (also known as low tension) glaucoma.

Etiology (Study of causes of disease):

Optic nerve damage caused by the different types of glaucoma is a result of a variety of initiating factors. Genetic predisposition, physical changes, systemic diseases, or medications may increase a person's risk of developing damage that may be broadly classified as intraocular pressure dependent (most commonly) or intraocular pressure independent. Increased intraocular pressure remains the major etiologic risk factor for the development of glaucoma. Myopia may be an additional risk factor, especially in younger patients. Glaucoma can occur as a secondary manifestation of systemic disorders or trauma.

Pathophysiology:

Shields et al describe five stages in the pathogenesis of glaucoma: (1) a variety of initial events, causing (2) Changes in aqueous outflow, resulting in
Increased IOP, which leads to Optic nerve atrophy, and finally, Progressive loss of vision. This description highlights the importance of aqueous humor production and elimination in the progression of glaucoma and subsequent complications.

Aqueous Humor Production and Elimination:

The relative production and elimination of aqueous humor physiologically determines intraocular pressure. Increased intraocular pressure usually is the result of decreased elimination, but may also be caused by increased production of aqueous humor or both.

Aqueous humor is secreted by the ciliary process into the posterior chamber of the eye, where it flows to the trabecular meshwork and through the canal of Schlemm. Owing to diurnal variability in aqueous humor production, intraocular pressure measurements vary depending upon the time of day. Many patients with open-angle glaucoma have the greatest intraocular pressure in the morning and the lowest intraocular pressure during the sleeping hours. Because a decrease in the outflow facility of aqueous humor is the primary mechanism for producing an increase in intraocular pressure, anatomic changes associated with open angle and angle closure glaucoma are important.

Open-Angle Glaucoma:

In open-angle glaucoma, a physical blockage occurs within the trabecular meshwork that retards elimination of aqueous humor. The obstruction is presumed to be between the trabecular sheet and the episcleral veins, into which the aqueous humor ultimately flows. The impairment of aqueous drainage elevates the intraocular pressure to between 25 and 35 mm Hg (normal intraocular pressure is 10 to 20 mm Hg), indicating that the obstruction is usually partial. This increase in intraocular pressure is sufficient
to cause progressive cupping of the optic disk and eventually visual field defects.

Angle-Closure Glaucoma:

In angle-closure glaucoma, increased intraocular pressure is caused by pupillary blockage of aqueous humor outflow and is more severe. The basic requirements leading to an acute attack of angle closure are a pupillary block, a narrowed anterior chamber angle and a convex iris. When a patient has a narrow anterior chamber or a pupil that dilates to a degree where the iris comes in greater contact with the lens, there is interference with the flow of aqueous humor from the posterior to the anterior chamber. Because aqueous humor is continually secreted, pressure from within the posterior chamber forces the iris to bulge forward. This may progress to complete blockage.

The pathologic complications of angle closure and open angle glaucoma include the formation of cataracts, adhesion of the iris to the cornea, atrophy of the optic nerve and retina, complete blockage of aqueous outflow, and ultimately, blindness.

Congenital Glaucoma:

Congenital glaucoma is a rare disorder in which intraocular pressure is increased as a result of developmental abnormalities of the ocular structures in the newborn or infant. It may occur in association with other congenital abnormalities and anomalies such as homocystinuria and Marfan’s syndrome. Congenital glaucoma should be considered in newborns and infants who have sensitivity to light or exhibit excessive tearing or spasm of the eyelids.
The aqueous humor is the clear fluid that flows through the inside of the eye, nourishing the lens, the iris and the inside of the cornea. This fluid is not the same as tears, which bathe the outside of the eye.

The anterior chamber is the eye's "sink". Fluid is pumped from the ciliary body through the pupil into this space in front of the iris.

The trabecular meshwork is the eye's "drain". Fluid flows through these tiny holes that surround the iris and then back into the bloodstream.

Photograph-1.2: Normal Drainage of Aqueous Humor

The aqueous humor is the clear fluid that flows through the inside of the eye, nourishing the lens, the iris and the inside of the cornea. This fluid is not the same as tears, which bathe the outside of the eye.

The ciliary body is the eye's "faucet" or "tap" where fluid is made.

Photograph-1.3: Open-Angle Glaucoma

The angle between the iris and the cornea is normal, but the drainage holes get clogged from the inside. Why this happens isn't fully understood.

Photograph-1.4: Closed-Angle Glaucoma

The angle is narrower than normal. If fluid can't flow easily through the opening in the pupil, the iris pushes forward and blocks the drainage holes.
Normal-Tension Glaucoma:

The etiology and pathogenesis of normal tension glaucoma remain to be completely understood. Normal tension glaucoma is thought to be related, at least in part, to decreased blood flow to the optic nerve. This may eventually cause neuronal damage. In addition, these eyes appear to be more susceptible to pressure related damage within the normal or high normal range, and therefore a pressure lower than normal is often necessary to prevent further visual loss.

Drug-Induced Glaucoma:

Several therapeutic classes of drugs, such as those with anticholinergic, adrenergic, or corticosteroid effects, have been implicated in inducing or worsening glaucoma. Medications affect open angle and closed angle glaucoma differently. Drugs that dilate the pupil, for instance, may precipitate an acute attack of angle closure glaucoma but usually do not produce harmful effects in those with open angle glaucoma. Dilation of the pupil in angle closure glaucoma may cause the peripheral iris to bulge forward, blocking the trabecular meshwork. The aqueous humor is prevented from reaching the outflow channels, which results in increased IOP. Because excessive resistance to outflow in open angle glaucoma is caused primarily by changes within the trabecular outflow channels, dilation of the pupil usually will not increase the intraocular pressure.

Diagnosis:

Four common tests may be performed that allow diagnosis of glaucoma before visual loss occurs.

First test: Direct ophthalmoscopy, also known as slit lamp examination, allows the physician to observe changes in the optic nerve head.
Second test: Tonometry measures intraocular pressure and may be useful as a screening test. Several different devices, such as Goldmann’s tonometer, Schiotz indentation tonometer, or electrical strain gauges measure how much force is required to flatten the central cornea (applanation of the cornea). As previously discussed, some patients with normal intraocular pressure may still develop glaucomatous damage. In addition, as many as 70% of patients with ocular hypertension never develop visual problems due to glaucoma. Therefore, many physicians use tonometry in combination with other diagnostic tests.

Third test: A third screening method is perimetry. Perimetry measures visual field defects by producing visual stimuli in various locations of the patient’s field of vision. Because defects in the visual field and loss of vision are made apparent by perimetry, it is currently considered the “gold standard” diagnostic procedure. Unfortunately, perimetry is too time consuming and expensive to be a practical screening tool; it should be reserved for those patients who have detectable optic nerve damage by other tests.

Fourth test: Gonioscopy is a procedure that allows quantitative measurement of the angle of the anterior chamber. Gonioscopy requires considerable training and is usually only performed by ophthalmologists.

TREATMENT
Pharmacotherapy:

The goal of glaucoma therapy is the immediate and sustained reduction of intraocular pressure to prevent deterioration of the optic nerve and loss of vision. Medications used in the treatment of glaucoma may be classified as those that increase the elimination of aqueous humor and those that decrease its formation. The five major classes of medications used for the management of
glaucoma include β-adrenergic blocking agents, miotics, adrenergic agonists, topical and oral carbonic anhydrase inhibitors, and prostaglandin analogs. Additionally, hyperosmotic agents are used for the short-term rapid decrease of intraocular pressure necessary in the management of acute angle closure glaucoma.

**β-Blockers:**

β-Blockers are the most widely prescribed drugs for the treatment of glaucoma and may be used alone or in combination with other agents. The ocular hypotensive effect caused by β-blockers is probably due to suppression of aqueous humor formation by blockage of the β-adrenoreceptors in the ciliary body. β-Blockers decrease aqueous humor production by approximately one-third. All of the agents are available as solutions and are usually administered one to two times daily. Additionally, timolol maleate is available in a gel formulation, which may be given once daily.

Commonly used β-blockers for the treatment of open angle glaucoma includes timolol maleate, betaxolol HCl, levobunolol HCl, carteolol, and metipranolol. Timolol is a potent, short-acting, nonselective β-blocker. It is available as 0.25 and 0.5% solutions and a longer acting gel forming solution.

1.4 **OPHTHALMIC DRUG DELIVERY SYSTEMS**

Pharmaceutical preparations are applied topically to the eye to treat surface or intraocular conditions, including infections of the eye or eyelids due to bacterial, fungal and viral pathogens, allergic or infectious conjunctivitis or inflammation, elevated intraocular pressure and glaucoma, and dry eye due to an inadequate production of fluids bathing the eye.
Pharmaceutical dosage forms and drug delivery systems applied topically to the eye include solutions, suspensions, gels, ointments and drug impregnated ocular inserts.

CONVENTIONAL OPHTHALMIC PRODUCTS:

Eye Solutions: Eye drops are the conventional dosage forms that account for 90% of currently accessible ophthalmic formulations. Despite the excellent acceptance by patients, one of the major problems encountered is rapid precorneal drug loss. Simple aqueous solutions are known to remain in cul-de-sac for 60 seconds. Solutions are the most common means of administering a drug to the eye. Nearly all the major ophthalmic therapeutic agents are water-soluble or can be formulated as water-soluble salts. A homogeneous solution offers the assurance of greater uniformity of dosage and bioavailability. The principal disadvantage of solutions is the relatively brief contact time between the medication and absorbing surfaces.

Suspensions: If the drug is not sufficiently soluble, it can be formulated as a suspension. Suspensions are dispersions of finely divided relatively insoluble drug substances in an aqueous vehicle containing suitable suspending and dispersing agents. A suspension may also be desired to improve stability, bioavailability or efficacy. An ophthalmic suspension should use the drug in a microfine form, usually 95% or more of the particles have a diameter of 10μm or less. This is to ensure that the particles do not cause irritation of the sensitive ocular tissues and that a uniform dosage is delivered to the eye.

Powders for reconstitution: Drugs that have only limited stability in liquid form are prepared as sterile powders for reconstitution by the pharmacist prior to dispensing to the patient. The sterile powder is usually manufactured by lyophilization in individual glass vials. In powder form, the drugs have a much
longer shelf-life than in solution. A separately packed sterile diluent and sterile dropper assembly is provided with the sterile powder and requires aseptic technique to reconstitute.

Ointments: Ointments represent an attractive ocular drug delivery system because of their increased contact time. They do, however, interfere with vision and for this reason are sometimes disliked by patients. On positive side, there are wide varieties of ointments. Two important requirements for ocular ointments are that they are sterile and that they melt at body temperature. Melting or softening at body temperature is important to achieve good mixing with the tear film and to prevent irritation to the eye.

NEW/NOVEL OPHTHALMIC DRUG DELIVERY SYSTEMS:

Inserts/ Discs: Ocular inserts are meant for placement in the eye cavity and are intended to release contained drug at a pre-programmed rate for a specific time period. The inserts may be bioerodible or non-erodible. The erodible type discs dissolve slowly in ophthalmic fluids at definite rate while non-erodible ones remain in eye only for a definite time and are removed and discarded thereafter. The “ocusert” therapeutic systems developed by Alza Corporation, a device/insert releasing the drug at a vigorously constant and reproducible rate for over one week.

Mucoadhesive Solutions/ Suspensions: These products are either polymeric solutions or microparticulate suspensions designed for retention in cul-de-sac by bonding with mucus or epithelium. They enable increased contact of drugs with corneal tissues.

Contact Lenses: Contact lenses are substitutes for spectacles are enjoying a certain degree of popularity. Use of soft contact lenses soaked in drug solution has been suggested for slow but prolonged drug delivery particularly to corneal tissues. Timolol maleate has been experimented for antiglaucoma activity. Contact lenses soaked in 0.5% solutions released nearly 100% drug in four
hours. The release period can be further enhanced by about 25% if polymers like polyvinyl alcohol are incorporated in drug solutions.

**Microspheres/ Nanoparticles**: Nanoparticles are solid particles of polymeric nature ranging in size from 10 to 1000 nm. Biologically active materials can be incorporated into the carrier or adsorbed on the surface of the nanoparticles. Nanoparticles are not only comfortable but give prolonged release of drugs. The drugs are bound to small particles, which are then dispersed in aqueous vehicles. They are akin to colloidal solutions. Polymeric colloidal dispersions and film forming agents termed psuedoplastics have also been used for sustained action in topical ophthalmic products.

**Vesicular systems**: In view of some drawbacks of the ocular drug delivery systems, a research is concentrated on the development of some systems having vesicular structure. The possible vesicular systems are liposomes, niosomes, etc. The vesicular systems enable controlled drug availability by interfering with the enzyme metabolizing drugs. These systems are also reported to have problems of drug leakage, limited drug loading capacities and opacity, etc.

**Liposomes**: Liposomes are microscopic vesicles composed of membrane like lipid layers surrounding aqueous compartments. The lipid layers are comprised mainly of phospholipids.

**Niosomes**: Vesicles based on some non-ionic surfactants like dialkyl polyoxyethylene ethers.

**Phase-transition solutions**: These solutions, after placement in cul-de-sac get converted into gels. This phase change increases the residence time and hence the availability of the drug to the tissue gets extended.
OBJECTIVES OF THE WORK

- There is a need for a novel ophthalmic drug delivery system which improves the ocular bio-availability and reduced systemic side effects.

- Phase-transition solutions offers the advantages of both conventional dosage forms and solid dosage forms (NDDS) like:
  - Ease of administration, patient acceptance and dosage uniformity.
  - Extended corneal contact time and sustained release of the drug from the system.

- Sol-gel systems were prepared with a view to develop a delivery systems which improves the residence time on the cornea.

- Sol-gel systems are liquids in container and thus can be instilled as eye drop to convert to gel on contact with tear fluid.

- The present research work is pH-triggered in-situ gelling system.

- Since the delivery system is a liquid in container, it improves patient acceptance and easy administration of the delivery system.

- The development of sol-gel systems prolongs the release of drug from the formulation.

- Decreased frequency of dosing is achieved with the sol-gel systems.

- Sol-gel systems will not interfere with vision (free from blurred vision which is associated with semisolid dosage forms).

- Sol-gel systems will not cause irritation to the sensitive ocular tissues and they are safe.