IJPSR (2016), Vol. 7, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 31 March, 2016; received in revised form, 01 July, 2016; accepted, 14 July, 2016; published 01 September, 2016

CURRENT AND NOVEL TECHNIQUES IN THE OPHTHALMIC DRUG DELIVERY SYSTEMS

Pravin K Shende * and Rashmi Godbole

Shobhaben Pratapbhai Patel-School of Pharmacy and Technology Management, SVKM's NMIMS University, Mumbai, India.

Keywords:

Ocular drug delivery, nanosuspensions, dendrimers, niosomes, liposomes

Correspondence to Author:
Dr. Pravin K. Shende

Associate Professor
Shobhaben Pratapbhai Patel-School of Pharmacy and Technology Management, SVKM's NMIMS University, V. L. Mehta road, Vile Parle (west) Mumbai, India.

Email: shendepravin94@gmail.com

ABSTRACT: For human survival, vision or sight is extremely important. Ocular drug delivery has been a major challenge to pharmacologists and drug delivery scientists due to its unique anatomy and physiology. There are both conventional and novel drug deliveries available as topical administration for the treatment of diseases related to the eye. Conventional dosage form includes ophthalmic solutions, suspensions, ointments, gels, inserts etc. Novel dosage form includes microemulsions, nanosuspensions, dendrimers, niosomes, liposomes etc. Novel drug delivery systems provide increased bioavailability of the drug compared to that of conventional drug delivery system. Current developments in the field of ophthalmic drug delivery promise a significant improvement in overcoming the challenges posed by various anterior and posterior segment diseases. Here in this article, we are going to discuss about the anatomy of the eye, the most common disorders of the eye, and the conventional and novel formulation approaches for ophthalmic drug delivery and the current market scenario.

INTRODUCTION: Anatomy of the Eye: The most used of the five senses is Vision and is one of the primary means that is used to gather information from our surroundings. Visual information gives more than 75% of the information about the world around us. [1]

Components of an eye:

- **Iris:** The light that enters the eye is regulated by iris. It is the coloured visible part of eye in front of the lens. Light enters through pupil which is the central opening.
- **Pupil:** The opening in the center of the eye is called pupil. Iris controls the widening and narrowing (dilation and constriction) of the pupil.
- **Cornea:** It is the eye's outermost layer. It is a clear dome-shaped surface that covers the front of the eye. It refracts the light entering the eye onto the lens, which then focuses it onto the retina. The cornea contains no blood vessels to protect or nourish it against infections, unlike most tissues in the body. Instead, the cornea recieves its nourishment from tears and aqueous humor (a fluid in the anterior portion of the eye)
- **Lens:** The transparent structure in the eye that helps to refract light to be focused on the retina. If the lens becomes cloudy, then a cataract operation is required which

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(9).3557-66

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (9).3557-66

involves the replacement of the cloudy lens with an artificial plastic lens.

- **Choroid:** Also known as the choroid coat, it is the middle layer of the eye, which contains the connective tissues lying between the retina and the sclera. The outer layers of retina are provided with oxygen and nutrition by choroid. Blurring of vision is prevented by a pigment which is present in choroid that absorbs excess light hence prevents blurring of vision.

- **Ciliary body:** It is the part of the eye that includes the ciliary muscle, which controls the shape of the lens.

- **Retina:** a light sensitive layer that lines the interior of the eye. The retina works much in the same way as film in a camera. It is composed of light sensitive cells known as rods and cones.

  The human eye contains about 125 million rods, which are necessary for seeing in dim light. They are photoreceptor cells in the retina of the eye that can function in less intense light. Rod cells are almost entirely responsible for night vision.

  Cones, on the other hand, function best in bright light and are between 6 and 7 million in the eye which helps in receiving a sharp accurate image and for distinguishing colours. These are the second type of photoreceptor cells in the retina of the eye. They function best in bright light and are essential for acute vision (receiving a sharp accurate image). It is thought that there are three types of cones, each sensitive to the wavelength of a different primary colour – red, green or blue. Other colours are seen as combinations of these primary colours.

- **Macula:** It is a yellow spot on the retina at the back of the eye which surrounds the fovea.

- **Fovea:** A small pit at the centre of the macula and is the area with the greatest concentration of cone cells and is responsible for central, high resolution vision. When the eye is directed at an object, the part of the image that is focused on the fovea is the image most accurately registered by the brain.

- **Optic disc:** It is the visible (when the eye is examined) portion of the optic nerve, also found on the retina. The optic disc identifies the start of the optic nerve where messages from cone and rod cells leave the eye via nerve fibres to the optic centre of the brain. This area is also known as the 'blind spot'.

- **Optic nerve:** Is a paired nerve that transmits visual information from the retina to the brain

- **Sclera:** It is the white part of the eye, a tough covering with which the cornea forms the external protective coat of the eye. [2]

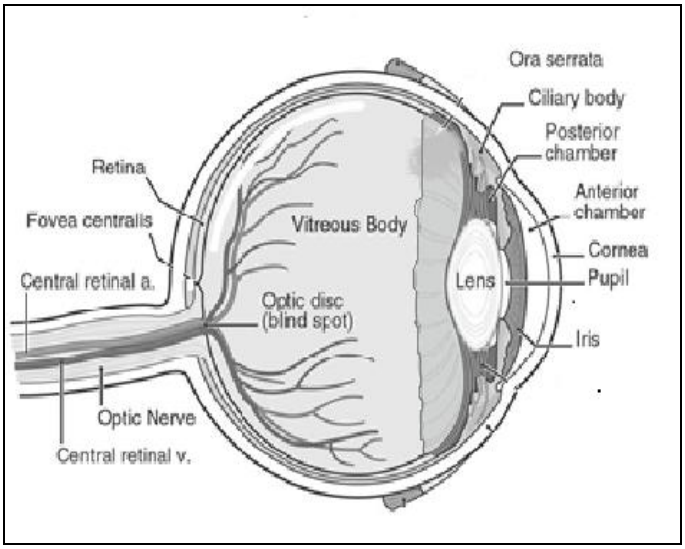

FIG.1: ANATOMY OF THE EYE

Tear Formation and Drainage:

Tear fluid is generated through Lacrimal gland to keep the eye moist, which are reabsorbed through puncta region. Puncta is a small opening that drains tear fluids to nasolacrimal sac and eventually to the back of the throat. Although some parts of the fluid is aqueous, meibomian glands produces oleaginous meibum along eyelid to reduce tear evaporation. This oil spreads over the aqueous layer of tears when a person blinks eye, to form a protective barrier to prevent fluids from drying out. Abnormal

overflow of the tear fluid down the cheek is called epiphora, which is caused by nasolacrimal duct obstruction. [3]

Common Eye Disorders:

Approximately 11 million people are affected by disorders related to ophthalmology. More than 3.3 million population aged 40 years and older have low vision or are either blind. Age related eye diseases such as cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration are the leading causes of blindness and low vision.

1. **Refractive Errors:**
   United States has the most frequent eye problems of Refractive errors. Myopia (near - sightedness), hyperopia (farsightedness), astigmatism (distorted vision), and presbyopia occurs in the age between 40-50 years are the types included in Refractive errors. Eyeglasses, surgery, or contact lenses can be used to increase the vision. Vision could be improved among 11 million Americans by improving proper refractive correction.

2. **Age-related Macular Degeneration:**
   Age-related macular degeneration (AMD), often called Macular degeneration is an eye disorder associated with aging and results in damaging sharp and central vision. AMD affects the central part of retina i.e. the retina which allows the eye to see fine details. 2.95 million people are estimated to have permanent impairment of fine or close up vision, or reading in people aged 65 years and older by AMD by the year 2020.

   a. **Wet AMD:**
      Wet AMD occurs when there is leakage in the fluid and blood which happens because of abnormal blood vessel behind the retina start to grow under macula. Rapid central vision loss occurs, because of bleeding, leaking and scarring from these blood vessels. Early symptom of wet AMD include straight lines appearing wavy.

   b. **Dry AMD:**
      Dry AMD causes blurring of central vision of both eyes, which occurs when the macula thins overtime as part of aging process. Dry AMD accounts for 70-90% of cases and is more common form of AMD which progresses slowly than the wet form. Early symptoms of Dry AMD is drusen, which is the tiny white or yellow deposits under the retina. Drusen is observed in people aged 60 years and older, which does not cause vision loss and is very common. However, the presence of large number of drusen raises the risk of developing Dry AMD or Wet AMD.

3. **Cataract:**
   Worldwide, Cataract is the leading cause of blindness and vision loss which is buildup of protein in the lens which causes clouding of the eye's lens. This prevents light from passing clearly through the lens causing loss of vision. Since new lens cells form on the outside of the lens, all the older cells are compacted into the center of the lens resulting in the cataract. Cataract is age bound, although treatment for removal of cataract is widely available. [4]

Various types of Cataracts:

a. **Age related cataracts:** This type of cataract develops as a result of aging, as the name suggests.

b. **Congenital cataracts:** Congenital cataracts are seen in babies born with cataract which may be because of injury, infection or poor development.

c. **Secondary cataracts:** Secondary cataracts develop as a result of medical conditions like diabetes, exposure to toxic substances, certain drugs (such as corticosteroids or diuretics), radiation or ultraviolet light.

d. **Traumatic cataracts:** Traumatic cataract is formed after injury to the eye.

e. Other factors include cigarette smoke, air pollution, and heavy alcohol consumption. [5]

4. **Diabetic Retinopathy:**
   Diabetic retinopathy (DR) is one of the cause of blindness in adults which is caused by complication in diabetes. DR is characterized by progressive damage to the blood vessels of the retina, the light-sensitive tissue at the back of the eye which is important for good vision.

   DR progresses through four stages:

   a. Mild nonproliferative retinopathy:

   b. Moderate nonproliferative retinopathy: caused due to blockage in some retinal vessels

   c. Severe nonproliferative retinopathy: caused by blockage because of deprived blood supply in retina which help in growing new blood vessels

   d. Proliferative retinopathy: most advanced stage

Disease management can reduce the risk of DR's which include control of blood sugar, blood pressure and lipid abnormalities. The risk of vision loss can be reduced by early diagnosis and timely treatment of DR, however 50% of patients are late in the diagnosis and treatment.

5. **Glaucoma:**
   Glaucoma causes vision loss and blindness because of damage to the eye's optic nerve. When the normal fluid pressure inside the eye increases, it leads to Glaucoma. With early treatment, glaucoma can often be protected against serious vision loss.

The two main types of Glaucoma are:

1. Open angle Glaucoma: It is termed as a chronic condition where the disease progresses slowly over a period of time. It is often referred as "sneak thief of eye".

2. Closed angle Glaucoma: This condition is sudden and painful. Vision loss can progress quickly, however medical attention is seeked by patients because of pain and discomfort to avoid permanent damage.

6. **Amblyopia:**
Amblyopia causes vision impairment in children, which is also referred as 'lazy eye'. Approximately 2-3% population suffers from Amblyopia. When the co-ordination of eye and brain are not working properly, the vision in one of the eye is reduced and the medical terminology given to it is Amblyopia. In this condition, the brain favors other eye, and hence diseased eye does not work normally, irrespective of looking normal. Strabismus, which is an imbalance in positioning of two eyes; nearsighted, farsighted, and rarely other eye conditions such as cataract is the condition leading to amblyopia. Unless it is successfully treated in early childhood amblyopia usually persists into adulthood, and is the most common cause of permanent one-eye vision impairment among children and young and middle-aged adults.

7. **Strabismus:**
   Strabismus is linked with an imbalance in the positioning of two eyes which is because of the lack of coordination in the two eyes. It can cause the eyes to cross in (i.e. esotropia) or turn out (i.e. exotropia). As a result of which, the eyes do not focus on same point simultaneously, and look in different directions. When the two eyes fail to focus on the same image, there is reduced or absent depth perception and the brain may learn to ignore the input from one eye, causing permanent vision loss in that eye (one type of amblyopia) [4]

Dosage forms for topical application to the eye:
Sterility and sensitivity of the product toward eye of the finished product is the most critical requirement in ophthalmic drug delivery system. All ophthalmic dosage forms may consist of excipients which control the osmotic pressure, the pH, and viscosity of the preparation.

a) Conventional dosage form:

1. **Solutions:** Ophthalmic solutions are sterile aqueous solutions used for instillation in the

eye. Aqueous solutions may also contain preservative if stored in multiuse packaging. This dosage form also includes solid preparations that, when reconstituted according to the label instructions, result in a solution.

Increasing the viscosity of the ophthalmic solutions upto 20 centipoise (cP) can increase the corneal contact time. There is reflux tearing and blinking in order to gain the original viscosity of the lacrimal fluid (1.05–5.97 cP) if the viscosity of ophthalmic solution is more than 20 centipoise. Increase in viscosity leads to increase in bioavailability which in turn leads to reduction in frequency of dosing. Because of physiological compatibility and satisfactory physiochemical properties, Synthetic polymers, such as polyvinylalcohol (PVA), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyacrylic acid (PAA), and many cellulose derivatives, are commonly employed as viscosity enhancers.

A more sophisticated approach in ophthalmic solution is in-situ gels which consists of using polymers that provide the liquid formulation with semisolid consistency only when it is placed in the conjunctival or corneal area. In this way, ease of handling of the solution is followed by prolonged permanence as a result of the viscoelastic properties of the formed hydrogel. This in situ gelling phenomenon is caused by a change in the conformation of the polymer(s) that can be triggered by external stimuli such as temperature, pH, ionic content and lacrimal fluid upon delivery into the eye. Two of the major drawbacks of viscous and mucoadhesive formulations are blurring and an unpleasant sticky feeling in the eye. As consequence, patients may find compliance with treatment schedules difficult.

2. Suspensions:

Corneal contact time of a drug substance can be increased with the use of ophthalmic suspensions and hence providing a more sustained action. This dosage form includes solid preparations those, when reconstituted according to label instructions result in suspension. The sterile powder can be manufactured by lyophilization in the individual container. In powdered form the drug may have a much longer shelf life than in solution or suspension. Usually, a separately packaged sterile diluent is provided with the sterile powder. When the active ingredient is insoluble in desired vehicle or is unstable in solution, then an ophthalmic solution may be required. The insoluble drug is made in a micronized form (less than 10 µm in diameter) and then dispersed in a suitable vehicle to prevent irritation or scratching of cornea. The major disadvantage of suspensions is that the concentration of the dissolved drug cannot be predicted due to its relative insolubility in the vehicle.

Particle size in ophthalmic suspensions is extremely important, and particle size above 10 µm in diameter may result in reflux tearing because of foreign body sensation. Patient comfort and acceptability can be improved by reduction in particle size. Stability testing can evaluate the potential for any changes in particle size due to Ostwald ripening or particle agglomeration.

For effective dispersion of drug surfactants may be used during manufacture of suspensions. Non-ionic surfactants are generally used since they are less toxic. There must be careful evaluation of the amount of surfactant added because excessive amount may lead to irritation in the eye, interactions with other excipients, foaming on shaking while manufacturing.

Physical stability of a suspension must be considered. The particles must redisperse to achieve dosage uniformity if they settle at the bottom of the container and form a cake. Viscosity enhancing agents may help keep the particles suspended.

3. Ointments:

Sterility is the main concern of ointments. Ointments can be terminally sterilized, or must be manufactured from sterile ingredients in an aseptic environment. Filtration through a suitable membrane or dry heat sterilization is

often used. The ointment base selected for an ophthalmic ointment must be nonirritating to the eye and must permit the diffusion of the active ingredient throughout the secretions bathing the eye. The ointment base used for ophthalmics have melting point or softening point close to body temperature. As compared to ophthalmic solutions, ophthalmic ointment must have a longer contact time with eye. The only disadvantage in ophthalmic ointments is blurred vision that occurs as ointment base melts and is spread across the lens.

4. Gels:

Ophthalmic gels compose of mucoadhesive polymers which provide localized delivery of an active ingredient to the eye. Mucoadhesive polymers have a property of bio adhesion which means attachment of a drug carrier to a specific biological tissue. Ocular bioavailability is improved because of the increased contact time of the drug with the biological tissue. The release kinetics of the drug from the dosage form wholely depends on the choice of polymer. Few examples of polymers used in ophthalmic gels are carboxymethylcellulose, carbopol, polycarbophil, and sodium alginate.

5. Emulsions:

The rationale for developing an ophthalmic suspension is, limited aqueous solubility of the drug substance. Ophthalmic emulsions are manufactured by dissolving or dispersing the active ingredient(s) into an oil phase, along with suitable emulsifying and suspending agents and mixing with water vigorously to form a uniform oil-in-water emulsion. Each phase is individually sterilized during the manufacturing process and then mixed properly. Reduction in oil droplet size to sub-micron size can be achieved by high shear homogenisation which improves the physical stability of the oil micelles so that they do not coalesce. The final dosage form must contain small oil droplets, which are uniformly suspended. The drug substance(s) can be added to the phase in which it is soluble at the beginning of the manufacturing process, or it can be added after the emulsion is prepared by a suitable dispersion process. Surfactants may be added to the ophthalmic suspensions to prevent flocculation, creaming and coalescence of the emulsions which increases the kinetic stability of the emulsion. Emulsions may exhibit three types of instability: flocculation, creaming, and coalescence. Flocculation describes the process by which the dispersed phase comes out of suspension in the form of flakes. Coalescence is another form of instability in which small droplets within the media continuously combine to form progressively larger droplets. Emulsions can also undergo creaming, where one of the phases migrate to the top (or the bottom, depending on the relative densities of the two phases) of the emulsion.

6. Strips:

Ophthalmic strips are individually packed hence are sterile until time of use, and are made up of filter paper. They are used in detecting corneal abrasions and diagnosing Dry eye syndrome. These strips can be used by staining the cornea with fluorescin sodium (used as a diagnostic strips to visualize defects or aberrations in the corneal epithelium by staining the areas of cellular loss; to evaluate hard contact lens fitting and to evaluate applanation tonometry), lissamine green (used to stain damaged or devitalized cells and to indicate dry patches as well as any mucus-deficient or damaged corneal epithelial cells), and rose Bengal (used to stain degenerating epithelium in the outer layer of cornea as well as mucous filaments) upon instillation. If there is visible speckling of the cornea, it can be indicated that an individual is suffering from dry patches, or is muco-deficient or has damaged corneal cells.

7. Inserts:

Ophthalmic inserts and ocular systems are solid dosage forms which are placed in the conjunctival fornix, in the lachrymal punctum or on the cornea. There are two types of inserts: erodible (soluble) and nonerodible (insoluble). These devices have accurate dose delivery and increase ocular bioavailability. They also avoid the usage of preservatives.

There are two methods in which the drug release from soluble inserts takes place:

a. fast release of a portion of the drug as the tear fluid penetrates into the system; and

b. slow release as a gel layer is formed on the surface of the insert.

At initial stages, the dissolution of the solubilized components is fast and hence cause blurred vision. Erodible inserts can be made from bioerodible polymers (e.g. crosslinked gelatin derivatives, poly vinyl alcohol, hypromellose, and polyesters). The release of the drug is controlled by the ease with which the bonds can be broken of the interaction of drug with the labile bonds which are matrices of simple reservoirs. Inserts can dissolve within 12 – 24 hours. The drug release profile of inserts show a high inter- and intraindividual variability, as the erosion rate is highly dependent on the conditions of the physiological environment. Insoluble inserts can have a reservoir or matrix structure and has release of drug for longer periods of time. Despite the remarkable therapeutic advantages of these inserts, difficulties with handling, the sensation of a foreign body in the eye, and the high risk of accidental expulsion greatly limit their practical use.

7.1 Contact Lenses:

Extended release of drugs into the eye can be provided by contact lenses. Current challenges in this mode of drug delivery are to sustain drug release for longer periods and also to incorporate sufficient drug amounts in the lens matrix. Some drugs can be absorbed into the hydrogel soft contact lenses and released in the lacrimal fluid, which reduces clearance and sorption through the conjunctiva. The ability to be a drug reservoir strongly depends on the water content and thickness of the lens, the molecular weight of the drug, the concentration of the drug loading solution and the time the lens remains in it. However, the ability of contact lens to load drugs and to control their release is in general inadequate and the following approaches, based on modifications of the polymer network, are under evaluation:

1. Covalent binding of the drug to the lens network via labile bonds;

2. Inclusion of the drug in colloidal structures that are dispersed in the lens and are responsible for controlling drug release;

3. Functionalization of the network with chemical groups that work as ion-exchange resins; and

4. Creation in the lens structure of imprinted pockets that memorize the spatial features and bonding preferences of the drug and provide the lens with a high affinity and selectivity for a given drug.

8. Implants:

Implants provide extended release of drug in the ocular fluid and tissue of posterior segment, whereas the delivery rate can be altered with varying polymer concentration. The two types of implants based on their degradation properties are: biodegradable and nonbiodegradable. There are solid, semisolid or particulate based delivery systems of implants. Biodegradable polymers can be used in two forms, either as solid or injectable implants, or they can be used to encapsulate particular systems as nano- and microparticles. Depending on the size and composition the distribution in the ocular media varies and the particulate systems have different behaviour on injecting through thin needles. Polymers are slow release intra ocular implant which is viscous or semisolid materials.

Examples of Biodegradable polymers used in solid implants include poly lactic acid (PLA), poly glycolic acid (PGA), poly(lactic-coglycolic acid) (PLGA). After implantation, bulk erosion occurs, which causes release of encapsulated drug, which is caused by cleavage of polymeric chains by enzymatic and nonenzymatic hydrolysis. These devices can be manufactured in various shapes including rods, plugs, pellets, discs, and sheets. Accordingly, they can be implanted into the anterior chamber, the vitreous cavity through the pars plana, or into the intrascleral space.

Examples of non-biodegradable polymers used in solid implants include polyvinyl alcohol (PVA), poly ethylene vinyl acetate (EVA), and silicon. After implantation, diffusion of the ocular fluid into the implant dissolves the encapsulated drug which saturates the solution and causes diffusion out of the drug from the device. The non-biodegradable polymer devices provide a long lasting effect (more than a year) and provides a controlled release.
The major drawback of this type of device is the need for surgical implantation and need to remove it after the encapsulated drug is released.

b) Novel Ophthalmic Dosage Forms:

1. **Colloidal Systems:** The colloidal systems in ocular drug delivery include nanoparticles, liposomes, Nano emulsions, microemulsion etc. The advantages of colloidal systems include controlled and sustained release of drug at the targeted site, ability to overcome blood ocular barriers, reduced frequency of administration which contributes to better patient compliance. Colloidal systems encapsulate the drug which significantly enhances permeation across the membrane and prevent degradation by occular enzymes. Such biodegradable carriers can be an alternative for implants which has to be removed surgically after release of drug. Although very promising, commercial development of colloidal systems remains limited because of the complexity of manufacturing, mainly with stability problems during sterilization. For sterilization, required autoclaving temperatures can cause irreversible damage to colloidal systems, while filtration is only applicable to microparticulates with a size less than 0.2 µm.

1.1 Microemulsion:

Microemulsions are thermodynamically stable systems consisting dispersion of water and oil by a combination of surfactant and cosurfactant in a manner to reduce interfacial tension. Microemulsions have a small droplet size (approximately 100nm) and clear appearance. The high level of dispersion of the internal phase imparts a transparent appearance to the microemulsion. Microemulsion also improves the permeation across the cornea and provides extended drug release which reduces the frequency of administration. Despite of excellent advantages, there are limitations in selection of surfactant/cosurfactant system and potential toxicity associated with higher concentrations of surfactant/cosurfactant which restricts its use.

1.2 Nanosuspension:

Nanosuspensions are colloidal systems consisting of poorly soluble drug in sub-micron size, suspended in an appropriate dispersion medium stabilized by surfactants. Usually nanosuspensions carry polymeric resins which are inert in nature and increase the solubility of the drug hence increasing the bioavailability. Nanosuspensions are non-irritant and they carry a charge which facilitates their adhesion to the cornea. Nanosuspensions have a particle less than 1 µm, and consisting of various biodegradable or non-biodegradable polymers, lipids, phospholipids or metals. They may be classified in two types, i.e. Nanospheres (where the drug has been uniformly dispersed) or Nanocapsules (where the drug has been coated within the polymeric material). The size of the particles determines the uptake and distribution of the nanoparticles.

1.3 Liposomes:

Liposomes were first introduced in 1956 and are lipid vesicles which contains an aqueous core. Liposomes have been widely used for ocular drug delivery containing various drug substances and are within the size range of 10nm to 1µm or greater. Structurally, liposomes are classified as small unilamellar vesicles (SUV) or multi lamellar vesicle (LUV). [4] Unilamellar vesilcles are composed of single layer of lipid such as lecithin or phosphatidylglycerol encapsulating aqueous core. Multilamellar vesicle is composed of various layers of lipid bilayers. The selection of lipid composition is extremely important as it will decide the release pattern of the drug. The disadvantage of liposomes is variable purity of phospholipids and high cost. [6]

1.4 Niosomes:

Niosomes are bilayered structural vesicles which comprise of non-ionic surfactant and are capable of encapsulating both lipophilic and hydrophilic compounds. They can release the drug, independent

of pH, which enhances ocular bioavailability. An admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media will form a microscopic lamellar structure. Structurally niosomes are similar to liposomes, where in case of niosomes the bilayer is made up of non-ionic surface active agents whereas liposome bilayer are made up of phospholipids. Depending on the method used for preparation of niosomes, they can be unilamellar or multilamellar. They have advantage like good stability, low cost (where liposomes have high cost).

1.5 Dendrimers:

Dendrimers are macromolecular compounds having branched polymers entrapping hydrophilic and lipophilic drugs in the central core. The advantages of dendrimer is having a nanosize, ease of preparation, functionalization and possibility to attach multiple surface groups having suitable alternative vehicles for extended ocular drug delivery. In designing a delivery system few of the important parameters are selection of functional group on the surface (amine, carboxylate and hydroxyl), size and molecular weight of dendrimer.

2. **Hydrogels:**

   Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of taking in large amounts of water or biological fluids. Hydrogel formulation can significantly enhance residence time. Alteration in the temperature and pH can help in gelation. The most widely used polymer, poloxamer contains the hydropobic part in the centre surrounded by a hydrophilic part. The major drawback of hydrogel is weak mechanical strength, rapid erosion and nonbiodegradability. In case of polymers like cellulose derivatives like hypromellose, there is interaction of hydrophobic components at higher temperature which leads to gelation. Another approach is dissolving polymer in a suitable carrier, where the polymer and carrier are both biodegradable and biocompatible. When the hydrogels are injected in the subcutaneous space, precipitation of the polymer occurs because of water in the surrounding tissues which releases the drug in controlled manner.

3. **Microneedle-, Ultrasound-, and Iontophoresis-Based Ocular Drug Delivery Systems**

   Microneedle based drug delivery system, Ultrasound based drug delivery system, Iontophoresis based drug delivery system are non-invasive methods designed for delivery of drug to the intraocular regions, for the treatment of posterior segment diseases. The required drug is coated with a solid metal with a length of 500-750 µm. On administration, the coated molecules dissolve rapidly and subsequently microneedles are removed from the tissue. This drug delivery system generated a much higher concentration of drug as compared to free drug solution.

   Similarly ultrasound drug delivery is a novel drug delivery where drug is attempted with ultrasound application (20 kHz for 1h) across the cornea. Ultrasound significantly enhances corneal permeability and hence this delivery system has received lot of attention in the recent years. Examples of Ultrasound drug delivery is delivery of beta-blockers such as atenolol and timolol for the treatment of glaucoma.

   Iontophoresis delivers the drug across cornea and sclera. Example of Iontophoretic drug delivery includes active ingredients such as ciprofloxacin hydrochloride, gentamicin, dexamethasone. [4]

TABLE 1: MARKETED FORMULATIONS FOR OPHTHALMIC DRUG DELIVERY SYSTEMS

Dosage form	Active ingredient	Indication	Manufactured by	Trade Name
Solution	Timolol Maleate	Antiglaucoma agent	Poen Laboratories	POENTIMOL
Solution	Phenylephrine hydrochloride	Vasoconstrictor	Alcon Laboratories	Phenylephrine hydrochloride Ophthalmic Solution
Ointment	Tobramycin and dexamethasone	Anti-infective	Alcon Laboratories	TobraDex
Ointment	Aciclovir	Anti-infective	Cipla	Acivir

Emulsion	Difluprednate	Anti-inflammatory corticosteroid	Alcon Laboratories	DUREZOL
Insert	Hydroxypropyl cellulose	Ophthalmic protectant and lubricant	ATON Pharma Inc.	Lacrisert
Implant	Dexamethasone	Macular edema	Allergan	Ozurdex
In situ gel	Timolol maleate	Dry eye and keratoconjuctivitis	Alcon Laboratories	Timolol GFS
Bioadhesive gel	Carbomer	Dry eye (such as soreness, burning, irritation or dryness)	Bausch & Lomb U.K Limited	Geltears

CONCLUSION: Ophthalmic dosage forms have a very wide application and have been developed as a promising treatment in terms of ocular diseases. Irrespective of the side effects of conventional dosage forms like easy washing out of the formulation, less bioavailability yet they are the most preferred dosage forms worldwide as compared to novel drug delivery systems.

CONFLICT OF INTEREST: Authors have no conflict of interest.

REFERENCES:

1. http://www.webmd.com/eye-health/glaucoma-eyes. Date of retrival: November 2015.
2. http://www.moorfields.nhs.uk/content/anatomy-eye. Date of retrival: December 2015.
3. https://learn.pharmacy.unc.edu/pharmacopedia/pharmaceutics411/index.php/Ophthalmic_Dosage_Forms. Date of retrival: December 2015.
4. Dale Aldrich, Cynthia M. Bach, William Brown, Wiley Chambers, Jeffrey Fleitman, Desmond Hunt, Margareth R. C. Marques, Ashim K. Mitra, Stacey M. Platzer, Tom Tice, Georgr W. Tin: Ophthalmic Preparations. USP Vol. 39(5). Sept – Oct 2013.
5. http://www.webmd.com/eye-health/cataracts/health-cataracts-eyes. Date of retrival: 18th Feb 2016.
6. Gyan P. Mishra, Mahuya Bagui, Viral Tamboli, and Ashim K. Mitra: Recent Applications of Liposomes in Ophthalmic Drug Delivery. Journal of Drug Delivery Volume 2011 (2011). Article ID 863734.
7. Hitesh A. Patel, Jayvadan K. Patel, Kalpesh N. Patel, Ravi R. Patel : Ophthalmic Drug Delivery system –A Review. Scholars Research Library Der Pharmacia Lettre. 2010, 2(4). 100-115.
8. Hongming Chen : Recent developments in ocular drug delivery. Journal of Drug Targeting Volume 23, Issue 7-8, 2015; 597-604.
9. Renu Agarwal, Igor Iezhitsa, Puneet Agarwal, Nurul Alimah Abdul Nasir, Norhafiza Razali, Renad Alyautdin & Nafeeza Mohd Ismail : Liposomes in topical ophthalmic drug delivery: an update Drug Delivery. Volume 23. Issue 4. 2016. 1075-1091.
10. Susanne Kirchhof, Achim M. Goepferich, Ferdinand P. Brandl : Hydrogels in ophthalmic applications. European Journal of Pharmaceutics and Biopharmaceutics. Volume 95 Part B. September 2015. 227–238.
11. Li Gan, Jing Wang, Min Jiang, Hanah Bartlett, Defang Ouyang, Frank Eperjesi, Jianping Liu ,Yong Gan: Recent advances in topical ophthalmic drug delivery with lipid-based nanocarriers. Drug Discovery Today. Volume 18. March 2013. 290–297.
12. Djamila Achouri, Kamel Alhanout, Philippe Piccerelle & Véronique Andrieu : Recent advances in ocular drug delivery. Drug Development and Industrial Pharmacy. Volume 39. 2013. 1599-1617.
13. Ramaiyan Dhanapal and J. Vijaya Ratna: Ocular Drug Delivery System – A Review. International Journal of Innovative Drug Discovery. Vol 2. Issue 1. 2012. 4-15.
14. Kumar Manish, Kulkarni G.T.; Recent Advances in Ophthalmic Drug Delivery System. International Journal of Pharmacy and Pharmaceutical Sciences. vol 4. Issue 1. 2012. 387-394.
15. Nagare Rupali B, Bhambere Deepak S, Kumar Rachana S, Kakad Vidya K, Nagare Sujata N: In Situ Gelling System: Smart Carriers for Ophthalmic Drug Delivery. International Journal for Pharmaceutical Research Scholars (IJPRS). Volume-4. 2015. 10-23.
16. Tortora, G. S., Derridkson, B. Principal of Anatomy and Physiology. Published by Hoboken John Wiley and Sons. Edition 10. 2003. 579-587.
17. Ross and Wilson. Anatomy and Physiology in Health Education and Illness. Published by churchill livingstone elsewier. Edition 12. 2014. 196-205.
18. Patil, A: A novel ophthalmic drug delivery system: in situ gel. International Journal of Pharmaceutical Sciences and Research. 3(09). 2938–2946.
19. More, P.K.: Nasal in-situ gel: a novel approach for nasal drug. World Journal of Pharmaceutical Research. 2015. 4(2). 686–708.
20. Nerkar, T., Gujarathi, N.: In situ gel: novel approach in sustained and controlled drug delivery system. Pharma science monitor. 4(4). 1–18.
21. Aishwarya, J. Jadhav, Sheetal. B. Gondkar, Ravindra, B. Saudagar: A Review on nasal drug delivery system. World Journal of Pharmacy and Pharmaceutical Sciences. 3(8). 231-254.
22. Gambhire, S., Bhalerao, K. & Singh, S.: In situ hydrogel: Different approaches to ocular drug delivery. International Journal of Pharmacy and Pharmaceutical Sciences. 5(2). 27–36.
23. Deepak, S. & Singh, T. R.: In-situ gel system for ophthalmic preparation. Innovare Journal of Health Science. 1(1). 6-15.
24. Zarikar, N., Kulkarni, A., Patel, R.: Opthalmic in-situ drug delivery system: a review. International Journal of Pharmaceutical Research and Development. 5(05). 48-55.

How to cite this article:
Shende PK and Godbole R: Current and Novel Techniques in the Ophthalmic Drug Delivery Systems. Int J Pharm Sci Res 2016; 7(9): 3557-66.doi: 10.13040/IJPSR.0975-8232.7(9).3557-66.