Current Trends Towards an Ocular Drug Delivery System: Review

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Abstract
The purpose of this review is to provide an update on the current knowledge within this field of ocular drug delivery. Ocular drug delivery has been a major challenge for scientists due to its unique anatomy and physiology which contains various types of barriers such as different layers of cornea, sclera and retina including blood aqueous and blood–retinal barriers, choroidal and conjunctival blood flow etc. These barriers cause a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment of the eye. To overcome these problems, the newly developed particulate and vesicular systems like liposomes, pharmacosomes and discomes are useful in delivering the drug for a longer extent and helpful in reaching the systemic circulation. The most recent advancements of the ocular delivery systems provide the delivery of the genes and proteins to the internal structures which were once inaccessible and thus are of great importance in treating the diseases which are caused due to genetic mutation, failure in normal homeostasis, malignancy but also maintaining the physiological function of eye. This review focuses on recent development in conventional and non-conventional ophthalmic dosage formulation and products used to achieve prolonged contact time of drugs with the cornea and increase their bioavailability.

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1.0 Introduction
Eye is the window of our soul. The eye is unique organ from anatomical and physiological point of view. Without eye we cannot enjoy the beauty of the nature. 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. Eye ailment can cause distress and angst in patients, with the ultimate fear of loss of vision or even facial disfigurement. Many parts of the eye are relatively inaccessible to systemically administered drugs and as a result, topical drug delivery remains the preferred route in most cases. Drugs may be delivered to treat the precorneal region for such infections as conjunctivitis and blepharitis or to provide intraocular treatment via the cornea for disease such as glaucoma and uveitis [1]. With conventional ophthalmic solution normal dropper used which delivers about 50-75µl per drop and portions of these drops rapidly drain until the eye is back to normal resident volume of 7 µl. Due to this drug loss in front of the eye, very small drug is available to enter the cornea and inner tissue of the eye. Actual corneal permeability of the drug is relatively low and very small corneal contact time (about 1-2min) in humans for instilled solution usually less than 10%. Therefore only small amount of drug actually penetrates the cornea and reaches intraocular tissue. Due to these limitations, controlled delivery to the eye is restricted imposed by the efficient protective mechanism. It is necessary to optimize drug delivery by adding polymers of various grades, development of colloidal suspension or using erodible or non erodible insert, development of viscous gel to prolong the precorneal drug retention. Microparticle suspension or polymeric system can be bioadhesive system. In situ activated gel forming systems provide better sustained release properties than drops. This type of dosage form are used now a day in various type of eye disease like combat glaucoma, dry eye syndrome, eye infection, etc[2].

2.0 Physiology of Eye [3-6]
The human eye is essential sense organ of the body and its anatomy is quite complex. Eye is able to refract light and produce a focused image that can stimulate nervous system and enable the ability to see. The structure of eye and different parts of the eye (Figure 1):

2.1 Aqueous Humour: It is a jelly like substance located in the anterior chamber of the eye.
2.2 Choroid: The choroid layer is located behind the retina and absorbs unused radiation.

2.3 Ciliary muscle: The ciliary muscle is a ring shaped muscle attached to iris. It is important because contraction and relaxation of the ciliary muscle controls the shape of the lens.

2.4 Cornea: Cornea is a clear transparent epithelial membrane. Light rays pass through the cornea to reach the retina. The cornea is convex anteriorly and is involved in refracting light rays to focus them on the retina.

2.5 Fovea: The fovea is a small depression (approx. 1.5mm in diameter) in the retina. This is the part of the retina in which high resolution vision of the fine details is possible.

2.6 Hyaloids: The hyaloids diaphragm divides the aqueous humour from the vitreous humour.

2.7 Iris: The iris is the visible colored part of the eye and extends anteriorly from the ciliary body, lying behind the cornea and in front of the lens. It divides the anterior segment of the eye into anterior and posterior chamber which contains aqueous fluid secreted by the ciliary body. The iris is supplied by parasympathetic and sympathetic nerves. Parasympathetic stimulation constrasts the pupil and sympathetic stimulation dilates it.

2.8 Lens: The lens of the eye is flexible units that consist of layers of tissue enclosed in a tough capsule. It is suspended from the ciliary muscles by the zonule fibers.

2.9 Optic nerves: The optic nerve is the second cranial nerve and is responsible for vision. Each nerve contains approximately one millions fibers transmitting information from the rod and cone cells of the retina.

2.10 Papilla: The papilla is also known as the “blind spot” and is located at the position from which the optic nerve leaves the retina.

2.11 Pupil: The pupil is the aperture through which light and hence images we see and “perceive” enters the eye. This is informed by the iris. As the size of iris increases (or decreases) the size of the pupils decreases (or increase) correspondingly.

2.12 Retina: The retina may be described as the “screen” on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, then the hyaloids and finally the vitreous humour before reaching the retina. The retina contains photosensitive elements (called rods and cones) that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.

2.13 Sclera: The sclera is tough white sheath around the outside of the eye-ball. It consists of a membrane that maintains the shape of the eye and gives the attachment to the extrinsic muscle of the eye.

2.14 Vitreous Humour: The vitreous humour (vitreous body) is a jelly like substances.

3.0 Advantages of Ocular Drug Delivery Systems [7-10]
- Easy convenience and needle free drug application without the need of trained personnel
- Assistance for the application, self medication, thus improving patient compliances compared to parenteral routes.
- Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.
- Rapid absorption and fast onset of action because of large absorption surface area and high vascularisation. Ocular administration of suitable drug would therefore be effective in emergency therapy as an alternative to other administration routes.
- Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.

4.0 Disadvantages of Ocular Drug Delivery Systems [7-10]
- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen.

5.0 Ophthalmic Disorders [1,8,11]
- Conjunctivitis: an inflammation of the conjunctiva that may be caused by bacterial and viral infection, pollen and other allergens, smoke and pollution.
- Dry eye syndrome: the inadequate wetting of the ocular surface.
- Glaucoma: the buildup of pressure in the anterior and posterior chambers of the choroid layer that occurs when the aqueous humour fails to drain properly.
- Iritis: commonly has an acute onset with the patient suffering pain and inflammation of the eye.
- Keratitis: an inflammation of the cornea, caused by bacterial, viral or fungal infection.
- Other conditions: the ophthalmic complications of rosacea, blepharitis (inflammation of the lid margins) and chalazia (meibomian cysts of the eyelids).

6.0 Routes of Delivery
There are three main routes commonly used for administration of drugs to the eye: topical, intraocular and systemic. The topical route is the most common method to administer a medication to the eye. Introducing the drug directly to the conjunctival sac localizes drug effects, facilitates drug entry that is otherwise hard to achieve with systemic delivery and avoids first pass metabolism.
The intraocular route is more difficult to achieve practically. Now research is concentrating on the development of intravitreal injections and use of intraocular implants to improve delivery to eye. In systemic route, several studies have shown that some drugs can distribute into ocular tissues following systemic administration. Oral administration of carbonic anhydrase inhibitors including acetazolamide, methazolamide demonstrates the capacity of a systemic drug to distribute into the ciliary process of eye.

**7.0 Conventional Delivery Systems**

**7.1 Eye Drops [12]**

Drugs which are active at eye or eye surface are widely administered in the form of Solutions, Emulsion and Suspension. Generally eye drops are used only for anterior segment disorders as adequate drug concentrations are not reached in the posterior tissues using this drug delivery method. Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye. Less than 5 Percent of the dose is absorbed after topical administration into the eye.

**7.2 Ointment and Gels [12, 13]**

Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but, the major drawback of this dosage form like, blurring of vision and matting of eyelids can limits its use. Pilopine HS gel containing pilocarpine was used to provide sustain action over a period of 24 hours. Upon instillation in the eye, ointment breaks up into small droplet and remains as depot of drug in the cul-de-sac for extended periods. A number of workers reported that ointments and gels vehicles can prolong the corneal contact time of many drugs administered by topical ocular route, thus prolonging duration of action and enhancing ocular bioavailability of drugs.

**7.3 Ocusert [11, 12]**

Ocular insert (Ocusert) are sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage. Ocusert was one of the earlier ocular insert in use. The technology used in this is an insoluble delicate sandwich technology. In Ocusert the drug reservoir is a thin disc of pilocarpine vinylpyrrolidone and ethylacrylate called as ABE.

**7.4 Lacrisert**

Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca and was introduced by Merck. Sharp and Dohme in 1981. They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea. It dissolves in 24 hours.

**7.5 SODI [11-14]**

Soluble ocular drug insert (SODI) is a small oval wafer which was developed by Soviet scientist for cosmonauts who could not use eye drops in weightless condition. It is sterile thin film of oval shape made from acrylamide, N-vinylpyrrolidone and ethylacrylate called as ABE. It is used in the treatment of glaucoma and trachoma. It is inserted into the inferior cul-de-sac and gets wets and softens in 10-15 seconds. After 10-15 min the film turn into a viscous polymer mass, after 30-60 mins it turns into

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Table 1: Marketed ophthalmic products

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Drug</th>
<th>Dosage Form</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acivir eye</td>
<td>Acyclovir</td>
<td>Ointment</td>
<td>For eye infection</td>
</tr>
<tr>
<td>Acuvail</td>
<td>Ketonolac tromethamine</td>
<td>Eye solution</td>
<td>Cataract surgery</td>
</tr>
<tr>
<td>Alcrot</td>
<td>Nedocromil</td>
<td>Eye solution</td>
<td>Allergic conjunctivitis</td>
</tr>
<tr>
<td>Betnoil N</td>
<td>Betamethasone</td>
<td>Eye drops</td>
<td>In eye infection</td>
</tr>
<tr>
<td>Chloromycetin</td>
<td>Chloramphenicol palmitate</td>
<td>Ointment</td>
<td>In conjunctivitis and eye inflammation</td>
</tr>
<tr>
<td>Ciplox</td>
<td>Ciprofloxacin</td>
<td>Eye drops</td>
<td>In eye infection and conjunctivitis</td>
</tr>
<tr>
<td>Dextin</td>
<td>Dexamethasone</td>
<td>Eye drops</td>
<td>In eye infection</td>
</tr>
<tr>
<td>Dichol</td>
<td>Carbocoll</td>
<td>Sterile solution and prefilled syringes</td>
<td>In ophthalmic surgery</td>
</tr>
<tr>
<td>Elestat</td>
<td>Epinastine solution</td>
<td>Eye solution</td>
<td>Allergic conjunctivitis</td>
</tr>
<tr>
<td>Geltear</td>
<td>Carbomer</td>
<td>Bioadhesive gel</td>
<td>As a lubricant, in burning, irritated an dried eye</td>
</tr>
<tr>
<td>Ocupol</td>
<td>Polymixin-B</td>
<td>Eye drops and ointment</td>
<td>In bacterial infection, corneal ulcer</td>
</tr>
<tr>
<td>Ozurdex</td>
<td>Dexamethasone</td>
<td>Ocular implant</td>
<td>Retinal vein occlusion</td>
</tr>
<tr>
<td>Pred forte</td>
<td>Prednisolone acetate</td>
<td>Suspension</td>
<td>As anti allergic and anti inflammatory</td>
</tr>
<tr>
<td>Refresh classic</td>
<td>Artificial tear fluid</td>
<td>Single use vials</td>
<td>Relieves dry and irritated eyes</td>
</tr>
<tr>
<td>Refresh tears</td>
<td>Hydroxypropyl methylcellulose</td>
<td>Eye drops</td>
<td>In dryness of eye and eye lubricant</td>
</tr>
<tr>
<td>Restasis</td>
<td>Cyclosporine</td>
<td>Emulsion</td>
<td>In dry eye</td>
</tr>
<tr>
<td>Timolol xe</td>
<td>Timolol maleate</td>
<td><em>In situ</em> gel</td>
<td>For dried eye and keratoconjunctivitis</td>
</tr>
<tr>
<td>Trivarls</td>
<td>Triamicinolone acetonide</td>
<td>Suspension</td>
<td>Sympathetic ophthalmia</td>
</tr>
<tr>
<td>Zymair</td>
<td>Gatifloxacin</td>
<td>Solution</td>
<td>Bacterial conjunctivitis</td>
</tr>
<tr>
<td>Zymaxid</td>
<td>Gatifloxacin</td>
<td>Solution</td>
<td>Bacterial conjunctivitis</td>
</tr>
</tbody>
</table>
polymer solutions and delivers the drug for about 24 hours.

7.6 Minidisc [11-14]

The minidisc consists of a contoured disc with a convex front and concave back surface in the contact with the eyeball. It is like a miniature contact lens with a diameter of 4.5mm. The minidisc is made up of silicone based pre polymer-α-ψ-bis (4-methacryloxy) butyl polydimethyl siloxane. Minidisc can be hydrophilic or hydrophobic to permit extend release of both water soluble and insoluble drugs.

8.0 Vesicular System

8.1 Prodrugs [8, 12]

Prodrugs are simple, chemically or enzymatically liable derivatives of drugs which are converted to their active parent drug typically as a result of hydrolysis within the eye. Most ophthalmic drugs contain alcohol, phenol, carboxylic acid and amines that lend themselves to derivatization. Prodrugs technology is usually considered as a useful technique in improving corneal permeability. It is also useful in solving pharmaceutical problems such as poor solubility. The only commercial prodrug is dipivaly epinephrine.

8.2 Liposomes [8, 11, 12]

Liposomes are vesicles composed of lipid membrane enclosing an aqueous volume. These structures are formed simultaneously when a matrix of phospholipids are agitated in an aqueous medium to disperse the two phases. Phospholipids commonly used are phosphodicholine, phosphotidylserine, phosphatic acid, sphingomyelins and cardiolipins. They may be multilamellar vesicle or unilamellar depending upon the number of concentric alternating layers of phospholipid and aqueous phases. They can be prepared by sonication of dispersion phospholipids, reverse phase evaporation, solvent injection, detergent removal or calcium induced fusion. Lipophilic drugs are delivered to a greater extent to the ocular systems by these liposomes. They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weights and thus increases the probability of ocular drug absorption. The corneal epithelium is thinly coated with negatively charged mucin to which the positive charged surface of the liposomes may bind.

8.3 Niosomes and Discomes [8, 11, 12]

The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids. To avoid this niosomes are developed as they are chemically stable as compared to liposomes and can entrap both hydrophobic and hydrophilic drugs. They are non toxic and do not require special handling techniques.

Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site.

8.4 Pharmacosomes [8, 11, 12]

This term is used for pure drug vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. The amphiphilic prodrug is converted to pharmacosomes on dilution with water. The pharmacosomes show greater shelf stability, facilitated transport across the cornea, and a controlled release profile.

9.0 Control Delivery Systems

9.1 Implants [8, 11, 12, 15]

For chronic ocular diseases like cytomegalovirus (CMV) retinitis, implants are effective drug delivery system. Earlier non biodegradable polymers were used but they needed surgical procedures for insertion and removal. Presently biodegradable polymers such as Poly Lactic Acid (PLA) are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs. Intravitreal implants of fluocinolone acetonide were developed for the treatment of posterior segment and reported to control the ocular inflammation of retina.

9.2 Iontophoresis [12, 16]

Iontophoresis is a new concept in ocular drug delivery system in which charged drug molecules are used. Positive charge drug molecules were driven into the tissue at anode and negative charge drug molecule driven respectively at cathode. Ocular iontophoresis is safe, fast and easy. It is also proficient to hold high concentration of drug at targeted tissue. Application of drugs such as antibiotics and anti-inflammatory by using iontophoresis, increase the antibacterial activity and reduced the side effect.

9.3 Dendrimer [12]

Dendrimers can successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility. It’s based on the influence of size, molecular weight and number of amine, carbohydrate and hydroxyl surface groups in several series of dendrimers. The residence time was longer for the solutions containing dendrimers with carboxylic and hydroxyl surface groups.

9.4 Cyclodextrin [12, 17]

Cyclodextrins (CDs) are cyclic oligosaccharides capable of forming inclusion complexes with many guest molecules. CD complexes are reported to increase corneal permeation of drugs like dexamethasone, dexamethasone acetate, cyclosporine and pilocarpine resulted in higher bioavailability than the conventional eye drops. This complexation of CD does not interrupt the biological membrane compared to conventional permeation enhancer like benzalkonium chloride. Due to inclusion, the free drug is not available, so drugs with inherent irritant properties can be successfully delivered by this approach. CD molecules are inert in nature and were found to be non irritant to the human and animal eye.

9.5 Contact lenses [12, 16]

Water soluble drugs soaked in drug solutions can be absorbed through Contact lenses. The drug saturated contact lenses are placed in the eye which releases the drug in eye for a long period of time. For prolongation of ocular residence time of the drugs, hydrophilic contact lenses can be used. Greater penetration of fluorescein has been
reported by Bionite lens made from hydrophilic polymer (2-hydroxy ethyl methacrylate) in human.

9.6 Collagen Shield [12, 17]
Collagen is a structural protein of bones, tendons, ligaments and skin and comprises more than 25% of total protein in mammals. Collagen shield have been used in animal model and in humans (e.g. antibiotics, antiviral, etc.) or combination of these drugs often produces higher drug concentration in the cornea and aqueous humor when compared with eye drops and contact lens.

9.7 Microemulsion [12, 18]
Microemulsion is dispersion of water and oil stabilized using surfactant and co-surfactant to reduce interfacial tension and usually characterized by small droplet size (100 nm), higher thermodynamic stability and clear appearance. Selection of aqueous phase, organic phase and surfactant/co-surfactant systems are critical parameters which can affect stability of the system. Optimization of these components results in significant improvement in solubility of the drug molecule e.g. indomethacin, chloramphenicol for eye diseases.

9.8 Nanosuspensions [12]
Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect. For commercial preparation of nanosuspensions, techniques like media milling and high-pressure homogenization have been used. The higher drug level in the aqueous humour was reported using Eudragit RS100 nanosuspensions for the ophthalmic controlled delivery of ibuprofen.

9.9 Microneedle [12, 19]
Microneedle had shown prominent in vitro penetration into sclera and rapid dissolution of coating solution after insertion while in vivo drug level was found to be significantly higher than the level observed following topical drug administration like pilocarpine.

9.10 Penetration Enhancers [8, 12, 17]
An alternative approach in ocular delivery is by incorporation of penetration enhancers. The preservative agent used in most ophthalmic preparation serve as penetration enhancers 0.01% benzalkonium chloride has been used. An increase in the penetration of fluorescein in normal eye has been found in the presence of chlorohexidine gluconate and benzalkonium chloride.

9.11 Mucoadhesive Polymers [12, 16]
They are basically macromolecular hydrocolloids with plentiful hydrophilic functional groups, such as hydroxy, carboxyl, amide and sulphate having capability for establishing electrostatic interactions. A mucoadhesive drug formulation for the treatment of glaucoma was developed using a highly potent beta blocker drug, levobetaxolol (LB) hydrochloride and partially neutralized poly acrylic acid (PAA).

9.12 Phase Transition Systems/Insitu gel system [1, 12, 16, 17, 30]
Phase transition of the formulation from the liquid form to the gel or solid phase occurs when these systems instilled into the cul-de-sac of eye lead to increase the viscosity of a drug formulation in the precorneal region results in increased bioavailability, due to slower drainage from the cornea. These systems can be influenced by pH, temperature or by ion activation. A sol to gel system with mucoadhesive property to deliver the steroid fluorometholone to the eye.

10.0 Particulates (Nanoparticles and Microparticles) [1, 12, 16, 17, 20-29]
The maximum size limit for microparticles for ophthalmic administration is about 5-10 mm above which a scratching feeling in the eye can result upon ocular instillation. That is why microspheres and nanoparticles are promising drug carriers for ophthalmic application. Nanoparticles are prepared using bioadhesive polymers to provide sustained effect to the entrapped drugs. An optimal corneal penetration of the encapsulated drug was reported in presence of bioadhesive polymer chitosan. Nanospheres made up of poly lactic acid (PLA) coated with Poly Ethylene Glycol (PEG) shown better efficacy compared to conventional dosage form of Acyclovir for the treatment of ocular viral infections. Microspheres of poly lacto glycolic acid (PLGA) for topical ocular delivery of a peptide drug vancomycin were prepared by an emulsification/ spray-drying technique.

11.0 Advanced Delivery System
11.1 Cell Encapsulation
The entrapment of immunologically isolated cells with hollow fibres or microcapsules before their administration into the eye is called Encapsulated Cell Technology (ECT) which enables the controlled, continuous, and long-term delivery of therapeutic proteins directly to the posterior regions of the eye. The polymer implant containing genetically modified human RPE cells secretes ciliary neurotrophic factor into the vitreous humour of the patients’ eyes. ECT can potentially serve as a delivery system for chronic ophthalmic diseases like neuroprotection in glaucoma, anti-angiogenesis in choroidal neovascularization, anti-inflammatory factors for uveitis.

11.2 Gene Therapy
Several kinds of viruses including adenovirus, retrovirus, aden-associate virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications. Topical delivery to the eye is the most expedient way of ocular gene delivery. Retroviral vectors have been widely used due to their high efficacy; however, they do not have the ability to transduce nondividing cells, leads to restrict their clinical use. The advanced delivery systems that prolong the contact time of the vector with the surface of the eye may enhance transgene expression, thereby facilitate non-invasive administration.

11.3 Stem cell Therapy
Emerging cell therapies for the restoration of sight have focused on two areas of the eye that are critical for visual function, the cornea and the retina. The most successful ocular application has been the use of limbal stem cells, transplanted from a source other than the patient for the renewal of corneal epithelium. The sources of limbal cells include donors, autografts, cadaver eyes, and (recently) cells grown in culture. Stem-cell Therapy has demonstrated great success for certain maladies of the anterior segment.
11.4 Protein and Peptide therapy
The design of optimized methods for the sustained delivery of proteins and to predict the clinical effects of new compounds to be administered in the eye, the basic knowledge of Protein and Peptide is required. However, several limitations such as membrane permeability, large size, metabolism and solubility restrict their efficient delivery. A number of approaches have been used to overcome these limitations. Poor membrane permeability of hydrophilic peptides may be improved by structurally modifying the compound, thus increasing their membrane permeability. Ocular route is not preferred route for systemic delivery of such large molecules. Immunoglobulin G has been effectively delivered to retina by transscleral route with insignificant systemic absorption.

11.5 Scleral Plug therapy
Scleral plug can be implanted using a simple procedure at the pars plana region of eye, made of biodegradable polymers and drugs, and it gradually releases effective doses of drugs for several months upon biodegradation. The release profiles vary with the kind of polymers used, their molecular weights, and the amount of drug in the plug. The plugs are effective for treating vitreoretinal diseases such as proliferative vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require vitrectomy.

11.6 siRNA therapy
For various angiogenesis-related diseases, the use of siRNA is considered as a promising approach. Feasibility of using siRNA for treatment of choroidal neovascularization has been demonstrated using siRNA directed against vascular endothelial growth factor (VEGF) or VEGF receptor 1 (VEGFR1), and both of these approaches are being tested in clinical trials. Topical delivery of siRNAs directed against VEGF or its receptors has also been shown to suppress corneal neovascularisation. New encapsulated siRNA have been developed using liposomes, coupled antibodies or others polymer vesicles. Therapeutic approach using siRNA provides a major new class of drugs that will shed light the gap in modern medicine.

11.7 Oligonucleotide therapy
Oligonucleotide (ON) therapy is based on the principle of blocking the synthesis of cellular proteins by interfering with either the transcription of DNA to mRNA or the translation of mRNA to proteins. Among several mechanisms by which antisense molecules disrupt gene expression and inhibit protein synthesis, the ribonuclease H mechanisms are the most important. A number of factors have been determined to contribute to the efficacy of antisense ON.

11.8 Aptamer
Aptamers are oligonucleotide ligands that are used for high-affinity binding to molecular targets. They are isolated from complex libraries of synthetic nucleic acid by an iterative process of adsorption, recovery, and reamplification. They bind with the target molecules at a very low level with high specificity.

11.9 Ribozyme therapy
RNA enzymes or ribozymes are a relatively new class of single-stranded RNA molecules capable of assuming three dimensional conformations and exhibiting catalytic activity that induces site-specific cleavage, ligation, and polymerization of nucleotides involving RNA or DNA. A disease named, Autosomal dominated retinitis pigmentosa (ADRP) is caused by mutations in genes that produce mutated proteins, leading to the apoptotic death of photoreceptor cells.

12.0 Various ophthalmic marketed products in different dosage form [31-33]
Different ophthalmic marketed products (Table 1).

13.0 Conclusion
The extensive work in ocular drug delivery during the earlier period. It has been intend, to extend the residence time of topically applied drugs in the corneal and conjunctiva section. Some new approaches such as nanoparticles, liposome, contact lenses, ocular inserts, collagen shield, in situ activated gel formation, non corneal route of ocular drug diffusion, and nanoparticles-based polymeric solutions and gels are being developed by the pharmaceutical sciences.

The novel advanced delivery systems offer more protective and effective mean of therapy for the nearly inaccessible diseases or syndromes of eyes. Progress in the field of oculer drug delivery has been established recently with controlled loading and sustained release. Hence, effective drug delivery and targeting is faced by challenges to overcome these barriers.

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