Ocular Drug Delivery Systems for Treatment of Glaucoma

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ABSTRACT

Glaucoma is a common eye disease that can cause irreversible blindness if left undiagnosed and untreated. Glaucoma is a prevalent neurodegenerative disorder of the eye. Glaucoma can be roughly divided into two main categories "open angle" and "closed angle" (or "angle closure") glaucoma. Every available treatment to prevent progressive glaucoma involves a certain amount of risk and financial expense. Conventional first-line treatment of glaucoma usually begins with the use of a topical selective or nonselective β-blockers or topical prostaglandin analogs. Second-line drugs of choice include α-agonists and topical carbonic anhydrase inhibitors. Parasympathomimetic agents, most commonly pilocarpine, are considered third-line treatment options. For patients who do not respond to antiglaucoma medications, laser trabeculoplasty and incisional surgery are further methods that can be used to lower intraocular pressure. Ocular drug delivery is hampered by the barriers protecting the eye. The bioavailability of the active drug substance is often the major hurdle to overcome. Conventional ocular dosage form, including eye drops, is no longer sufficient to combat ocular diseases. This article reviews the better understanding about glaucoma disease like prevention and diagnosis and explores various approaches like niosomes, liposomes, hydrosols, nanoparticles, nanosuspensions, microparticles, microemulsions, prodrugs and ocular inserts to improve the ocular bioavailability of drug and provide continuous and controlled release of the drug to the anterior and posterior chamber of the eye. In near future, a great deal of attention will be paid to develop a suitable and effective treatment for the vision threatening disorders like glaucoma.

KEYWORDS: Ocular drug delivery system; Glaucoma; Hydrogel; Niosomes; Liposomes; Ocular Inserts.

Introduction

Glaucoma is a disease and characterized by an intraocular pressure higher than the eye can tolerate. Glaucoma comprises a group of mainly chronic conditions that is characterized by progressive deformation of the optic nerve head and elevated intraocular pressure (IOP) is a risk factor. It affects primarily the middle aged and elderly, glaucoma is the second commonest cause of visual disability in the world as it affects between 70 and 90 million people, with about 10% of them becoming blind in both eyes. Increased intraocular pressure (IOP) and subsequent retinal ganglion cell (RGC) death leading to the loss of visual field characterizes the pathology of primary open angle glaucoma, which is the most common form. Possible factors leading to glaucoma include glutamate-induced neurotoxicity; nitric oxide based damage, disruption of neurotrophic factor transport and immune-induced neurodestruction.

Ophthalmic drug delivery is one of the most interesting and challenging tasks facing the pharmaceutical scientist at present. Eye is the most important and sensitive organ; in fact, it is the window of our soul. The eye is unique organ from anatomical and physiological point of view (Bloomfield, 1977). The eye has special attributes that allows local drug delivery and non-invasive clinical assessment of disease but also makes understanding disease pathogenesis and ophthalmic drug delivery challenges. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. Drug delivery to the eye can be broadly classified into anterior and posterior segments. Conventional systems like eye drops, suspensions and ointments cannot be considered optimal in the treatment of vision-threatening ocular diseases. However, more than 90% of the marketed ophthalmic formulations are in the form of eye drops. These formulations mainly target the diseases in the anterior segment of eye. Topical ocular medications do not reach the posterior segment of the eye. Posterior segment (retina, vitreous, choroid) can be treated by high drug dosage regimen given intravenously or by intravitreal administration or implants or by periocular injections. Currently, the posterior segment drug delivery is a rapidly growing interest area in ophthalmic drug delivery (Broadway, 1993).

The goal of researchers is to treat a disease consistently and accurately. Currently the knowledge in this field is rapidly expanding and many concepts and drug delivery strategies are emerging out. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. Development of novel techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. An assumption is made that a correlation exists between the...
concentration of a drug at its intended site of action and the resulting pharmacological effect. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration. Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology. A successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug molecule and the constraints offered by the ocular route of administration (Chen, 2003).

An overview of glaucoma

Glaucoma is an eye disease in which the optic nerve is damaged in a characteristic pattern. This can permanently damage vision in the affected eye(s) and lead to blindness if left untreated. It is normally associated with increased fluid pressure in the eye (aqueous humour). The term 'ocular hypertension' is used for people with consistently raised intraocular pressure (IOP) without any associated optic nerve damage. Conversely, the term 'normal tension' or 'low tension' glaucoma is used for those with optic nerve damage and associated visual field loss but normal or low IOP (Agnihotri, 2004). The nerve damage involves loss of retinal ganglion cells in a characteristic pattern. There are many different subtypes of glaucoma, but they can all be considered to be a type of optic neuropathy. Raised intraocular pressure (above 21 mmHg or 2.8 kPa) is the most important and only modifiable risk factor for glaucoma. However, some may have high eye pressure for years and never develop damage, while others can develop nerve damage at a relatively low pressure. Untreated glaucoma can lead to permanent damage of the optic nerve and resultant visual field loss, which over time can progress to blindness. Fig.1 (A) and (B).

Glaucoma can be roughly divided into two main categories, "open angle" and "closed angle" (or "angle closure") glaucoma. The angle refers to the area between the iris and cornea, through which fluid must flow to escape via the trabecular meshwork. Closed angle glaucoma can appear suddenly and is often painful; visual loss can progress quickly, but the discomfort often leads patients to seek medical attention before permanent damage occurs. Open angle, chronic glaucoma tends to progress at a slower rate and patients may not notice they have lost vision until the disease has progressed significantly (Brad, 2008).

Glaucoma has been called the "silent thief of sight" because the loss of vision often occurs gradually over a long period of time, and symptoms only occur when the disease is quite advanced. Once lost, vision cannot normally be recovered and so treatment is aimed at preventing further loss. Worldwide, glaucoma is the second leading cause of blindness after cataracts. It is also the leading cause of blindness among African Americans. Glaucoma affects one in 200 people aged fifty and younger, and one in 10 over the age of eighty. If the condition is detected early enough, it is possible to arrest the development or slow the progression with medical and surgical means (Bloomfield, 2008).

There are two main types of glaucoma: open-angle glaucoma and closed-angle glaucoma (also called angle closure glaucoma). Open-angle glaucoma accounts for 90% of glaucoma cases in the United States. It is painless and does not have acute attacks. The only signs are gradually progressive visual field loss, and optic nerve changes (increased cup-to-disc ratio on fundoscopic examination) (Baudowin, 2004). Closed-angle glaucoma accounts for less than 10% of glaucoma cases in the United States, but as many as half of glaucoma cases in other nations (particularly Asian countries) (Bloomfield, 1977). About 10% of patients with closed angles present with acute angle closure crises characterized by sudden ocular pain, seeing halos around lights, red eye, very high intraocular pressure (> 30 mmHg), nausea and vomiting, sudden decreased vision, and a fixed, mid-
dilated pupil. Acute angle closure is an emergency (Broadway, 1993).

Over the last decade the prevalence of glaucoma has been reported by the Vellore Eye Survey, Andhra Pradesh Eye Disease Study, Aravind Comprehensive Eye Survey, Chennai Glaucoma Study, and West Bengal Glaucoma Study. There have been some differences largely because of methodological variations. We use the reported age and gender stratified prevalence estimates from these studies and the Indian population census estimates to calculate the number of persons with glaucoma or at risk of the disease in the country. On the basis of the available data, we estimate that there are approximately 11.2 million persons aged 40 years and older with glaucoma in India. Primary open angle glaucoma is estimated to affect 6.48 million persons. The estimated number with primary angle-closure glaucoma is 2.54 million. Those with any form of primary angle-closure disease could comprise 27.6 million persons. Most of those with disease are undetected and there exist major challenges in detecting and treating those with disease (Bharath, 2009). In the light of the existing manpower and resource constraints, we evaluate options for improving case detection rates in the country (Fig 2).

**Fig. 2.** Incidence of glaucoma in India.

**Glaucoma risks:** A risk factor is something that increases your likelihood of getting a disease or condition. It is possible to develop glaucoma with or without the risk factors listed below (Chen, 2003; Derek, 2012; Douglas, 1995). However, the more risk factors you have, the greater your likelihood of developing glaucoma. Risk factors for glaucoma include:

**Family history of glaucoma:** If someone in the family has glaucoma, then there is a likely chance of getting glaucoma increased, as the disease may be inherited. However, this is not necessarily being the reason for the development of disease many a times or many a times other members in the family or the next generation of the family not necessarily develop the disease.

**Race:** In black people, open-angle glaucoma is the leading cause of blindness and is six to eight times more common than in Caucasians. In addition, the risk among black people increases after age 40. Hispanics also have a high risk of developing glaucoma. Eskimos and Asians are more likely to develop closed-angle glaucoma than other races.

**Age:** According to the American Academy of Ophthalmology, the risk of getting glaucoma increases after age 50. For black people the risk generally increases after age 40. However, glaucoma can occur in anyone at any age. Guidelines recommend starting regular screening for glaucoma at the age of 40.

**High intraocular pressure:** People with an elevated intraocular pressure (IOP) have an increased risk of developing glaucoma. "Elevated" is usually defined as greater than 21 mm mercury (Hg). However, even people with “normal” pressures can develop glaucoma. Research indicates that taking eye drops to lower elevated intraocular pressure on a regular basis diminishes the risk of developing glaucoma.

**Thin cornea:** A recent large clinical trial discovered that patients with thinner corneas (the clear structure at the front of the eye) are at an increased risk of developing glaucoma. They also found that African-Americans have thinner corneas than Caucasians.

**High blood pressure:** Some studies have shown that having high blood pressure increases the risk of glaucoma. However, this is still controversial.

**Diabetes:** Some studies have shown that diabetes is associated with an increased risk of developing glaucoma.

**Refractive errors:** The nearsighted (myopic) people are at an increased risk of developing open-angle glaucoma. On the other hand, farsighted (hyperopic), are at an increased risk of developing closed-angle glaucoma.

**Regular, long-term steroid/cortisone use:** Long-term use of all forms of corticosteroids may increase the risk of glaucoma by increasing the pressure in the eye.

**Previous eye injury or eye surgery:** An eye injury may damage structures in the eye leading to impaired fluid drainage. Complications of eye surgery may also sometimes lead to glaucoma.

**History of severe anemia or shock:** A history of severe anemia or shock has been identified as possible risk factors associated with glaucoma or other optic nerve disorders.

**Cardiovascular disease or insufficient blood flow:** People with cardiovascular disease or conditions resulting in decreased blood flow to the eye may be at an increased risk of developing glaucoma.

**Obesity:** Overweight and Metabolic Syndrome have been identified as a possible risk factor associated with glaucoma.

**Hypothyroidism:** Hypothyroidism has also been identified as a possible factor.

**Diagnosis of glaucoma**

Glaucoma can be diagnosed with a series of tests given by an eye care specialist. These tests are given during an eye exam that is conducted in the eye care
professional's office. The exam will begin with the eye care professional or staff person asking you questions about your personal and medical history and your family's medical history. To detect glaucoma, eye care professionals will do the following:

**Visual acuity**: This test measures how well person can see at various distances. Patient will be asked to look at a chart of letters or numbers and identify what he/she see.

**Tonometry**: This test measures the pressure inside the eye. There are several types of tonometry; in air tonometry, a puff of air is blown onto the cornea to take the measurement. Another type uses a small plastic device (Goldmann tonometer) that lightly pushes against the eye in order to measure the intraocular pressure. For this test, the eye is first numbed with an eye drop, so person do not feel anything.

**Gonioscopy**: The eye care professional can see the drainage angle of the eye using a special lens. This can help determine if there is risk for closed-angle glaucoma.

**Pupil dilation**: Drops are put in the eyes that enlarge/dilate pupils. This allows the eye care professional to see more of the inside of your eye. Close-up (near) vision may remain blurred for several hours afterwards and it may be sensitive to bright light. Ask to doctor for a pair of sunglasses after the dilation.

**Ophthalmoscopy**: Once the pupils are dilated, the eye care professional will examine the optic nerve and the rest of retina with an instrument called an ophthalmoscope. The color and appearance of the optic nerve may indicate, if there is damage from glaucoma and how extensive it is? Doctor will probably take pictures of the optic nerve for future comparison.

**Perimetry (visual field test)**: This test produces a map of your field of vision. It is used to check whether there is damage to any area of vision. Since glaucoma slowly affects peripheral, or side vision, people may not know the presence of problems, until detected on this test.

**Pachymetry**: Physician may measure the thickness of cornea using a special machine called a corneal pachymeter.

If the eye care professional finds evidence of glaucoma, may ask the patient to begin a treatment program. Remember, glaucoma cannot be cured, but treatment can help to control the disease.

**Symptoms of glaucoma**: In the early stages of the disease, most cases of open-angle glaucoma present no noticeable signs or symptoms. Vision stays normal and there is no pain. But, even without symptoms, irreversible damage can be happening to your optic nerve (Dhaliwal, 2008). If glaucoma remains untreated for a long period of time, you may begin to notice some symptoms. Some cases of closed-angle glaucoma, especially during an acute attack, are associated with symptoms, which are discussed below.

The main symptom of glaucoma is loss of peripheral vision. This means that you can see things clearly in front of you, but objects to the side and out of the corner of your eye may be missed (Dale, 1995). As the disease progresses, it may seem as though you are looking through a tunnel. Over time, the remaining forward vision may decrease and the field of vision narrows until blindness results. Depending on the type of glaucoma one may have experience some of the following symptoms like blind spots, blurred vision, vague eye aching, inability to adjust the eye to darkened rooms, difficulty focusing on close work, loss of side vision (peripheral vision), and fluctuating vision. More serious symptoms associated with acute angle-closure glaucoma (a medical emergency) may require immediate medical attention which includes sore, redened eye decreased vision, seeing colored halos, rings, or rainbows around lights tearing swollen eyelids headache nausea or vomiting. **Fig 3**

**Prevention of glaucoma**

There are no specific guidelines for preventing or reducing the risk of glaucoma. Early detection and treatment of glaucoma, before it causes major vision loss, is the best way to control the disease (Durran, 1992; Evan, 1998, Ehlers, 1957). Since vision loss is gradual and usually only affects the peripheral vision at first, most patients don't notice any visual changes until significant damage has been done. One needs to examine
their eyes regularly by an eye care specialist, especially if they are at high risk for glaucoma. Many a times it might be the case of glaucoma, the patient may be unaware about the same due to lack of clinical evidences (symptomless). If left untreated, such people may lose the vision permanently. Hence, regular comprehensive eye examination may solve such cases.

**Screening tests:** Regular eye exams by an eye care professional are the best way to screen for glaucoma (Giacconi, 2009; Gurny, 1981). Because most people experience no symptoms with glaucoma, it is important to schedule a regular eye exam and the tests like visual acuity, tonometry, gonioscopy, pupil dilation, ophthalmoscopy, perimetry (visual field test), pachymetry, nerve fiber layer analysis.

**Screening guidelines:** Ask your doctor for guidelines specific for your individual situation (Kuno, 2011; Konstas, 1997). The American Academy of Ophthalmology recommends the following general screening guidelines healthy adults with no risk factors for eye disease:
- At least once between ages 20-29
- At least twice between ages 30-39
- Age 40-64: every 2 to 4 years
- Age 65 and older: every 1 to 2 years

**Treatment of glaucoma**

The management of glaucoma depends on the type, the underlying cause, and the severity of the disease. Treatment may involve medications, in the form of eye drops or oral drugs, laser procedures, or surgery; however glaucoma cannot be cured (Hitesh, 2012). The focus and goal of treatment is to control the disease and prevent or slow any further visual damage from occurring. Numerous studies have shown that lowering the pressure inside the eye (intraocular pressure) decreases the risk of glaucoma progression. Just how much to lower the pressure and exactly how to do it is a matter for every patient. In fact, some patients, medication fails to reduce IOP adequately. It is important therefore to balance efficacy, tolerability and side effects on a patient by patient basis. The treatment program can change over the time that glaucoma is treated. In some cases the change is necessary because of an unwanted side effect from the medication. In other cases, prescribing a stronger drug or adding another medication is necessary to maintain control of the eye pressure (Leopold, 2012). The most frequently used medical therapies are as follows:

**Beta blockers:** It lowers the pressure in the eye by reducing aqueous production. These drugs are divided into two classes: 1) nonselective beta-blockers (timolol, levobunolol, metipranolol, carteolol) and 2) beta 1 selective (betaxolol). Used in a variety of glaucoma eye drops, beta-blockers were at one time the drugs of first choice in treating glaucoma. These drugs work by decreasing fluid (aqueous) production in the eye and now are often prescribed as an adjunct to or in combination with prostaglandins. These eye drops have the potential to reduce heart rate and may cause adverse side effects in individuals with certain heart problems, lung problems (such as emphysema), diabetes, depression or other conditions. For these reasons, discuss about medical history in detail with eye doctor before using beta-blockers. Examples of beta-blockers used in glaucoma treatment are TimopticXE (Merck), IstaIol (ISTA) and Beotopic S (Alcon).

**Prostaglandins:** Drugs known as prostaglandins used in eye drops often have the best user compliance because they are required only once daily. Prostaglandins generally work by relaxing muscles in the eye's interior structure to allow better outflow of fluids, thus reducing buildup of eye pressure. These drugs have a few common side effects, including stinging and burning when put in the eye, eye color change (darkening of the eye) due to an increase of pigmentation in their is, and lengthening and curling of the eyelashes. Examples of prostaglandins used in the treatment of glaucoma-Xalatan (Pfizer), Lumigan (Allergan), Travatan Z(Alcon) and Rescula (Novartis). Latanoprost was the first of this class to be generally available, and it climbed rapidly to the position of most frequently prescribed drug for glaucoma, despite complaints about its cost. It has the advantage of effectiveness in lowering eye pressure with once daily dosing (Liu, 2003).
**Alpha-adrenergic agonists:** These drugs work by decreasing the rate of aqueous humor production and can be used alone or in combination with other anti-glaucoma eye drops. Common side effects associated with this classification include red or bloodshot eyes (ocular injection), upper lid elevation, an enlarged (dilated) pupil and itching. Examples of this class include Iopidine (Alcon), Alphagan (Allergan) and Alphagan-P (Allergan) (Mietzh, 1994).

**Carbonic anhydrase inhibitors:** These drugs work by decreasing the rate of aqueous humor production. They are usually used in combination with other anti-glaucoma eye drops and not alone. This classification of drug is also used in oral form (pills). Common side effects experienced with this classification of eye drop include burning, a bitter taste, eyelid reactions and eye redness (ocular injection). Examples of this class include Dismox (Sigma), Neptazane (Wyeth-Ayerst) and Daranide (Merck, Sharp & Dohme). About half of patients cannot tolerate oral CAIs due to their systemic side effects, which include fatigue, depression, loss of appetite, weight loss, loss of libido, kidney stones, metallic taste and tingling in fingers and toes (peripheral neuropathies) (Maurice, 1958).

**Parasympathomimetics:** These drugs work by increasing the outflow of aqueous humor from the eye. They are frequently used to control IOP in narrow-angle glaucoma. These eye drops cause the pupil to constrict, which assists in opening the narrowed or blocked angle where drainage occurs. Common side effects experienced with these types of eye drops include brow ache, pupil constriction, burning, and reduced night vision. Examples of this class include pilocarpine, carbachol, echothiophate and demecarium. (Pergande, 1990).

**Epinephrine:** The epinephrine class of drugs has a dual effect on the eye. These drugs work by decreasing the rate of aqueous humor production and increasing the outflow of aqueous humor from the eye. Common side effects experienced with this classification of eye drop include pigmented eye surface membrane (conjunctival) deposits, blocked tear ducts and eye palpitations with an increased heart rate. Examples of this class include epinephrine and Allergan's Propine (dipivalyl epinephrine) (Patel, 2011).

**Hyperosmotic agents:** These drugs are usually for people with a severely high IOP that must be reduced immediately before permanent, irreversible damage occurs to the optic nerve. Hyperosmotic agents reduce IOP by lowering fluid volume in the eye. They are usually given only on a one-time, emergency basis. Examples of these drugs include oral glycerin and isotosorbide orally, and mannitol and urea intravenously (Thuiefors, 1994).

**Combination glaucoma drugs:** Study results show that half of individuals with glaucoma require more than one type of medication to control IOP. For this reason, a few ophthalmic pharmaceutical companies have produced "combination" eye drops that can include two different anti-glaucoma medicines in the same bottle. For convenience, doctors might prescribe combined IOP-lowering medications. Typically, these combined medications have the additive effect of reducing IOP. Examples of medications of this type include Cosopt (Merk), Combigan (Allergan) and DuoTrav (Alcon) (Vandervort, 1999).

The following drugs are classified as Antiglaucomatous agents:
- Acetazolamide, Betaxolol, Brimonidine, Brizolamide, Carbidopa, Levadopa, Carteolol, Dorzolamide, Timolol, Epinephrine, Latanoprost, Timolol, Levobunolol.

**Challenges in the treatment of glaucoma**

The prime challenge of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration to provide ocular delivery systems with high therapeutic efficacy. The anatomy, physiology and barrier function of the cornea compromise the rapid absorption of drugs. Frequent instillations of eye drops are necessary to maintain a therapeutic drug level in the tear film or at the site of action. But the frequent use of highly concentrated solutions may induce toxic side effects and cellular damage at the ocular surface. Poor bioavailability of drugs from ocular dosage forms is mainly due to the precorneal loss factors which include solution drainage, lacrimation, tear dynamics, tear dilution, tear turnover, conjunctival absorption, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane are the major challenges to anterior segment drug delivery following topical administration. Due to these physiological and anatomical constraints, only a small fraction of the drug, effectively 1% or even less of the instilled dose, is ocularly absorbed. To be clinically effective, topical formulation has to possess balance between lipophilicity and hydrophilicity with higher contact time (Saini, 2012).

**Eye: Anatomical and physiological overview:** The human eye has spherical shape with 23 mm diameter. The structural components of the ball are divided in to three layers.

- The outer most coat of clear transparent cornea and white opaque sclera
- The middle layer comprises the iris anteriorly, the choroids posteriorly and ciliary body as intermediate part; and
- The inner layer is the retina which is an extension of the central nervous system.

The fluid systems in the eye, aqueous humor and vitreous humor also play an important role in maintaining ocular pressure. Cornea is optically transparent tissue that acts as the principle refractive element of the eye. The corneal diameter is about 11.7 mm with a radius of curvature (anterior surface) about 7.8 mm. The corneal thickness is 0.5-0.7 mm and it is thicker in the center. The cornea is composed of epithelium, bowen's membrane, strauma, descement's membrane and...
endothelium. The relative thickness of corneal epithelium (50-90 mm), strauma and endothelium are about 0.1, 1.0 & 0.01 respectively (Wierbowksa, 2012). The shape of cornea and lens is adjusted by ciliary body. A mesh of blood vessels, the choroids supplies oxygen and glucose to the retina. Lachrymal gland secretes tears that wash foreign bodies out of and keep the cornea from drying out. Blinking compresses the lachrymal sac and allows the lachrymal fluid to move out which moistures the eye surface (Rathore, 2009). The drugs in ophthalmic preparation reach inside the eye through cornea, because the structure of cornea consists of epithelium–strauma–endothelium, which is equivalent to a fat-water-fat system. The penetration of non-polar compound through the cornea depends on their oil/water partition coefficient. The blood ocular barrier normally keeps most drugs out of the eye. However inflammation breaks down this barrier allowing drug and large molecule to penetrate into the eye. As the inflammation subsides the barrier will return. The blood barrier comprises the following sites.

- The aqueous humor blood barrier between the ciliary epithelium and capillaries of iris.
- Blood retinal barrier: Non-fenestrated capillaries of the retinal circulation and tight junction between retinal epithelial cell preventing passages of the large molecule from choroid capillaries of retina.

**Absorption of drug in eye:** It is often assumed that drugs administered into the eye are totally and rapidly absorbed however these are few factors which affect the drug delivery to the eye. Absorption of drug takes place in corneal or non-corneal route. The non-corneal route involves absorption across the sclera and conjunctiva which restrains the entry of drug into aqueous humor. Maximum absorption takes place in cornea which leads drug to aqueous humor. A big portion of the drug that administered to the eye was lost leading to poor ocular bioavailability.

**Drug elimination from lachrymal fluid:** Drugs are mainly eliminated from the precorneal lachrymal fluid by solution drainage, lacrimation and nonproductive absorption by conjunctiva of the eye. Only little percentage of applied doses delivered in to intra ocular tissue, while the major part (50-100%) of dose is absorbed systemically. The pre-corneal constraints include:

1. Dilution of drug by over flow
2. Dilution of drug by tear turns over
3. Nasolachrymal drainage conjunctival absorption
4. Enzyme metabolism

The numbers refer to following processes: 1) Transcorneal penetration from the lachrymal fluid into the anterior chamber, 2) Non-corneal drug permeation across the conjunctiva and sclera into the anterior urea, 3) Drug distribution from the blood stream via blood-aqueous barrier into the anterior chamber, 4) Elimination of drug from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and Selemm’s canal, 5) Drug elimination from the aqueous humor into the systemic circulation across the blood-aqueous barrier, 6) Drug distribution from the blood into the posterior eye across the blood-retina barrier, 7) Intravitreal drug administration, 8) Drug elimination from the vitreous via posterior route across the blood-retina barrier and 9) Drug elimination from the vitreous via anterior route to the posterior chamber (Fig 4).

**Transcorneal penetration:** Trans-corneal penetration mainly affected by corneal barrier, physicochemical properties of drug and active ion transport system present at cornea. Corneal epithelium is the main barrier for drug absorption in the eye. The stratified corneal epithelium acts as a protective barrier against invasion of foreign molecule and also a barrier to ion transport. In a healthy corneal epithelium trans-cellular tight junction completely surround the most super facial cells. A tight junction serves as selective barrier for small molecules and they completely prevent the diffusion of macromolecules via Para cellular route, were as small molecules are able to penetrate through intercellular space of corneal epithelium. Corneal stroma is a highly hydrophilic tissue containing mostly water, and is a relatively open structure. Corneal stroma penetration rate is rate limiting step for lipophilic drug. Hydrophilic drug penetrate primarily through Para cellular pathway which involves passive and active diffusion, while lipophilic drug prefers Trans-cellular route. For a topically applied drug passive diffusion by Trans-cellular/Para-cellular way is the main mechanism of permeation. Lipophilicity solubility, molecular size, charge and degree of ionization also affect the route and rate of penetration in cornea. Various enzymes present in ocular tissue (protease, peptidase, and esterase) may metabolize many of ocular drugs during or after absorption. The corneal epithelium contains ionic channels that are selective for cation over anion and also contains an outwardly rectifying anion channel in the apical membrane and highly conductive potassium channel.

**Non corneal absorption:** This route involves drug penetration across the bulbar conjunctiva and underlying sclera in to the uveal tract and vitreous humor. This route is important for hydrophilic and large molecule with poor corneal permeability. Tight junctions of spherical conjunctival epithelium are main barrier of drug penetration. Conjunctival permeability of particular drug
have magnitude higher than that of corneal penetration through sclera is mainly through perivascular spaces, through the aqueous media of gel like muco polysaccharide or through spaces between collagen network. Sclera has more permeability compare to cornea.

**Conventional ocular delivery constrains:** For the ailments of the eye, topical administration is usually preferred over systemic administration so as to avoid systemic toxicity, for rapid onset of action, and for decreasing the required dose. Though topical administration offers many advantages to treat disorders of anterior structures of the eye, it suffers from a serious disadvantage of poor bioavailability due to several biological factors which exist to protect the eye and consequently limit the entry of ocular drugs. The constraints in topical delivery of the eye are shown in the Figure 5 (Whitacre, 1993).

**Disadvantage of topical ophthalmic formulations**
- They have poor bioavailability because of rapid precorneal elimination, conjunctival absorption solution drainage by gravity, induced lacrimation, normal tear turn over.
- Frequent instillation of concentrated medication is required to achieve therapeutic effect.
- Systemic absorption of drug and additives drained through nasolachrymal duct may result in undesirable effect.
- The amount of drug delivered during external application may vary. The drop size of ocular medication is not uniform and dose delivered is generally not correct.

**Requisites of controlled ocular delivery system**
- To overcome the side effects of pulsed dosing (frequent dosing) and high concentration produced by conventional system.
- To provide sustained and controlled drug delivery.
- To increase the corneal bioavailability of drug by increasing corneal contact time.
- This can be achieved by effective coating or adherence to corneal surface, so that the released drug effectively reaches the anterior chamber.
- To provide targeting within the ocular globe so as to prevent the loss to other ocular diseases.
- To circumvent the protective barrier like drainage, lacrimation and diversion of exogenous chemicals into the systemic circulation by the conjunctiva.
- To provide comfort and compliance to the patient and yet improve the therapeutic performance of the drug over conventional system.
- To improve the better housing of the delivery system in the eye so as the loss to other tissues besides cornea is prevented.

Ocular drugs and delivery system are currently undergoing a process of design optimization due to inherent physiological and anatomical constraints of the eye leading to limited absorption topically applied drug. Many ongoing clinical studies are trying to find neuroprotective agents (memantine, glatiramer acetate) that might benefit the optic nerve and certain retinal cells in glaucoma. The treatment of open angle glaucoma and secondary glaucoma is primarily with drugs, whereas the narrow-angle or congenital types is primarily surgical. Long-term use of ocular drugs, as in glaucoma patients who are treated for decades after they are diagnosed, frequently causes tear film and conjunctival involvement, sometimes resulting in sight threatening ocular surface disorders. Moreover, higher concentration of some drugs causes allergy at the ocular surface such as α-2-agonist brimonidine shows concentration dependent allergy due to oxidation of the drug. Prolonged use of eye medications with preservatives presents a certain risk to ocular surface, such as thickness of sub-epithelial collagen of conjunctiva, a chronic sub-clinical inflammation as shown by the presence of immunologic changes and inflammatory infiltrates. Medications placed in the eye are absorbed into the conjunctival blood vessels on the eye surface. A certain percentage of the active ingredient of the medication, though small, will enter the blood stream and may adversely affect functions such as heart rate and breathing. Hence, there is a need to develop an alternative ophthalmic preparation.

**Approaches in the treatment of glaucoma**

The goal of researchers is to treat a disease consistently and accurately. Currently the knowledge in this field is rapidly expanding and many concepts and drug delivery strategies are emerging out. The various approaches attempted in the early stages like bioavailability improvement and controlled release drug delivery for the treatment of glaucoma. The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of antiglaucomic drugs can be divided into two categories. (a) First to maximize the corneal drug absorption and minimize the precorneal drug loss through viscosity and penetration enhancers, prodrug, gel, liposomes and niosomes. (b) Second one is based on the use of sustained/controlled drug delivery systems which provide the controlled and continuous delivery of ophthalmic drugs, such as implants, inserts,
nanoparticles, micro particulates, and colloid. Traditional approaches like viscosity enhancers, gel, penetration enhancer, prodrug, improve the ophthalmic bioavailability of the drugs to the anterior segment of the eye. Various modern approaches like in situ gel, ocuserts, nanosuspenion, nanoparticles, liposomes, niosomes, punctal plug delivery system and implants improve the ophthalmic bioavailability of the drugs and controlled the release of the antiglaucomics drugs to the anterior segment of the eye. Moreover, approaches like intravitreal injections, iontophoresis, sub conjunctival injection, and periocular route are used to deliver ophthalmic drugs to the posterior segment of the eye.

**Hydrogel**

Hydrogel (also called aquagel) is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are highly absorbent (they can contain over 99.9% water) natural or synthetic polymers. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content. Hydrogels are cross-linked; three-dimensionally drophilic networks that swells but not dissolve when brought into contact with water. Hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. Hydrogels based drug delivery system for the treatment of glaucoma is the popular approach preferred by the researcher's nowadays. Hydrogel systems prepared from the polymers that exhibit reversible phase transition. Such systems can be formulated in liquid phase suitable to be administrated by instillation into the eye cavity and which upon exposure to the stimuli such as pH, temperature, and ion activated etc., changes to the gel phase and thus improves the residence time and corneal bioavailability of the drug. There are various methods used to cause sol to gel phase transition on ocular surface such as temp dependent concept (pluronics), pH triggered systems (including cellulose acetate hydrogen phthalate latex, Carbopol, Ion activated systems including gelrite, gellan and carbopol/pluronics. Vinod et al., had developed hydrogels which was therapeutically efficacious, stable, non-irritant and provide a sustained release of drug over 8 hr time period (Bharath, 2009); (Ah El Kamal, 2002).

**Liposomes**

Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments. Liposomes possess the ability to have an intimate contact with the corneal and conjunctival surfaces, which increases the probability of ocular drug absorption. This ability is especially desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility, or those with medium to high molecular weights. The behavior of liposomes as an ocular drug delivery system has been observed to be, in part, due to their surface charge. Positively charged liposomes seem to be preferentially captured at the negatively charged corneal surface as compared with neutral or negatively charged liposomes. It is droppable, biocompatible, and biodegradable in nature. It reduced the toxicity of the drug. It provides the sustained release and site-specific delivery. Liposomes are difficult to manufacture in sterile preparation. It has limitation like low drug load and inadequate aqueous stability. Liposomal formulation of brimonidine tartrate has prepared and IOP-lowering activity of liposomes was determined and compared with that of pure drug solution and showed that the IOP-lowering action of liposomes sustained for a longer period of time. The results of the study indicate that it is possible to develop a safe and physiologically effective topical formulation that is also convenient for patients (Durrani, 1992); (Livia Budai, 2007).

**Niosomes**

Niosomes are bilayered structural vesicles made up of nonionic surfactant which are capable of encapsulating both lipophilic and hydrophilic compounds. Niosomes reduce the systemic drainage and improve the residence time, which leads to increase ocular bioavailability. They are non-biodegradable and non-biocompatible in nature. In a recent approach to deliver cyclopentolate, niosomal formulation was developed. It released the drug independent of pH, resulting in significant enhancement of ocular bioavailability. Niosomal formulation of coated (chitosan or carbopol) timolol maleate exhibited significant IOP lowering effect in rabbits as compared with timolol solution. Niosomal formulation of brimonidine tartrate has prepared and IOP-lowering activity of niosomes was determined and compared with that of pure drug solution and showed that the IOP-lowering action of niosomes sustained for a longer period of time. The results of the study indicate that it is possible to develop a safe and physiologically effective topical formulation that is also convenient for patients (Tamizharasi, 2003; Uchegbu, 1998; Hitesh, 2012; Prabhu, 2008).

**Nanoparticles/nanosphers**

These are polymeric colloidal particles, ranging from 10 nm to 1 mm, in which the drug is dissolved, entrapped, encapsulated, or adsorbed. Encapsulation of the drug leads to stabilization of the drug. They represent promising drug carriers for ophthalmic application. They are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membrane) or nanocapsules (solid matricial spheres). Marchal-Heuissier et al., found that the nanocapsules show a better effect than the nanospheres, probably because the drug (betaxolol, carteolol) is in a unionized form in the oily core and can diffuse at a greater rate into the cornea. Several authors suggest that the better efficiency of nanocapsules is due to their bioadhesive properties, resulting in an increase in the residence time and biological response. Hence, it improved the ocular bioavailability of the drug and reduced dosing frequency. Alonso et al., have also reported that the nanoparticles of poly-e-caprolactone
containing cyclosporin show a better corneal absorption with respect to the oily solution of the drug (Agnihotri, 2004; Soppimath, 2001).

**Nanosuspension**

It is defined as sub-micron colloidal system which consists of poorly water-soluble drug, suspended in an appropriate dispersion medium stabilized by surfactants. It usually consists of colloidal carriers like polymeric resins which are inert in nature. It improves the ocular bioavailability of the drug by prolonging the contact time. Charge on the surface of nanoparticles facilitates its adhesion to the cornea. Cloricromene (AD6) was formulated in nanosuspension by using Eudragit RS100 and RL100. AD6-loaded eudragit retarded nanoparticles suspension offered a significant edge in enhancing the shelf life and bioavailability of the drug (Sahoo, 2008).

**Microemulsion**

Microemulsion is stable dispersions of water and oil, facilitated by a combination of surfactant and co surfactant in a manner to reduce interfacial tension. Microemulsion improves the ocular bioavailability of the drug and reduces frequency of the administration (Ansari, 2008); (Dhaliwal, 2008).

**Prodrug**

The principle of prodrug is to enhance corneal drug permeability through modification of the hydrophilicity (or lipophilicity) of the drug. Within the cornea or after corneal penetration, the prodrug is either chemically or enzymatically metabolized to the active parent compound. Thus, the ideal prodrug should not only have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility. Enzyme systems identified in ocular tissues include esterases, ketone reductase, and steroid 6-hydroxylase. Prodrug is considered as a new drug entity so extensive pharmacokinetic and pharmacologic information is required for proper design. Thus it is concluded that prodrug can be the drug delivery system for the treatment of glaucoma (Vinod, 2011).

**Ocular inserts**

The ocular inserts provides more controlled, sustained, and continuous drug delivery by maintaining an effective drug concentration in the target tissues and yet minimizing the number of applications. It reduces systemic adsorption of the drug. It causes accurate dosing of the drug. It has disadvantages like patient incompliance, difficulty with self-insertion, foreign body sensation, and inadvertent loss from the eye. A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, nonerodible, and hydrogel inserts. Ocular inserts can be the valuable technique for the treatment of glaucoma (Sharma, 2011).

**Laser and surgery**

Glaucoma can also be treated with the use of laser therapy. The primary strategy involves “burning” holes in various areas within the eyes including the ciliary and the pigmented trabecular meshwork cells. The benefits of such therapy areas include non-invasive, needing less patient compliance and lowering the possibility of infection or bleeding. The IOP of most patients can decrease about 20-30%, but the treatment effect wears off 5-10% every year. In combination with timolol, the two year IOP lowering success rate is 70%, compared with the laser alone (44%) and timolol alone (30%). A common form of surgery is trabeculectomy, which creates a guarded channel allowing aqueous humor to flow from the anterior chamber inside the eye to sub-Tenon and subconjunctival space. The benefits of surgery include stabilizing IOP and bypassing the requirements for strict patient compliance and continuous drug costs. Surgery is considered as the last option because if surgery fails then it may be immediate blindness due to complications such as choroidal effusion, hypotonic maculopathy, suprachoroidal hemorrhage and optic nerve snuffling (Kumarasamy, 2006).

**Conclusion**

Ocular drug delivery is difficult because of multiple barriers imposed by the eye against the entry of medicament. There are no specific guidelines for preventing or reducing the risk of glaucoma. Regular comprehensive eye examination may reduce the severity of disease. The modern goals of glaucoma management are to avoid glaucomatous damage and nerve damage, and preserve visual field and total quality of life for patients with minimal side effects. This requires appropriate diagnostic techniques and follow-up examinations and judicious selection of treatments for the individual patient. Effective and safe treatment is a massive challenge for scientists in the field because of the nature of disease and presence of the ocular barriers. Over the years attempt have been made to improve the bioavailability of drugs as well as sustained/controlled the effect of medicament through the various approaches like niosomal or liposomal delivery systems, hydrogel systems as well as implants or ocuserts. The risks and benefits of each type of treatment must be carefully considered to maximize the treatment’s benefits while minimizing adverse effects. So it is concluded that the development of novel techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy.

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