WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 9, 220-265. Review Article ISSN 2277– 7105

RECENT ADVANCES AND PATENTS OCULAR DRUG DELIVERY SYSTEM

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Article Received on
28 June 2017,
Revised on 18 July 2017,
Accepted on 08 August 2017
DOI: 10.20959/wjpr20179-9243

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ABSTRACT

Background- A wide variety of drug delivery system have been developed to treat the disease of eye. Some traditional ocular drug delivery system is used but it has some disadvantages is to eliminate from the anterior part of eye and lack of retention time of contact with eye due to specific anatomy and physiology barrier of eye. **Objective-** The main objective of the study to review the recent advance and patent nanoformulation for ocular drug delivery system. as well as various therapies which are targeted into gene and protein of anterior part of eye to treat the genetic disorder of eye with specific rout of administration. **Result-** Recently advance ocular drug delivery system have been developed to produced controlled drug release into eye segments. The most powerful advantage of recent drug delivery system over the traditional drug system is to increase solubility of poor soluble drugs into eye and cross the various barrier of the eye to reached the anterior parts as well as posterior parts of eyes. **Conclusion-** FDA website described that only 21 ocular drugs were approved in the last 10 years; 30 new drugs last back to 1995. No ocular drugs were approved in 1995 or 2003. It is proved that efficiency of nanoparticles for ocular drug delivery is much better than other novel drug delivery systems in terms of dose, stability, cell targeting, particle size etc. Nanohydrogel, lipid nanoparticles, nanosuspension, etc. are being used successfully in ocular nanotechnology.

KEYWORDS: Drug delivery, nanoemulsion, liposome, microemulsion, glaucoma, Nanotechnology, Patent.

INTRODUCTION

Ocular drug delivery system is targeted to a particular tissue of the eye, has remained as one of the challenging task for the scientists. Drug delivery to the eye can be classified into- (a) anterior segment (b) posterior segment. The specific aim of a therapeutic system is to achieve an optimal concentration of drug at the active site. An aim of a drug delivery system, consequently requires a knowledge of a drug molecule. Many conventional formulations are accessible in the market such as drops and ointments but when these preparations instilled in the eye they rapidly drained away from the ocular surface due to blinking and reflex lachrymation. In this review have been elucidated a various classification of drug delivery system and they are demonstrated with their application, advantage and actions. Recently advance ocular drug delivery system have been developed to produced controlled drug release into eye segments such as liposome, nanoemulsion ,contact lenses, implant penetration enhancer etc . **Nandini Gupta et.al.(2013)**, Developments in nanotechnology and in depth understanding of ocular drug absorption and disposition have led to the appearance of many of the nanotechnology-based ocular drug delivery systems including nanoparticles, solid lipid nanoparticles, light-sensitive nanocarrier systems, microemulsions, liposomes, etc**.** This technology is described by "The Next Industrial Revolution" by the National Nanotechnology Initiative 2000 **Gulati Net.al.(2012)**.

Disorder of eyes

Age- related macular degeneration (AMD)- Symptoms are breakdown of photoreceptors, growth of abnormal blood vessels behind the retina, deterioration of retinal pigment epithelium (RPE) and loss of vision.

Diabetic macular edema (DME)- Symptoms are small abnormality in retinal blood vessels via intra-retinal leakage, creation of microcysts and dilation of retinal capillaries.

Proliferative vitreoretinopathy (PVR)- Enhancement of cells in vitreous and inflammation of retina.

Uveitis- In uveitis inflammation occurs in the middle layer of the eyes (uvea).

Cytomegalovirus (CMV)- Inflammation of the retina and cause blindness**.**

Glaucoma- Glaucoma is an optic neuropathy result in the loss of vision. Prominent intra ocular pressure (IOP) is a risk factor for both (i) development of glaucoma and (ii)

development of optic nerve changes and visual loss. Symptom is the barrier to the outflow of aqueous humor from the anterior segment.

Conjunctivitis- It causes inflammation of the conjunctive, redness, itching and watering of eyes. The major causes are the result of infection and allergy.

Cataract- This may cause the obstruction of the passage of light due to lens opaqueness.

Kertitis- In this condition patient have an ocular pain, red eye, opaque cornea. Kertitis is caused by viruses, fungi**,** bacteria etc.

Trachoma- Trachoma is caused by chalmydia trachoma and is the most common cause of blindness.

Blepharitis- It is usually caused by staphylococcus aureus. It is an infection of lid structures with a dry eye and defect in lipid secretion.

1.2. Barrier of drug delivery system

Tear Tear film reduces the effective concentration of the administrated drugs due to dilution by the tear turnover (approximately 1 L/min), accelerated clearance, and binding of the drug molecule to the tear proteins. **Noriyuki Kuno et.al (2010).**

Cornea It consists of three layers; epithelium, stroma and endothelium, and a mechanical barrier to inhibit transport of exogenous substances into the eye. Each layer possesses a different polarity and a rate-limiting structure for drug permeation **Noriyuki Kuno et.al (2010)**

Corneal Epithelium The corneal lipophilic nature of epithelium and tight junctions among cells are formed to restrict paracellular drug permeation from the tear film.

Corneal Stroma The stroma is composed of an extracellular matrix of a lamellar arrangement of collagen fibrils. The highly hydrated structure of the stroma acts as a barrier to permeation of lipophilic drug molecules.

Corneal endothelium is the innermost monolayer of hexagonal-shaped cells, and acts as a separating barrier between the stroma and aqueous humor. The endothelial junctions are leaky and facilitate the passage of macromolecules between the aqueous humor and stroma.

Conjunctiva It has been reported that at least 10% of a small molecular weight hydrophilic model compound (sodium fluorescein), administered in the subconjunctival space, is eliminated via the lymphatics within the first hour in rat eyes . Therefore, drugs transported by lymphatics in conjunction with the elimination by blood circulation can contribute to systemic exposure, since the interstitial fluid is returned to the systemic circulation after filtration through lymph nodes. **Noriyuki Kuno et.al (2010).**

Sclera It consists of collagen fibers and proteoglycans embedded in an extracellular matrix . The permeability of sclera has been depend on the molecular radius. Additionally, the posterior sclera is composed of a looser weave of collagen fibers than the anterior sclera , and the human sclera is relatively thick near the limbus (0.53 ± 0.14 mm), thin at the equator (0.39 ± 0.17 mm), and much thicker near the optic nerve (0.9–1.0 mm). Thus, the ideal location for transscleral drug delivery is near the equator at 12–17 mm posterior to the corneoscleral limbus. Hydrophobicity of drugs affects scleral permeability; increase of lipophilicity shows lower permeability; and hydrophilic drugs may diffuse through the aqueous medium of proteoglycans in the fiber matrix pores more easily than lipophilic drugs. Furthermore, the charge of the drug molecule also affects its permeability across the sclera. Positively charged compounds may exhibit poor permeability due to their binding to the negatively charged proteoglycan matrix **Noriyuki Kuno et.al (2010).**

Choroid/Bruch's Membrane An Optical Coherence Tomography (OCT) can noninvasively measure the thickness of retina and choroid. Using an OCT, it has been shown, choroidal thickness becomes thinner with age. Previous histological studies have shown choroidal thickness changes from 200 m at birth decreasing to about 80 m by age 90. In addition, chorioretinal diseases including AMD with pigment epithelial detachment, central serous chorioretinopathy , age-related choroidal atrophy, and high myopia, affect choroidal thickness. In contrast, Bruch's membrane (BM) causes thickening with age. These changes cause increased calcification of elastic fibers, increased cross-linkage of collagen fibers and increased turnover of glycosaminoglycans **Noriyuki Kuno et.al (2010).**

Retina The elimination via the posterior route takes place by permeation across the retina. One of the barriers restricting drug penetration from the vitreous to the retina is the internal limiting membrane (ILM). The ILM separates the retina and the vitreous, and is composed of 10 distinct extracellular matrix proteins.

Blood-Retinal Barrier Blood-retinal barrier (BRB) restricts drug transport from blood into the retina. BRB is composed of tight junctions of retinal capillary endothelial cells and RPE, called iBRB for the inner and oBRB for the outer BRB, respectively. oBRB (RPE) restricts further entry of drugs from the choroid into the retina. RPE is a monolayer of highly specialized hexagonal-shaped cells, located between the sensory retina and the choroid. The tight junctions of the RPE efficiently restrict intercellular permeation into the sensory retina

Noriyuki Kuno et. al (2010).

Table 1: Classification of drug delivery system.

	On the basis of used in ocular part	**On the basis of chronological data**	**On the basis of formulation design**
1.	**DDSs used for anterior part**	**Conventional DDSs**	**Vasicular delivery system**
	Eye drop	Eye drop	Liposomes
	Contact lense	Ointment and gel	Niosomes and Discomes
	Cul-de –sac inserts	Insert- lacrisert and SODI(Soluble ocular drug)	Pharmacosomes
	punctual plugs		
	Subconjunctival/episclera implant		
2.	**DDSs used for posterior part**	**New Opthalmic delivery system**	**Control delivery system**
a.	**Intravitreal implants** Durasert technology system novadur technology I.Vation TA NT-501		Nano emulsion
b.	**Injectable particulate system** IBI 20089 RETAAC Cortiject Visudyne	Nanoparticals	Iontophoresis
c.		BODI(Bioadhesive Ocular Drug Insert)	Dendrimer
d.		Prodrug	Cyclodextrin
e.		Liposomes	Contact lanses
f.		Panitration enhancers	Collegen shield
g.			Microemulsion
h.			Nanosuspention
i.			Microneedle
j.			Prodrug
k.			Panitration enhancer
l.			Muco adhesive polymer

m.			Micro electromechanical intra ocular DDdevice
n.			Implant
3.			**Ocular therapy based DDSs**
a.			Cell encapsulation
b.			Gene therapy
c.			Stem cell therapy
d.			Protein peptide therapy
e.			Scleral plug therapy
f.			Si RNAtherapy
g.			Oligonucliotide therapy
h.			Aptamer
i.			Ribozyme therapy

2. Conventional Drug Delivery System

2.1. Eye drop Eye drop is the conventional dosage form, are used in anterior part disorder of eye. The main disadvantage of eye drop is to adequate drug concentrations are not reached in the posterior tissues using this drug delivery method. A various properties of eye drop such as hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye. . Ocular absorption is limited by the corneal epithelium, and it is only moderately increased by prolonged ocular. The reported maximal attainable ocular absorption is only about 10 Percent of the dose. To prolong the retention time of topically applied drugs, anterior DDSs for eye-drops utilizing interaction between drug carrier (excipients) and physiological environment of cornea and/or subconjunctiva are being developed.

Table 2: Marketed formulation of eye drop.

S. No.	Marketed name	Ingredient	Mechnism	Indecation
1.	Durasite DDS (InSite Vision Inc., Alameda, CA, U.S.)	Polycarboph (polyacrylic acid cross-linked with Divinyl glycol)	Hydrogen-bonding with the mucus, and corneal and conjunctival epitheliums, which are all negatively charged, to extend the effects of drug to several hours.	AzaSite(Durasite+AZ) In bacterial conjunctivitis. AzaSitePlus(Durasite+AZ+DEX)-blepharoconjunctivitis.(currently used in Phase III). ISV-303(durasite+ Bromfenac)-reduce inflammation and pain after ocular surgery(In Phase I/II).
2.	RysmonTG. Wakamoto Pharmaceutical Co.,Ltd.	Timolol maleate, methyl cellulose MC, sodium citrate and Polyethylene glycol	(MC) has a lower critical solution temperature (LCST) at approximately 50	Glaucoma

	(Tokyo, Japan).		°C , and sol-gel phase transition occurs. high concentration of electrolytes leads to salting-out and gelation of MC . in this formulation. sodium citrate and polyethylene glycol, which can act by lowering LCST of MC. timolol maleate is beta blocker ,use to reduced intra ocular pressure	
3.	Betoptic S marketed from 1990 (Alcon Laboratories, Inc., Fort Worth, TX, U.S.).	Betaxolol+ Amberlite IRP-69 (Polystyrene sulfonic acid resin cross-linked with Divinyl benzene).	Positively charged Betaxolol is bound to the negatively charged sulfonic acid groups in the resin. When Betaxolol-bound resin is applied to the eye, the cationic ions such as Na+ or K+ in the tear fluid induce the release of Betaxolol molecules from resin matrix into the tear film and lead to Betaxolol penetration across the cornea.	Glaucoma
4.	TobraDex ST (Alcon Laboratories, Inc.)	Tobramycin 0.3% and DEX 0.05%, + Xanthan gum(anionic polysaccharide with repeating unit of two D-glucose, two D-mannose and one D-glucuronic acid residues)	The Xanthan gum-Tobramycin interaction reduces sedimentation of DEX particles and improves suspension characteristics. The viscosity increases after mixing with tears as the interactions between xanthan gum and tobramycin are interrupted by pH and the ionic content of tears. The enhanced viscosity leads longer retention and	Anti-inflammatory and Anti-infective formulation for Blepharitis

			improves the ocular bioavailability of the drugs.	
.4	**Timoptic-XE**(Merck & Co., Inc., Whitehouse Station, NJ, U.S.)	timolol maleate+. Gellan gum(an anionic deacetylated polysaccharide with a tetrasaccharide repeating unit of one -L-rhamnose, one -D-glucuronic acid and two -D-glucuronic acid residues).	gelation occurs in the presence of mono- and divalent cations including Ca2+, Mg2+, K+ - and Na+.and it reduced the intra ocular pressure .	Glaucoma treatment
5.	Novasorb (Novagali Pharma S.A., Evry, France)	Cyclosporine+ Cationorm(composed of only cationic emulsion without any active ingredients, has been launched for mild dry eye)	It is a cationic emulsion, based on electrostatic attraction that occurs between the oily droplets of a positively-charged emulsion loaded with active ingredient, and negatively charged ocular surface.Therefore, Novasorb improves solubility and absorption of lipophilic drugs, reduces the number of instillation times and side effects, leading to better efficacy and compliance.	Used in Phase III studies for dry eye and Phase II/III studies for vernal Keratoconjunctivitis.

2.2. Ointment Ophthalmic ointments are still being marketed for night time applications and where prolonged therapeutic actions are required. Major disadvantage of the ophthalmic ointments is that they cause blurred vision due to refractive index difference between the tears and the non-aqueous nature of the ointment and inaccurate dosing. The desirable factor should be involved for development of ointment such as- (a) They should not be irritating to the eye (b) They should be uniform (c) They should not cause excessive blurred vision and (d) They should be easily manufacturable. Typical manufacturing process for an ophthalmic ointment includes micronization and sterilization of the active agent by dry heat, ethylene oxide irradiation or gamma irradiation. Antimicrobial preservatives (if required) such as

chlorobutanol or parabens are dissolved in a mixture of molten petrolatum and mineral oil and cooled to about 40 °C with continuous mixing to assure homogeneity. Sterilized and micronized active is then added aseptically to the warm sterilized petrolatum/ mineral oil mixture with continuous mixing until the ointment is homogeneous. The ointment is then filled into presterilized ophthalmic tubes Vivek Dave et.al.(2012).

2.3. Emulsions and suspensions

Eye emulsion easily penetrate into intraocular tissues compared with its suspension. example - Difluprednate emulsion, difluprednate emulsion (Durezol, Alcon Laboratories, Inc.), approved by FDA for the treatment of inflammation and pain associated ocular surgery. a pilocarpine emulsion in eye drop form has been reported to prolong therapeutic effect as compared to pilocarpine hydrochloride eyedrops, such that it may be administered only twice, rather than four times daily. In this formulation, pilocarpine is bound to a polymeric material and this complex makes up the internal, dispersed phase of the emulsion system. In vitro studies have indicated that the release time of 80% of the pilocarpine from this system is 6 hours, compared to 80% released in only 1 hour from pilocarpine hydrochloride solution thus, the prolonged therapeutic effect is apparently due both to an enhanced pulse entry of drug and to a prolongation of drug release from the vehicle.

Aqueous suspension of poorly water-soluble drugs has some pharmaceutical problems including caking and poor redispersibility, which may affect bioavailability due to dosing error, and difficulty of filtration sterilization due to the wide range of particle size.

Pilocarpine as a model drug, an eye drop formulation has been described that consists of an aqueous suspension of particles (average diameter 0.3 microns) of a cellulose acetate hydrogen phthalate latex, onto the surface of which pilocarpine HCl was previously adsorbed. The suspension had a low viscosity (180 cps), and was readily delivered as an eyedrop. The latex particles reportedly coagulate upon instillation due to a pH change, and therefore resist drainage from the eye. This system, containing 2% pilocarpine HCI, caused significant enhancement of the miotic response in rabbit eyes, with the leaching-out process extending past 4 hours.

2.4. Hydrogel Hydrogels are polymer masses constructed from a hydrophilic polymer that is insoluble in water Viscous solutions. Hydrogels, based upon the addition of hydrocolloids to simpler aqueous solutions, are the most common formulations. Gels are administered in the

same way as an ointment, which is less convenient for the patient than the instillation of a viscous drop. Gels permit longer residence time in the precorneal area than viscous solutions. The most common system of phase transition sol –to –gel of viscous polymer based liquid due to change in a specific physicochemical parameter (ionic strength, temperature, pH, or solvent exchange) is In Situ Gelling Systems. (i) Gelling of the solution is triggered by a change in the pH. CAP(cellulose acetate pthalate) latex cross linked polyacrylic acid and its derivatives such as carbomers are used. They are low viscosity polymeric dispersion in water which undergoes spontaneous coagulation and gelation after instillation in the conjunctival cul-desac.(ii) Gelling of the solution instilled is triggered by change in the ionic strength. For example, Gelrite is a polysaccharide, low acetyl gellan gum, which forms a clear gel in the presence of mono or divalent cations. The concentration of sodium in human tears is 2.6 g/l is particularly suitable to cause gelation of the material when topically installed into the conjunctival sac.(iii) In this method gelling of the solution is triggered by change in the temperature. Sustained drug delivery can be achieved by the use of a polymer that changes from solution to gel at the temperature of the eye. But high concentration of polymer is needed. Example- Methyl cellulose and smart hydrogels MarvinE.Myleset.al.(2005).

Table 3 Various types of polymers used in formulation containing in situ gelling system for ocular drug delivery.

S.n.	Drugs	Formulation	Polymers
1.	Pilocarpine	In situ gelling system	Pluronic F127, MC, HPMC
2.	Timolol	In situ gelling system	Pluronic F127, MC, HPMC, CMC
3.	Doxorubicin	In situ gelling system	Chitosan/glycerophosphate
4.	Indomethacin	In situ gelling system	Gellan gum
5.	Pefloxacinmesylate	In situ gelling system	Gelrite®
6.	Sezolamide	In situ gelling system	Gelrite®
7.	Ciprofloxacin HCl	In situ gelling system	Poloxamer/ Hyaluronic acid

Table 4: Adhesiveperformance properties of various type of polymers for containing in situ gelling system for ocular drug delivery.

S. No.	Polymer	Adhesiveperformance
1	Carboxymethyl cellulose	Excellent
2	Carbopol	Excellent
3	Carbopoland Hydroxypropyl	Good
	Cellulose	
4	Carbopol and EX 55	Good
5	Polyacrylamide	Good
6	Polycarbophil	Excellent

7	Gelatin	Fair
8	Dextran	Good
9	Pectin	Poor
10	Acacia	Poor

2.5. Cul-de sac inserts

2.5.1. Sandwitch shape (ocuserts) It is a sterile preparation composed by two layer of polymer in which active ingredient is placed just like a sandwitch form. example two outer layers of ethylene-vinyl acetate copolymer (EVA), and an inner layer of pilocarpine in alginate gel within di-(ethylhexyl)phthalate for a release enhancer, sandwiched between EVA layers. But it has major disadvantage due to this it has not widely used because of unsatisfactory IOP control. The various reason, including difficulty of inserting the device, ejection of the device from eye, and irritation during insertion Reeta Rani Thakur eta.l.(2011).

2.5.2. Rode shape (Lacrisert Aton Pharma, Inc., Lawrenceville, NJ, U.S.)- is also sterile preparation a rod-shaped, water-soluble cul-de-sac insert composed of hydroxypropyl cellulose without preservatives and other ingredients (1.27 mm diameter, 3.5 mm long), and is indicated in moderate to severe dry eye syndrome. **Reeta Rani Thakur eta.l.(2011).**

2.5.3. Type of insert

2.5.3.1. Soluble insert Developed by Soviet scientists made by all monolytic polymeric device, the device dissolve or erode. Soluble ophthalmic drug inserts is a soluble copolymer of acrylarnide, N-vinyl pyrrolidone and ethyl acrylate. It is a sterile thin film or wafer of oval shape. The system soften in 10-15 sec after introduction in to the upper conjuctival sac, gradually dissolves within 1 h, while releasing the drug. A soluble insert containing gentamycin sulphate and dexamethasone phosphate has been developed Pilocarpine Insert for glaucoma is also reported. But these systems have a disadvantage that that blur vision while the polymer is dissolving. Water soluble bioadhesive component in its formulation has been developed to decrease the risk of expulsion and ensure prolonged residence in the eye, combined with controlled drug release. They are bioadhesive ophthalmic drug inserts. A system based on gentamycin obtained by extrusion of a mixture of polymers, showing a release timer of about 72 h has been reported. Due to difficulty with self-insertion.

2.5.3.2. Insoluble inserts Insoluble inserts are polymeric systems into which the drug is incorporated as a solution or dispersion. Ophthalmic inserts (ocuserts) have been reported

using alginate salts, PVP, modified collagen and HPC, Ocufit is a silicone elastomer based matrix that allows for the controlled release of an active ingredient over, a period of at least 2 weeks. Osmotically controlled inserts have also been described, where release is by diffusion and osmotically controlled.

3. Recent and Nanotechnology Based Delivery Systems

3.1. Nanopartical

Nanoparticles are particulate drug delivery systems having a size 10-1000 in which the drug may be dispersed, encapsulated, or absorbed.the various formulation are prepared by using nano size of particle such as- nanosuspension,nanoemulsion. Nanosuspensions have capability to deliver of hydrophobic drugs because they enhanced the rate and extent of ophthalmic drug absorption as well as the intensity of drug action with significant extended duration of drug effect. The higher drug level in the aqueous humour was reported using Eudragit RS100 using nanosuspensions for the ophthalmic controlled delivery of ibuprofen. Nanoemulsion, nanoemulsion for ophthalmic drug delivery have been mainly produced by emulsion polymerization. In this process a poorly soluble monomer is dissolved in the continuous phase which can be aqueous or organic. Polymerization is started by chemical initiation or by irradiation with gamma rays, ultra violet or visible light. The materials that have been mainly used for ophthalmic nanoparticles are poly alkyl cyano acrylates.

SLNs (solid lipid nano partical) are submicron-sized carriers composed of a lipid solid matrix stabilized by a surfactant. Such systems have some advantages like low toxicity, high drug payload, capability of including lipophilic and hydrophilic drugs, drug targeting, controlled release (fast or sustained), and occlusive properties.. To overcome problems of conventional suspension, prepare nanosuspensions for successful drug delivery. Nanosuspension not only improves the saturation solubility of drug in media but it is also ideal approach for ophthalmic delivery of hydrophobic drugs in eye. Nanosuspensions can also use to achieve sustained release of the drug by incorporating or formulating with suitable hydrogel or mucoadhesive base or in ocular inserts. Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by suitable surfactants. Nanosuspensions are prepared using poorly water soluble drugs without any matrix material suspended in dispersion. These can be used to enhance the solubility of drugs that are poorly soluble in water as well as lipid media. It also improves drug stability as well as bioavailability of poorly soluble drug. .Recently nanotechnology can be used in drug delivery and gene therapy by applying novel

self-assembled materials and devices of nanoscale size. For example polyplexes (DNA/polycation complexes), block copolymer micelles and nanogels. Among these, polymer micelles have been evaluated for the delivery of anti-cancer agents in human trials. . Nanaosuspensions can also be formulated for drugs which are insoluble in both water and organic solvents. Hydrophobic drugs can also be formulated as nanosuspensions such as naproxen, clofazomine, nimesulide, mitotane, amphotericin B, omeprazole and spironolactone. Nanosuspensions can be given through various routes administration like oral, parenteral, topical, ocular and pulmonary routes. Nanoparticles can easily adsorb, bind and carry drugs or proteins as they have a large surface area. . Formulation of nanosuspension includes stabilizers like poloxamers, lecithins, povidones, polysorbates etc. Solvents used in formulation includes water miscible solvents like butyl acetate, benzyl alcohol, ethyl acetate and other pharmaceutically acceptable and less hazardous solvents. Tweens and spans are widely used as surfactants which are added the dispersion by reducing interfacial tension. Surfactants act as wetting or deflocculating agents. Ethanol, glycofurol, isopropanol etc can be used as co- surfactants, buffer salts, osmogent, cryoprotectants, polyols are used as additives in nanosuspension formulation. Nanosuspensions offers many advantages: firstly, the physical and chemical stability of drugs in the nanosuspension can be increased as they are actually in the solid state.; secondly, dose and toxicity can be reduced and the high drug loading can be achieved.; thirdly, It is valuable for those molecules which are insoluble in oils.; finally, nanosuspensions can be used for the passive targeting. **Meetali mudgil et.al.(2012).** Proposed that nanoparticles are prepared from different biodegradable polymers like poly(lactic acid).31poly (alkyl cyanoacrylate) (PACA),32poly(lactic-co-glycolic acid)(PLGA),33poly(epsilon caprolactone) (PCL), as well as different natural polymers like chitosan,35gelatine,36sodium alginate, and albumin,can be used effectively for drug delivery to ocular tissues. Nanosuspensions can be valuable for the drugs which have poor solubility in lachrymal fluids. The nanoparticulate nature of the drug shows sustained release effect by increasing its residence time in the cul-de-sac.

Table 5: The following table show the various nanoparticles formulation ,prepared by various researcher.

S. No	Researcher	Active ingredient	Polymer and other excipents	Technique	Dosage form	Indication
1.	YadavAV et.al.	Carvedilol	Eudragit E-100 poloxamer F-407	Nanoprecipitation by Solvent displacement	Nanosuspension	Hypertension
2.	MandalB et.al.	Sulfacetamide	Eudragit RL-100	Solvent evaporation	Nanosuspension	ocular bacterial infections.
3.	GuptaH et.al.	Sparfloxacin	poly lactide co-glycolic acid (PLGA)	Nanoprecipitation by Solvent evaporation	_	ocular bacterial infections
4.	Kerur et.al.	Acyclovir	Eudragit RS-100 tween 80	Solvent evaporation	Nanosuspension	ocular viral infection
5.	PignatelloR et.al.	Cloricromene	_	solvent evaporation	_	_
6.	Aksungur P et.al.	Cyclosporine (CsA)	PLGA and Eudragit RL-100 carbopol	Solvent evaporation	_	severe dry eye syndrome
7.	AdibkiaK et.al.	Piroxicam	Eudragit RS100	Solvent evaporation	_	inflammatory uveitis (EIU).
8.	Javadzadeh et.al.	Naproxen	lactic-co-glycolic acid) (PLGA)	Solvent evaporation	Nanoemulasion	nti-inflammatory
9.	Wadhwa et.al.	Dorzolamide hydrochloride (DH) or timolol maleate (TM)	Hyaluronic acid (HA) or modified chitosan (CS)	Ionic gelation	-	glaucoma
10.	Mahmoud et.al.	Econazole nitrate (ECO	Chitosan and sulfobutylether-β-cyclodextrin sodium	Ionic gelation	-	Ocular fungal infection
11.	Pardeike et.al.	Phospholipase A2 inhibitors PX-18 and PX-13	-	Homogenization	nanosuspension	Eye irritation
12.	Chattopadhyay P.et.al.	Dexamethasone Phosphate and griseofulvin	-	Supercritical fluid method	-	Fungal infection

Table 6: Summary of methods used for preparation of polymeric nanoparticles for ocular delivery.

S.N.	Technique	Active drug	Polymer	Stabilizer	Category
1.	Solvent DIS.M.	Sulfacetamide	Eudragit RL100	Pluronic F109	Antibiotic
		Carvedilol	Eudragit E100	Poloxamer 407	Non-selective beta blocker
		Sparfloxacin	PLGA	PVA	Fluroquinolone
		Levofloxacin	PLGA	PVA	Antibiotic
		Cloricromene	Eudragit RS100, Eudragit RL100	Tween 80	Antibiotic
		Cyclosporine A	PLGA,Eudragit RL100	PVA	Immunosuppressant
		Piroxicam	Eudragit RS100	PVA	NSAID
		Amphotericin B	Eudragit RS100	PVA	Antifungal
		Diclofenac	Eudragit S100	Poloxamer 188	NSAID
		Diclofenac	PLGA,PLDL	Tween 80	NSAID
		Hydrocortisone	HPMC	SLS	Glucocorticoid
		Pilocarpine	PLGA,Chitosan	-	Para-sympathomimetic
		Ibuprofen	Eudragit RS100	--	NSAID
		Flurbiprofen	Eudragit RS100R,Eudragit RL100R		NSAID
		Ganciclovir	Chitosan	-	Antiviral
		Clarithromycin	PLGA	-	Macrolide Antibiotic
		Brimonidine	Eudragit	TPP	Non-selective beta blocker
		Naproxen	PLGA	-	NSAID
2.	Homogenization	Dexamethasone	Hydroxy ethyl cellulose	PLuronic F68	Antiinflamatory
3.	Ionic Gelation	Fluconazole	Gum cordial	Di octyl sod.	Triazole antifungal
		Mycophenolate mofetil	Chitosan	-	Immunosupperssant
		Brimonidine tratrate	Chitosan	-	Non-selective beta blocker
		Econazole nitrate	Chitosan	-	Antifungal
		5- Fluro Uracil	Chitosan	-	Anticancer
		Indomethacin	Chitosan	-	NSAID
4.	Milling	Cyclosporine A	-	PVA	Immunosuppressant

3.2. Bodi(bio adhesive ocular drug insert).

Bio adhesive ophthalmic drug inserts (BODI), patented by Gurtler and Gurny in 1993, belong to the group of soluble inserts made of synthetic and semisynthetic polymers. The major

composition of BODI inserts consists of rod-shaped inserts obtained by the extrusion of a dried homogeneous powder mixture composed of the polymeric vehicle and the active compound using a specially designed ram extruder. It composed of ternary mixture of hydroxypropylcellulose (HPC), ethyl cellulose (EC), and carbomer (Carbopol 934P).The replacement of natural polymers such as collagen by synthetic polymers is definitely advantageous regarding their safety of use. certainly, natural biopolymers may be associated with inflammatory response in the ocular tissues due to the presence of residual proteins. In addition, at present, devices based on collagen may encounter difficulties in being accepted by regulatory authorities, because of possible prior infection description of BODI technology.The first developed BODIs contained Gentamicin sulphate, an aminosidic antibiotic, as a model drug. However, despite good pharmacokinetic performance when compared with conventional formulations such as eye drops **Baeyens et.al**.. Studied different approaches to reduce the solubility of Gentamicin using cellulose acetate phthalate (CAP) to obtain either a solid dispersion or a coprecipitate **Baeyens et. al.**

3.3. Prodrugs

In the present circumstance, 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. Prodrug technology is usually considered as a useful technique in improving corneal permeability. It is also useful in solving pharmaceutical problems such as poor solubility and stability. The only commercial prodrug available is dipivalyl epinephrine .Such an approach have been extended to Phenylepinephrine and timolol .The concept of double prodrug is also gaining importance where a double prodrug is a prodrug of a prodrug. The partition coefficient of Ganciclovir found to be increased using an acyl ester prodrug, with substantially increased the amount of drug penetration to the cornea which is due to increased susceptibility of the Ganciclovir esters to undergo hydrolysis by esterases in the cornea. **A.Rajasekaran et.al.(2010).**

3.4. Panitration enhancers

The transport of drug across the cornea is increased by increasing the permeability through corneal epithelial membranes. To proceed this work , Penetration enhancers can act by increasing corneal uptake by modifying the integrity of corneal epithelium . Examples of enhancers include actin filament inhibitors, surfactants, bile salts, chelators, and organic compounds. Selection of enhancer is critical due to unique characteristics and great

sensitivity of the corneal conjunctival tissues. Penetration enhancers themselves can penetrate the eye and may lead to unknown toxicological complications e.g., benzalkonium chloride (BAC) was found to accumulate in the cornea for days.Penetration enhancers have also been reported to reduce the drop size of conventional ophthalmic solutions especially if they do not elicit local irritation. Patel Vishal et.al.(2011).

3.5. Liposomes

Liposomes were first reported by Bangham in the 1960s and have been investigated as drug delivery systems for various routes , These are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter.They make a contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, p 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. A liposome or so - called vesicle consists of one or more concentric spheres of lipid bilayers separated by water compartments with a diameter ranging from 80 nm to 100 μ m. Owing to their amphiphilic nature, liposomes can accommodate both lipohilic (in the lipid bilayer) and hydrophilic (encapsulated in the central aqueous compartment) drugs . According to their size, liposomes are classified as either small unilamellar vesicles (SUVs) (10 – 100 nm) or large unilamellar vesicles (LUVs) (100 – 300 nm). If more than one bilayer is present, they are referred to as multilamellar vesicles (MLVs). Depending on their lipid composition, they can have a positive, negative, or neutral surface charge. The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids Kumar manish et.al (2012). developed a novel delivery system for oligonucleotides by incorporating them into liposomes and then dispersing them into a thermo sensitive gel composed of poloxamer 407. They compared the in vitro release of the model oligonucleotides pdT16 from simple poloxamer gels (20 and 27% poloxamer) with the ones where pdT16 was encapsulated into liposomes and then dispersed within the gels. They found that the release of the oligonucleotides from the gels was controlled by the poloxamer dissolution, whereas the dispersion of liposomes within 27% poloxamer gel was shown to slow down the diffusion of pdT16 out of the gel Bochot et.al..

3.6. Visudyne

Visudyne (QLT Ophthalmics, Inc., Menlo Park, CA, U.S.) is an intravenous liposomal formulation containing photosensitizer, verteporfin, in photodynamic therapy for predominantly classic subfoveal choroidal neovascularization due to AMD, pathologic myopia or presumed ocular histoplasmosis. Plasma lipoproteins, such as low-density lipoprotein (LDL), have been proposed to enhance the delivery of hydrophobic verteporfin to malignant tissue since tumor cells have been shown to increase numbers of LDL receptors . verteporfin released in blood flow from liposome, is associated with LDL, and uptakes in neovascular tissues and undissociated verteporfin still encapsulated in liposome, is accumulated in vascular endothelial cells via LDL receptor-mediated endocytosis since phosphatidylglycerol is a major constitute of Visudyne formulation.

3.7. Niosomes

Niosomes are nonionic surfactant vesicles which exhibit the same bilayered structures as liposomes. their advantages over liposomes include improved chemical stability and low production costs. moreover, niosomes are biocompatible, biodegradable, and non-immunogenic. they were also shown to increase the ocular bioavailability of hydrophilic drugs significantly more than liposomes Kumar manish et.al.(2012). This is due to the fact that the surfactants in the niosomes act as penetrations enhancers and remove the mucous layer from the ocular surface. 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. Vyas and coworkers reported that there was about 2.49 times increase in the ocular bioavailability of timolol maleate encapsulated in niosome as compared to timolol maleate solution. Non-ionic surface active agents based discoidal vesicles known as (discomes) loaded with timolol maleate were formulated and characterized for their in vivo parameters. In vivo studies showed that discomes released the contents in a biphasic profile if the drug was loaded using a pH gradient technique. Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site.

3.8. Pharmacosomes

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, thusgenerating 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.

3.9. Iontophoresis

It is the process direct current drives ions into cells/tissues. When iontophoresis is used for drug delivery, the ions of importance are charged molecules of drug. If the drug molecules carry a positive charge, they are driven into the tissue at anode; if negatively charged, at cathode. Ocular iontophoresis suggest a drug delivery system that is fast, painless, safe and in most cases result in the delivery of high concentration of drug at specific site. But there were some findings of neutralization effects of drug adversely affecting the optimum zeta potential. Along with all the above delivery systems some advanced drug delivery systems like cell encapsulation, stem cell therapy, protein and peptide therapy, sclera plug therapy, oligo nucleotide therapy, aptomer technology and ribosome therapy also available and all are having their own limitations.

3.10. Dendrimers

Dendrimers can successfully use for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility. Vandamme and coworkers have developed and evaluated poly (amidoamine) dendrimers containing fluorescein for controlled ocular drug delivery. They determined the influence of size, molecular weight and number of amine, carboxylate and hydroxyl surface groups in several series of dendrimers. The residence time was longer for the solutions containing dendrimers with carboxylic and hydroxyl surface groups.

3.11. Cyclodextrin- Cyclodextrins (CDs) are cyclic oligosaccharides capable of forming inclusion complexes with many guest molecules. CD complexes are reported to increase corneal permeation of drugs likedexamethasone, 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 foundto be non-irritant to the human and animal eye.

3.12. Collagen shield

Collagen shield basically consist of cross linked collagen, fabricated with foetalcalf skin tissue and developed as a corneal bandage to promote wound healing. Topically applied antibiotic conjugated with the shield is used to promote healing of corneal ulcers. Tear fluid makes these devices soft and form a thin pliable film which is having dissolution rate up to 10, 24 or 72 hours. Because of its structural stability, good biocompatibility and biological inertness, collagen film proved as a potential carrier for ophthalmic drug delivery system. Collagen ophthalmic inserts are available for delivery of pilocarpine to the eye.

3.13. Microneedle

As an alternative to topical route Researchers have developed microneedle to deliver drug to posterior segment. The extent of lateral and transverse diffusion of sulforhodamine was reported to be similar across human cadaver sclera. Microneedle had shown prominent in vitro penetration into sclera and rapid dissolution of coating solution after insertion while in vivo drug level was found to be significantly higher than the level observed following topical drug administration like pilocarpine.

3.14. Mucoadhesive polymers

They are basically macromolecular hydrocolloids with plentiful hydrophilic functional groups, such as hydroxyl, carboxyl, amide and sulphate having capability for establishing electrostatic interactions. A mucoadhesive drug formulation for the treatment of glaucoma was developed using a highly potent beta blocker drug, levobetaxolol (LB). hydrochloride and partially neutralized poly acrylic acid (PAA). Complexes were prepared with varying degrees of drugloading, such that the same PAA chain would have free -COOH groups for mucoadhesion along with ionic complexes of LB with COO- groups. Thin films of the complexes dissociated to release the drug by ion exchange with synthetic tear fluid.

Table 7: Viscosifying polymers screened for ocular mucoadhesive capacity.

Polymer	Charge	Mucoadhesive Capacity
Carbomer (neutralized)	Anionic	Excellent
Hyaluronan	Anionic	Excellent
Poly(acrylic acid) (neutralized)	Anionic	Excellent
Pectin	Anionic	Good
Poly(galacturonic acid)	Anionic	Good
Na alginate	Anionic	Good
Na carboxymethylcellulose	Anionic	Good
Chitosan	Cationic	Good

Xyloglucan gum	Anionic	Poor/absent
Scleroglucan	Anionic	Poor/absent
Xanthan gum	Anionic	Poor/absent
Methylcellulose	Non ionic	Poor/absent
Poloxamer	Non ionic	Poor/absent
Poly(vinyl pyrrolidone)	Non ionic	Poor/absent
Poly(vinyl alcohol)	Non ionic	Poor/absent
Hydroxypropylmethylcellulose	Non ionic	Poor/absent

3.15. Microemulsion

The term microemulsions were first described by Hoar and Schulmanin 1943.Microemulsion is a transparent biphasic dispersion system of water and oil stabilized using surfactant and cosurfactant to reduce interfacial tension and usually characterized by small droplet size (100 nm), higher thermodynamic stability and clear appearance. . Usually, the average droplet size is between 100 and 500 nm. Due to their characteristics size they are optically transparent. Medically, the oil-in-water (o/w) nanosized emulsions are used mainly as delivery carriers for lipophilic drug molecules which show therapeutic activity when administered ocularly. Nano sized emulsions as have been utilized as ocular eye drops in virtue of their distinct advantages. These include sustained release of the drug applied to the cornea, high penetration in the deeper layers of the ocular structure, and aqueous humor as well as ease of sterilization. Thus, these systems can achieve therapeutic action with a smaller dose and a fewer systemic and ocular side effects.

The main advantages of novel emulsion for ocular purpose are-

1. Overcome the side effects of pulsed dosing produced by conventional systems.
2. Provide sustained and controlled drug delivery.
3. Increase ocular bioavailability of drug by increasing corneal contact time.
4. Provide targeting within the ocular globes so as to prevent the loss to other ocular sites.
5. Circumvent the protective barriers like drainage, lacrimation and diversion of exogenous chemicals into systemic circulation by conjunctiva.
6. Provide comfort and compliance to the patient and yet improve the therapeutic performance of the drug over conventional systems.
7. Ease of sterilization
8. Improved stability
9. Provide better housing of the delivery system in the eye so that the loss to other besides cornea is prevented .However the nano sized emulsions are also associated with certain

limitations that pose serious concerns and need to be addressed viz., selection of surfactants/cosurfactants and aqueous/organic affects its stability and toxicity issues.

Table 8: Excipients used in Micro emulsion.

S.No.	Oils	Emulsifiers	Cationic lipids and polysaccharide	Miscellaneous
1.	Soya oil	Phospholipid	Stearylamine	α–Tocopherol
2.	Castor oil	Polysorbate 80	Oleylamine	Glycerol
3.	Paraffin oil	Transcutol P	Chitosan	Xylitol
4.	Paraffin light	Cremophor RH		Sorbitol
5.	Lanolin	Poloxamer 407		Thiomersal
6.	Vaselin	Poloxamer 188		EDTA
7.	Corn oil	Miranol C2M		Methyl paraben
8.	Glycerin	MHT		Propyl paraben
9.	Monostearate	Tyloxapol		
10.	Medium chain	Cholesterol		
11.	Monoglyceride			
12.	Medium chain			
13.	Triglycerides			
14.	Sesame oil			

3.15.1. Type of o/w nanosized emulsion

Classified into three types . Emulsifiers with the capacity to produce a negative charge at the o/w interface are termed anionic and those able to provide a positive charge at the o/w interface are called cationic. conventional or anionic emulsions are able to significantly sustain the incorporated lipophilic drug release in simulated or real physiological environments under sink conditions .Therefore in an attempt to prolong and/or optimize the drug release, cationic lipid or polysaccharide emulsifiers are added to the emulsions to elicit mucoadhesion with anionic ocular tissues by an electrostatic adhesion. Indeed, cationic emulsions prepared using stearylamine, oleyamine and chitosan can serve this purpose electrostatic attraction between the cationic emulsified droplets and anionic cellular moieties of the ocular and topical skin surface tissues enhance the bioavailability of emulsions containing lipophilic drugs. There is another type of emulsion that is neutral in terms of the charge on the dispersed droplets. These are instead stabilized through steric effects exerted by the emulsifier molecule present in the emulsion formulation. According to Capek the stability of the electrostatically- and sterically-stabilized o/w nanosized emulsions can be controlled by the charge of the electrical double layer and the thickness of the droplet surface layer formed by non-ionic emulsifier, respectively.

3.15.2. Optimization of Nanoemulsion Preparation, optimization is directed to be obtain minimum droplet size and/or minimum polydispersity. polydispersity. Another aim in nanoemulsion optimization is to improve the stability because, as stated above, stability is the main problem to overcome to find practical applications for nano-emulsions. Optimization is also directed to obtain an optimum in the function for which the nano-emulsions are used (e.g. drug delivery). The properties to be optimized, for example droplet size and polydispersity, will depend, of course, on composition variables and could depend on preparation variables, so optimization can be carried out with respect to these two types of variables Optimization is presently classified according to the following

Methods

1. Phase behavior studies for optimization
2. Optimization by selective variation of parameters
3. Experimental designs for optimization

Table 9: Nano-sized emulsion in ocular delivery.

S. No.	DRUGA	RESULTS
1.	Pilocarpine	(i) Physically stable for 6 months at 4 º C
		(ii) Bioavailability is pH dependent
2.	Cyclosporine	(i) On dilution with tear fluid viscosity of
		formulation is increased
		(ii) Prolonged precorneal residence time
3.	Adaprolol maleate	Safe and effective in human studies
4.	Indomethacin	Improved ocular bioavailability
5.	Piroxicam	positively charged submicron emulsion shows
		pronounced effect on both the ulceration rate and
		epithelial defects in the management of corneal
		alkali-burning
6.	Dorzolamide HCl	(i) More intensive treatment of glaucoma
		(ii) Higher therapeutic efficacy
		(iii) Better patient compliance
7.	delta-8- tetrahydro	(i) Intense and long-lasting intraocular pressure
8.	Cannabinol	(IOP)-depressant effect
		(ii) No irritation
9.	Dexamethasone	Improved pharmacokinetic parameters
10.	Timolol	Bioavailability of timolol was increased
11.	Levobunolol	Higher apparent lipophilicity
12.	Chloramphenicol	Stability of the chloramphenicol in the microemulsion formulations was increased

3.16. Contact lanse

There are several properties of contact lense for this properties the contactlense are used as a drug delivery system. (1) Soak and absorption of drug solution (2) piggyback contact lens combined with a drug plate or drug solution (3) surface-modification to immobilize drugs on the surface of contact lenses (4) incorporation of drugs in a colloidal structure dispersed in the lens (5) ion ligand-containing polymeric hydrogel and (6) molecularly imprinting of drugs. Noriyuki Kuno et.al.(2010). SEED Co., Ltd. (Tokyo, Japan) and Senju Pharmaceutical Co., Ltd. (Osaka, Japan)- Co-developed a disposable soft contact lens to release incorporated sodium cromoglicate for one day. It currently used in clinical trials for allergic conjunctivitis in Japan will be conducted in 2010.Vistakon Pharmaceuticals, LLC (Philadelphia, PAU.S.)- Completed a multicenter Phase III clinical trial for a contact lens presoaked to release an antihistamine drug, ketotifen, to prevent allergic conjunctivitis in contact lens wearer. The property of contact lense, use as a DDS is initiate when water soluble drugs soaked in drug solutions. Then it 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.example - Bionite lens -It is reported that it has greater penetration of fluorescein made from hydrophilic polymer (2-hydroxy ethyl methacrylate) in human.

3.17. Subconjunctival/episcleral implants

The implant DDS for anterior part of eye containing a flat bottom contact eith the episclera, and rounded top ,in contact with anterior surface of eye . example LX201 (Lux Biosciences Inc., Jersey City, NJ, U.S.) is a silicone matrix episcleral implant designed to deliver cyclosporine A to the ocular surface for one year.having different lengths of 0.5 and 0.75 inches. Each implant is 0.08 inches wide and 0.04 inches high. In preclinical studies using rabbits and dogs, the episcleral cyclosporine implant delivered continuously potentially therapeutic cyclosporine levels to the lacrimal gland, and showed efficacy in a model of keratoconjunctivitis. Another example an episcleral implant developed by 3T Ophthalmics (Irvine, CA, U.S.) is also composed of silicone and looks like a tiny bathtub, less than 1.0 cm long. It can be re-filled with drugs in any form, such as a solution, gel or matrix. A subconjunctival insert containing latanoprost (Latanoprost SR insert) in Phase I clinical study developed by Pfizer, Inc. (New York, NY, U.S.) is composed of a poly (DL-lactide-co-glycolide) (PLGA) tube containing a latanoprost-core. One end of the tube is capped with an impermeable polymer, silicone, and the other end is capped with a permeable polymer,

polyvinyl alcohol (PVA). Latanoprost is released across the PVA-end and its release rate is regulated by an internal diameter of PLGA tube. Duration of latanoprost release is designed for 3–6 month.

3.18. Intravitreal implant

The goal of the intraocular implant design is to provide prolonged activity with controlled drug release from the polymeric implant material. Intraocular administration of the implants always requires minor surgery. In general, they are placed intravitreally, at the pars plana of the eye (posterior to the lens and anterior to the retina).

Advantage (1) by-passing the blood–ocular barriers to deliver constant therapeutic levels of drug directly to the site of action, (2) avoidance of the side effects associated with frequent systemic and intravitreal injections, and (3) smaller quantity of drug needed during the treatment.

The ocular implants are classified as non-biodegradable and biodegradable devices . Non-biodegradable implants can provide more accurate control of drug release and longer release periods than the biodegradable polymers do, but the non-biodegradable systems require surgical implant removal with the associated risks.

Table 10: Recent ophthalmic implants.

Intravitreal implant	Technology	Shape and size	Drug and polymer	Drug Administered Mechanism	Uses
Vitrasert (Bausch & Lomb Inc., Rochester, NY, U.S.)	Durasert technology system	millimeter in size	ganciclovir (GCV) EVA and PVA	Surgical implantation at the pars plana. Drug release by passive diffusion through a small opening in EVA at the base of the device for 6-8 months	cytomegalovirus retinitis
Retisert (Bausch & Lomb Inc.)	Durasert technology system	Central core of drug 1.5mm	fluocinolone acetonide (FA) 1000 days	Surgical implantation at the pars plana.	non-infectious posterior uveitis.

		diameter Tablet 3 mm _ 2mm _ 5 mm	PVA and silicone adhesive and the silicone elastomer	silicone elastomer cup's release orifice and the permeability of the PVA layer between the tablet and the orifice, the rate of drug release from the implant can be controlled. Release of FA from the cup reservoir occurs as water from the exterior of the implant penetrates into it and dissolves some of the drug. The dissolved drug substance then diffuses across the release orifice through the semi-permeable layer of PVA into the medium.	
Iluvien (Alimera Sciences, Alpharetta,GA,U.S.)	Durasert technology system	An injec.table, rod-shaped intravitreal implant with FA (length: 3.5 mm, diameter: 0.37 mm)	polyimide and PVA	Injected using an inserter with a 25-gauge needle and is expected to provide sustained delivery of FA to the back of the eye for three	Diabetic macular edema (DME)

				year	
Ozurdex(Allergan, Inc., Irvine, CA, U.S.)	novadu technology	length: 6.5 mm, diameter: 0.45 mm	DEX composed of PLGA	Ozurdex is administered by specially designed injector with a 22-gauge needle into vitreous cavity.	Macular edema due to branch retinalvein central vein occlusion (BRVO) (CRVO)

SurModics,Inc. (Eden Prairie, MN, U.S.)	I-vation TA	titanium helical coil (length; 0.5 mm, width; 0.21 mm)	triamcinolone acetonide (TA)and non-biodegradable polymers poly(methyl methacrylat and EVA	This implant will have an in vivo sustained delivery for a minimum of two years	Diabetc maculr edema (DME)
Neurotech Pharmaceuticals, Inc. (Lincoln, RI, U.S.)	NT-501 Encapsulated Cell Technology	Cylindrical tube 6 mm in length and 1 mm in diameter	CNTF secreted by encapsulated cells , polyethylene terephthalate yarn	Surgical implantation at the pars plana	AMD,GA
Surodex (Allergan, USA)	-	Microsized implant	Dexamethasone 60 µg And poly lactic-co-glycolic acid (PLGA) implants	Placed underneath the scleral flap	postoperative inflammation after filtering surgery on eyes with glaucoma
Posurdex (Allergan, USA	-	Microsized implant	Dexamethasone 700µg And poly lactic-co-glycolic acid (PLGA) implants	Injected or through small incision at the pars plana	Macular edema due to retinal vein occlusion, diabetic macular edema and uveitis
Medidur (Alimera Sciences, USA and pSivida Inc., USA)	-	cylindrical tube 3.5 mm in length and 0.37 mm in diameter	Fluocinolone acetonide	njected in the vitreous cavity	diabetic macular edema

4. OTHER

4.1. Punctal plugs

Inc. (Vancouver, Canada) and Vistakon Pharmaceuticals, LLC have individually developed punctal plugs as DDSs for latanoprost and bimatoprost, respectively. QLT Inc. has reported Phase II data for a punctual plug containing a latanoprost dose of 44 g, 81 g, and two different release rates of 95 g. A retention rate based on available data from 185 eyes with 12 weeks of follow-up in conjunction with previous studies was 81%, but a dose-response for IOP reduction was not observed and it also plans a clinical trial of punctal plug containing an antihistamine drugolopatadine, for the treatment of allergic conjunctivitis. Vistakon Pharmaceuticals, LLC developed punctal plug containing bimatoprost in phase II trial. The various advantage of punctual plug are –1. To prolong the retention time and increase absorption and efficacy after instillation of eye-drops. 2. To inhibit the drainage through nasolacrimal system using punctal plug into the pancta is a long-standing approach .3. Efficacy of an ocular hypotensitive agent in eye-drops in conjunction with punctual occlusion by punctual plug has been evaluated.4. Although punctal occlusion significantly decreased approximately 2 mmHg of IOP in the plugged eyes ($p < 0.001$), it was not concluded that this IOP decrease is clinically significant.

4.2. Verisome, IBI-20089

Icon Bioscience, Inc. (Sunnyvale, CA, U.S.) is developing IBI-20089 containing TA using Verisome drug delivery platform technology.

The Verisome is a translucent liquid. When the IBI-20089 mixes with saline, the solution becomes a milky, slightly opaque color and forms gel. , IBI-20089 might be a solution of TA in biodegradable benzyl benzoate and designed to last up to one year with a single intravitreal injection.it used in , Phase I study for cystoid macular edema associated with BRVO or CRVO, has been completed.

4.3. Retaac

RETAAC was injected intravitreously into patients with diffuse DME and their efficacy compared to naked TA-injections. RETAAC-treated eyes showed marked decrease of retinal thickness as well as improved visual acuity for 12 months RETAAC was found to be safe and well tolerated by the retina. No drug or procedure related side effects were observed in this study. A Phase I/II study has been conducted for 21 patients with DME unresponsive laser photocoagulation and demonstrated central macular edema measured by OCT showed a

reduction from baseline exceeding 59% at 3 months after injection of RETAAC, which remained at 6 and 12 months, but significant improvement of visual acuity was not achieved.

4.4. Cortiject

Cortiject (NOVA63035, Novagali Pharma S.A.) is a preservative free emulsion composed of oily carrier and phospholipid as surfactant, encapsulating a target tissue-activated corticosteroid prod rug. Released DEX palmitate is de-esterified by a retina-specific esterase, and activated to be DEX. A single intravitreal injection provides sustained release over 6–9 months. Although an open-label, Phase I study for DME is currently under way, details are not disclosed.

4.5. 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.

4.6. Gene therapy

Along with tissue engineering, gene therapy approaches stand on the front line of advanced biomedical research to treat blindness arising from corneal diseases, which are second only to cataract as the leading cause of vision loss. Several kinds of viruses including adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications. Topical delivery to the eye is the most expedient way of ocular gene delivery. However, the challenge of obtaining substantial gene expression following topical administration has led to the prevalence of invasive ocular administration. Retroviral vectors have been widely used due to their high efficacy; however, they do not have the ability to transduce nondividing cells, leads to restrict their clinical use.46 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 Patel Vishal et.al.(2011).

4.7. 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.47 Current strategy for management of ocular conditions consists of eliminating the injurious agent or attempting to minimize its effects. 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

4.8. Protein and peptide therapy

Delivery of therapeutic proteins/ peptides has received a great attention over the last few years.49 The intravitreous injection of ranibizumab is one such example. The designing of optimized methods for the sustained delivery of proteins and to predict the clinical effects of new compounds to be administered in the eye, the basic knowledge of Protein and Peptide is required.50 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 trans scleral route with insignificant systemic absorption.

4.9. 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.

4.10. Sirna Therapy

For various angiogenesis-related diseases, the use of siRNA is considered as a promising approach.52 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. siRNA has become a valuable tool to explore the potential role of various genes in ocular disease processes. It appears that siRNAs may be valuable in the pathogenesis and development of new treatments for several ocular diseases, based on in vivo and in vitro studies.53 However, its use in vivo remains problematic, largely due to unresolved difficulties in targeting delivery of the siRNA to the tumor cells. Viral gene delivery is very efficient however it currently lacks adequate selectivity for the target celltype. 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.

4.11. Oligonucliotide therapy

Proposed that a major goal of ocular gene therapy is the delivery of genes to treat ocular diseases, inflammations, etc., at the genetic level (i.e. transduced genes expressing anti-inflammatory proteins to limit an inflammatory process or growth factors and/or cytokines to modulate a wound healing process).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 is the most important. A number of factors have been determined to contribute to the efficacy of antisense ON. One primary consideration is the length of the ON species. Lengths of 17– 25 bases have been shown to be optimal, as longer ONs have the potential to partially hybridize with nontarget RNA species. Biological stability is the major barrier to consider when delivering both DNA and RNA oligonucleotides to cells. Protection from nuclease action has been achieved by modification of phosphate backbones, sugar moiety, and bases Marvin E. Myles et.al.(2005).

4.12. 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. One of the earliest aptamers studied structurally was the

15 mer DNA aptamer against thrombin, d(GGTTGGTGTGGTTGG).56 Pegaptanib sodium (Macugen; Eyetech Pharmaceuticals/Pfizer) is an RNA aptamer directed against VEGFb165, where VEGF isoform primarily responsible for pathological ocular neovascularization and vascular permeability.

4.13. 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. They function by binding to the target RNA moiety through Watson-Crick base pairing and inactivate it by cleaving the phosphodiester backbone at a specific cutting site. 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. Lewin and Hauswirth have worked on in the delivery of ribozymes in ADRP in rats shows promise for ribozyme therapy in many other autosomal dominant eye diseases, including glaucoma.

5. Patent Drug Delivery Formulation

Table 11: A list of Patented nanostructure and other recent advanced ocular drug delivery system.

Patent no.	Inovator	Title	Formulation	Year/ Publishing date	Ref
US20080287341	Chen D	Intravitreal administration of sustained-release NP loaded with angiogenic inhibitors or expression plasmids or vectors for these inhibitors.	Polymeric NP (eg, PLGA)	(2008)	12
US7550154 B2	Saltzman WM et al.	Drugs and/or targerting moieties are encapsulated in the NP or chemically bound to their surface. NP shows a ‘high density’ of targeting	NP made of PLGA or poly(hydroxylalkanoates	(2009)	68

		molecules on the surface, and can be administered by intravitreal or subretinal injection.			
WO2008094659	Utecht RE et al.	Bioadhesive carriers for the local or periocular application of different drugs, such as prostaglandins, NSAIDs and corticosteroids.	NP of chitosan and modified chitosans	(2008)	73
US2004224010	Hofland H et al.	Vesicles composed of phospholipids, a cationic lipid and a mucoadhesive compound for the topical delivery of different kinds of drugs.	Liposomes	(2004)	32
US2011008421	Hara H & Takeuchi H	Rigid liposomes with a special composition that, upon topical instillation, are able to delivery drugs to the posterior segment of the eye.	Liposomes	(2011)	28
US20070275048	Liu JJ et al.	Vesicles with a special composition are highly stable in the bloodstream. Twenty-four hours after their injection, they are claimed to release the carried drug to the neovessels in the eye.	Liposomes	(2007)	47
WO2005120469	Gasco MR	SLN prepared by dilution of a hot microemulsion are proposed as vehicles of nucleic acids or	Lipid NP	(2005)	22

		oligonucleotides. The carrier can be applied topically on the eye surface and is able to release the drug in the posterior segment.			
RM2010A000322	Aleo D et al.	The proposed 10-30 nm system can be obtained by simply mixing the ingredients (e.g., melted Medium Chain Triglycerides and vitamin E TPGS) with a PBS solution containing glycerine, at room temperature and with no need of solvents or high surfactant concentrations.	Self-emulsifying DDS	(2010)	3
CN101502485	Zhu J et al.	The carrier is based on an amphipathic lipid material (e.g., glyceryl monooleate, phytantriol or lecithins) able to produce a cubic liquid-crystal system. The latter could improve the ocular bioavailability of lipophilic drugs, like dexamethasone.	Nano-cubic liquidcrystal System	(2009)	77
CN101385697	Gan Y et al.	A fluid formulation based on an oil, an emulsifier and a thickener (an ion-sensitive macromolecule) which, upon	Gel-forming Nanoemulsion	(2009)	21

		application on the eye surface, spontaneously produces a hydrogel and ensures an extended residence time of drugs.			
US7638137	Chauhan A & Gulsen D	A contact lens having uniformly dispersed a drug encapsulated into NP with a particle size below 50 nm. The drug is slowly released and retained in the lacrimal film comprised between the lens and corneal surface, with a consequent reduction of drug loss, side effects and frequency of instillation.	NP-containing contact Lens	(2009)	10
WO2011017313	Cooper MJ	Intravitreal injections of NP produced by condensation between nucleic acids and polycation polymers can be used to transfect retinal pigment epithelium, or to deliver therapeutically active gene material to the retina.	DNA-based NP	(2011)	13
US20090226531	Lyons RT & Ma H	NP made of biodegradable polymers and/or co-polymers and oaded with an siRNA. The carrier can be then	Polymeric NP	(2009)	49

		injected intraocularly in an aqueous suspension or in a viscoelastic hydrogel.			
US8409606	Sawhney AS. etal.	Medical prosthesis for blocking or reducing tear flow through a punctum or canaliculus of a human eye and delivering a drug to the eye that comprises a dehydrated covalently crosslinked synthetic hydrophilic polymer hydrogel with dimensions to pass through a punctalacrimali.	Hydrogel plug	(2013)	69
US20120199995 A1	Pugh RB etal.	Apparatus and method for the formation of an energized ophthalmic device for light therapy.	ophthalmic device for light therapy	(2012)	62
US8034370	Shiah JG.etal.	Bio-erodible implant, useful for treating a medical condition (e.g. uveitis, macular edema, macular degeneration and ocular tumors) of the eye, comprises an active dispersed within a biodegradable polymer matrix	Implant	(2011)	70
US8034366	Shiah JG.etal.	Implant, useful for treating e.g. uveitis, macular edema, retinal detachment, uveal diffusion and ocular tumors,	Implant	(2011)	71

		comprises agent, e.g. cortisone, dispersed within biodegradable polymer matrix comprising poly(D, L-lactide-coglycolide).			
US8257745 B2	Ketelson HA,etal.	Relates to Inorganic Nanoparticles as Carriers for Ophthalmic and Otic Drugs .	Nanopartical	September 04, (2012)	41
US20100310622 A1	Chauhan A. etal.	Discloses Dry Eye Treatment by PUNCTA PLUGS.	Puncta plugs	(2010)	11
US8306613 B2	Roy P. etal.	Discloses Irritation-Reducing Ocular Iontophoresis Device.	Iontophoresis	Nov.06, 2012	67
WO/2012/021107	Venkatraman S.etal.	Liposomal Formulation for Ocular Drug Delivery.	Liposome	16 Feb 2012	75
US 8343471	Banerjee R.etal.	Nanoparticulate in-situ gels of TPGS, gellan and PVA as vitreous humor .	Nanopartical gell	January 1, 2013	6
US7622129	Haberstroh, K.M.etal.	Nano-structured polymers for use as implants	Implant	2009	29

6. PRODUCT AVAILABLE IN MARKET

Table 12: Medication in various ocular disease.

S.No.	Active ingredients	Brand name	Manufacturer	Dosage form	Indication
1.	Ketorolac	Acuvail	Allergan	Eye-drops	Inflammation
2.	Diclofenac	Voltarin	Novartis	Eye-drops	Inflammation
3.	Chloramphenicol	Chloptic	Allergan	Eye-drops	Infection
4.	Pilocorpin Hcl	Pilopini	Allergan	Gel	Miotics
5.	Ganciclovi	Zirgan	Alliance	Gel	Viral
6.	Gatifloxacin	Zymar	Allergan	Eye-drops	Infection
7.	Dexamethasone	Tobradex	Alcon	Eye Ointment	Inflammation
8.	Laxobetolol Hcl	Betaxon	Alcon	Eye-drops	Glaucoma
9.	Flurometholone	Fml	Allergan	Suspension	Inflammation
10.	Azithromycin	Azasite	Catalent	Eye-drops	Conjunctivitis
11.	Bipostatin	Bipreve	Ista	Eye-drops	Conjunctivitis
12.	Besifloxacin	Besivance	Bausch	Suspension	Conjunctivitis
13.	Betaxolol	Betaxolol	Alocon	Eye-drops	Glaucoma
14.	Ciprofloxacin	Ciloxin	Alocon	Eye-drops	Infection
15.	Ciprofloxacin	Ciloxin	Alocon	EyeOintment	Conjunctivitis

Table 13: Medication for anterior.

S.No.	Active ingredients	Brand name	Dosage form	Indication
1.	Azithromycin	AzaSite®	Eye-drops	Bacterial conjunctivitis
2.	Azithromycin/Dexamethasone (ISV-502)	AzaSite Plus™	Eye-drops	Blepharoconjunctivitis
3.	Bromfenac (ISV-303)		Eye-drops	Post cataract surgery
4.	Timolol maleate	Rysmon® TG	Eye-drops	Glaucoma
5.	Betaxolol	Betoptic S®	Eye-drops	Glaucoma
6.	Tobramycin/Dexamethasone	TobraDex ® ST	Eye-drops	Blepharitis
7.	Timolol maleate	Timoptic-XE®	Eye-drops	Glaucoma
8.	Cyclosporine (NOVA22007)		Eye-drops	Dry eye Vernal keratoconjunctivitis
9.	Ketotifen		Soft contact lens	Allergic conjunctivitis
10.	Latanoprost		Puctal plug	Glaucoma
11.	Bimatoprost		Puctal plug	Glaucoma
12.	Cyclosporine (LX201)		Episcleral implant	Aeratoconjunctivitis

13.	Latanoprost		Subconjunctiva l insert	Glaucoma
14.	Dexamethasone phosphate (EGP-437)	EyeGate II®	Iontophoresis	Dry eye Anterior uveitis

Table 14: Medication for posterior drug delivery system.

S.No.	Active ingredients	Brand name	Dosage form	Indication
1.	Ganciclovir	Vitrasert®	IVT, implant	CMV retinitis
2.	Fluocinolone acetonide	Retisert®	IVT, implant	Posterior uveitis
3.	Fluocinolone acetonide	Iluvien®	IVT, implant	DME Wet AMD
4.	Dexamethasone	Ozurdex®	IVT, implant	CRVO BRVO Posterior uveitis
5.	Brimonidine		IVT, implant	Dry AMD RP
6.	Triamcinolone acetonide	I-vation™ TA	IVT, implant	DME
7.	CNTF (NT-501)		IVT, implant	RP Dry AMD
8.	Triamcinolone acetonide (IBI-20089)		IVT, injection	CRVO BRVO
9.	Triamcinolone acetonide (RETAAC)		IVT, injection	DME
10.	Corticosteroid prodrug (NOVA-63035)	Cortiject	IVT, injection	DME
11.	Verteporfin	Visudyne	IVT, injection	Wet AMD
12.	Difluprednate	Durezol	Eye-drops	DME

7. CONCLUSION

Eye is the most important part of human anatomy and physiology. A wide variety of drug delivery system have been developed to treat the various type of disease. There are some traditional ocular drug delivery system such as eye drop, ointment, eye suspension etc is used but it has some disadvantages is to eliminate from the anterior part of eye and lack of retention time of contact with eye due to specific anatomy and physiology barrier of eye. Recently advance ocular drug delivery system have been developed to produced controlled drug release into eye segments such as liposome, nanoemulsion, contact lenses, implant penetration enhancer etc. The most powerful advantage of recent drug delivery system over the traditional drug system is to increase solubility of poor soluble drugs into eye and cross the various barrier of the eye to reached the anterior parts as well as posterior parts of eyes. The main objective of the study to increase the retention time of drug in contact with anterior part of eye and to reached the systemic circulation using recent drug delivery system prepared by biodegrable, nonbiodegrable polymers, micro and nano size particle preparation (nano emulsion and microemulsion) as well as developed various therapies which are targeted into

gene and protein of anterior part of eye to treat the genetic disorder of eye with specific rout of administration.

8. Current and Future Developments

The new drug delivery system for ophthalmic purpose is better challenge over the conventional drug delivery system for eye. Because most of the recent drug delivery system used by intravenously which are prove a best medication to overcome the problem of eye barrier. In present and future days, the new formulation of drug delivery system such as nanoemulsion, microemulsion, gene therapy, implants, liposome etc. are safe and effective as compare to conventional drug delivery system.

Abbreviations

AMD: age-related macular degeneration

ARPE: human retinal pigment epitheliums cells

BRVO: branch retinal vein occlusion

CMV: cytomegalovirus

CNTF: ciliary neurotrophic factor

CRVO: central retinal vein occlusion

DME: diabetic macular edema

EVA: ethylene-vinyl acetate copolymer

IV: Intravenous

IVT: intravitreal

PLGA: poly(lactide-co-glycolide)

PMMA: poly(methyl methacrylate)

PVA: poly(vinyl alcohol)

RP: retinitis pigmentosa.

CONFLICT OF INTEREST

The authors confirm that this review article content has no conflicts of interest.

ACKNOWLEDGEMENTS

I would like to express my heartfelt and sincere indebtedness to God, Parents and Guide.

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