Volume 2, Issue4,October- 2011
Available Online at www.ijppronline.com
International Journal Of Pharma Professional's Research
Review Article

RECENT RESEARCH AND ROLE OF NANOPARTICLE IN OCCULAR DISEASES TREATMENT

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ISSN NO:0976-6723

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Abstract

In the current review various eye diseases were studied with respect to the nanoparticulate ophthalmic drug delivery system which is one of the most challenging endeavors in the pharmaceutical research. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. The choice of drug delivery system and route of drug administration is driven by patient acceptability, the properties of the drug access to a disease location, or effectiveness in dealing with the specific disease. Particulate polymeric drug delivery systems include micro and nanoparticles. The upper size limit for microparticles for ophthalmic administration is about 5-10 mm and range of nanoparticles are less than 100nm, so nanoparticulate drug delivery is best suitable approach for the eye targeting and nanoparticle also enhances drug pharmacokinetic properties and also minimize side effect and toxicity of drug. Patents obtained for ocular drug delivery devices/strategies focus about the research in ocular drug delivery.

Keywords: - Ophthalmic, FDA, Drug delivery system, Nanoparticle, Patent

Introduction

The eye is a unique organ by anatomically and physiologically characteristics which containing several varied structures with independent physiological functions. For example, the cornea and the crystalline lens are the only tissues in the body besides cartilage that has no blood supply. [1] The complexity of the eye provides unique challenges to drug delivery strategies. Pharmaceutical treatment and drug delivery methods for treating eye diseases and disorders vary considerably depending on the nature and extent of the disease or disorder.[2][3]

Anatomy and physiology of eye in brief: [4]

Aqueous Humour: It is jelly-like substance located in the anterior chamber of the eye. It is very slightly alkaline salt solution that contains tiny particles of sodium and chlorine ions in lesser amount.

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Choroid: The choroid layer is located between the retina & sclera, which absorbs unused radiation. It contains blood vessel & pigment that absorbs excess light & so prevent blurred vision. The structure of choroid consists of a dense capillary plexus & of many arterioles & venules, transport blood to form this plexus.

Ciliary Muscle: The ciliary muscle is ring shaped muscle which connects the choroid with the iris. Contraction & relaxation of the ciliary muscle controls the shape of lens. When ciliary muscle relaxed, the suspensary ligaments attached to the ciliary body is stretched, causing the lens to relatively flat. This enables the eye to focus on distant objects. When ciliary muscles contracted, the suspensary ligaments attached to ciliary body is reduced, causing the lens to be relatively rounded. This enables the eye to focus on close objects.

Cornea: Cornea is a strong clear bulge located at the front of the eye. It has optical function as it refracts light entering the eye through the pupil & onto the lens.

The cornea has complex structures that describe in terms of following layers:-

a. Several strata of epithelial cells, continuous with those of the conjunctiva.

b. A thick central fibrous structure called substania propria.

c. A homogenous elastic lamina.

d. A single layer of endothelial cells forming part of the lining membrane of the anterior chamber of the eye ball **.**

Cornea is a non vascular structure (not contain blood vessel) so, the capillaries that supply nutrients, terminate at its circumference. It is supplied by many nerves derived from the ciliary nerves. These enter the laminated tissue of the cornea so extremely sensitive.

Structure of eye:

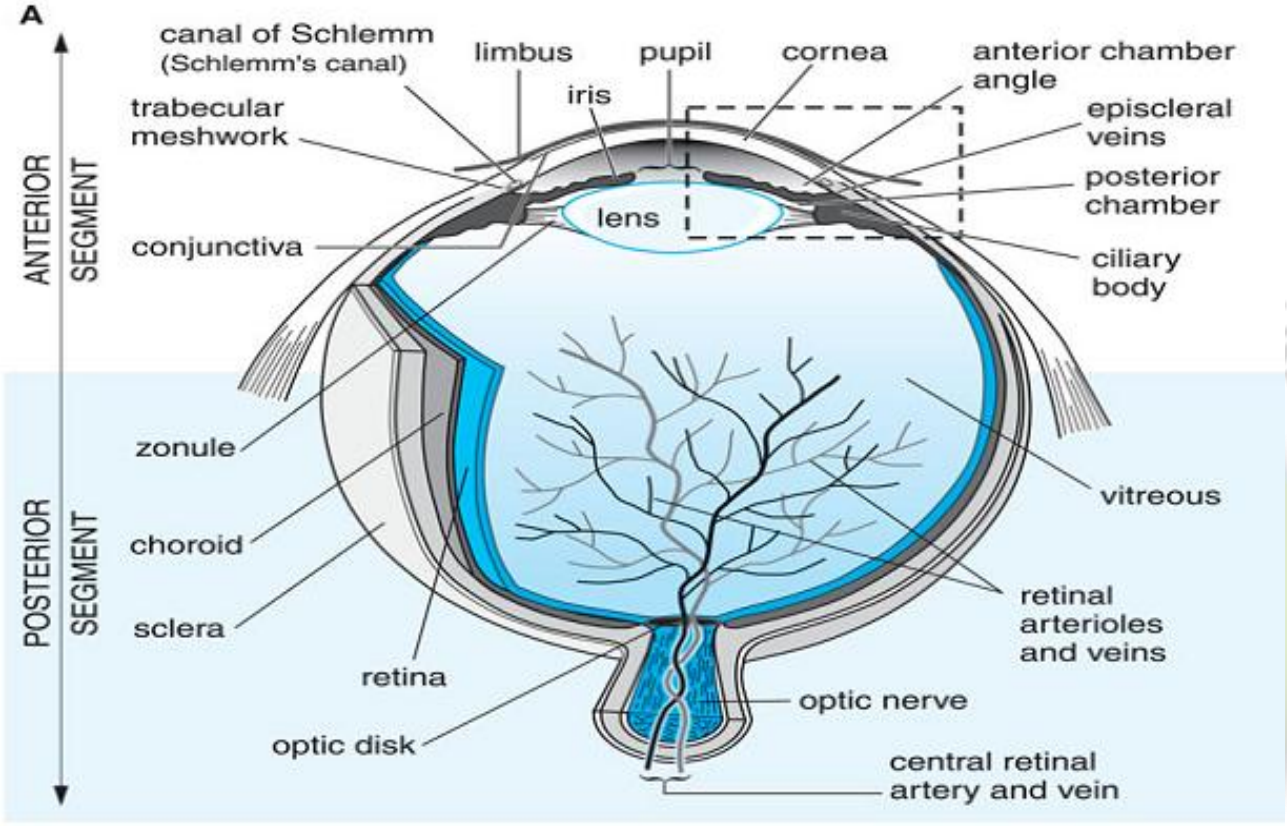
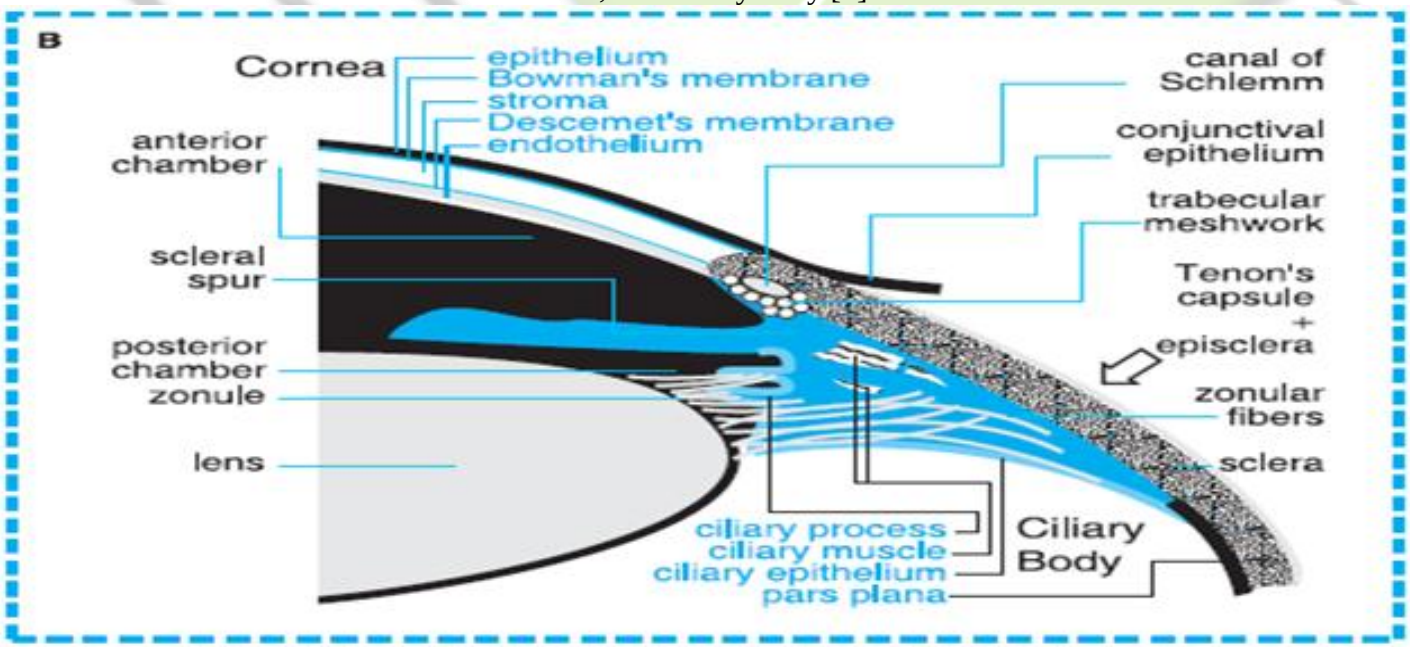


Fig: A. Anatomy of the eye, Fig: B. Enlargement of the anterior segment revealing the cornea, angle structures, lens, and ciliary body [5]



Fovea: Fovea is a small depression in the retina at the back of each eye.It contains a larger number of the light sensitive photo-detector cells called cones. The fovea is slightly yellow in appearance & so also known as yellow spot. When eye is directed at an object, the part of the image of the object formed on the retina that falls onto the fovea is the part of the image that will pre-received in full detail.

Hyaloid Membrane: Hyaloid membrane is a transparent membrane that encloses the vitreous humour, separating it from the retina. In the front of ora-serrate, the hyaloid membrane is thickened by radical fibers & is called the Zonula.

Iris: The iris is a thin circular contractile curtain located in the aqueous humour, in-front of the lens but behind the cornea. It contains a circular aperture called pupil. Iris is a coloured diaphragm of variable sizes whose function is to adjust the size of pupil to regulate the amount of light admitted into the eye.

Iris is composed of a series of layers:-

a.Flattened endothelial cells on a hyaline basement membrane.
b.Stroma consisting of fibers & cells.
c.Muscle fiber consisting of circular & radiating fibers.
d.Pigment.
e.Arteries of the iris.
f.Nerves of the choroid & iris.

Lens: The lens is transparent structure enclose in a thin transparent capsule. It is located behind the pupil of the eye. The capsule of the lens is a transparent, brittle, yet highly elastic membrane. The lens of the eye helps to refract light travelling through the eye. The lens focuses light into an image on the retina. The shape of lens is changed according to the distance from the eye of the object.

Optic nerve: Optic nerve is the second cranial nerve. Each optic nerve contains approx one million fibers carrying information from rods & cones of the retina. The optic nerve starts from posterior of the eye ball, into the skull, through the optic chaisma then to the cortex of the occipital lobe on each side of the brain.

Optic Papilla: Optic papilla is located on retina of the eye at which the optic nerve leaves the eye-transmitting signals from the eye to the brain.

Pupil: Pupil is located in the centre of each eye. The size of the pupil is regulated by the papillary reflex i.e. when bright light reaches the retina; nerves of the parasympathetic nervous systems are stimulated leading to the contraction of iris. In dim light, the pupil opens
due to stimulation of the sympathetic nervous system leads to increase the sizes of the pupil.

Retina has complex structure having various layers:-

a.Membrana limitans interna.
b.Layer of nerve fibers (Stratum opticum).
c.Ganglionic layer.
d.Plexiform layer.
e.Outer Plexiform layer.
f.Outer nuclear layer
g.Membrana limitans externa.
h.Jacob's layer (Rods & Cone layer).
i.Pigmentry layer.

Sclera: Sclera is the tough white sheath that forms the outer layer of the ball. It is a firm fibrous membrane that maintains the shape of the eyes. The white sclera is continuous around the eye. Sclera is composed of white fibrous tissue intermixed with fine elastic fibers & flattened connective tissue. The nerves connected to the sclera are from the ciliary nerves.

Vitreous humour: Vitreous humour is perfectly transparent this jelly likes substance that fills the chamber behind the lens of the eye. It is an albuminous fluid enclosed in a delicate transparent membrane called hyaloid membrane.

Barriers to Restrict Intraocular Drug Transport

Tear, Cornea, Conjunctiva, Sclera, Choroid/Bruch's Membrane, Retina, and Blood-Retinal Barrier.

These are the some anatomical and physiological characteristics of the eye, on the behalf physiological and anatomical characteristics some common and major diseases are classified as (see table 1):

Table 01: Ophthalmic diseases: [6-13]

S.N.	Eye Disease	Causative factor	Major Symptoms	Management
.	**Disorders of eyelid, lacrimal system and orbit:**			
	Hordeolum	A bacterial infection of sebaceous glands of eyelashes. *Staphylococcus*	A lump on the top or bottom, Localized swelling, pain, Redness Tenderness	By daily cleansing of the edges of the eyelids helps remove the skin oils that cause the bacteria to

		aureus bacterial infection,	to touch, Crusting of the eyelid margins, Burning in the eye, Mucous discharge in the eye, Discomfort during blinking and Sensation of a foreign body in the eye	overgrow, recommend using baby shampoo or special cleansers. Antibiotic ointments may also be helpful.
	Chalazion	a cyst in the eyelid (usually upper eyelid)	Swelling, tenderness and Heaviness of the eyelid, Sensitivity to light, Increased tearing	Topical antibiotic eye drops or ointment (e.g. chloramphenicol or fusidic acid)
	Blepharitis	inflammation of eyelids and eyelashes; characterized by white flaky skin near the eyelashes	The eyelids appear red and irritated, with scales that stick to the base of the eyelashes. The eyelids may be: Crusty, Reddened, Swollen, Itching, Burning	By daily cleansing of the edges of the eyelids helps remove the skin oils that cause the bacteria to overgrow, recommend using baby shampoo or special cleansers. Antibiotic ointments may also be helpful.
	Ptosis	It may be caused by damage/trauma to the muscle which raises the eyelid, damage to the superior cervical sympathetic ganglion or damage to the 3rd cranial nerve (oculomotor nerve), Use of high doses of opioid drugs such as morphine, oxycodone or hydrocodone can cause ptosis.	drooping of the upper or lower eyelid	Surgical procedures include: Levator resection, Muller muscle resection, Frontalis sling operation Non-surgical modalities like the use of "crutch" glasses or special Scleral contact lenses to support the eyelid may also be used.
	Xanthelasma of eyelid	sharply demarcated yellowish deposit of cholesterol underneath the skin, usually on or around the eyelids	Nodes around eyelids	It can be removed with a trichloroacetic acid peel, surgery, lasers/ cryothera py
.	**Disorders of conjunctiva:**			

	Conjunctivitis	Inflammation of the conjunctiva. Bacteria such as *Chlamydia trachomatis* or *Moraxella, Corynebacterium diphtheriae*	Red eye (hyperaemia), irritation (chemosis) and watering (epiphora) of the eyes.	It resolves in 65% of cases without treatment, within two to five days. Sometimes anti-inflammatory or antibiotics are used.
.	**Disorders of sclera, cornea, iris and ciliary body**			
	Scleritis	a painful inflammation of the sclera	Redness of the sclera and conjunctiva, sometimes changing to a purple hue Severe ocular pain which may radiate to the temple or jaw Photophobia and tearing Decrease in visual acuity, possibly leading to blindness	eye surgery to repair damaged corneal tissue For less severe cases, non-steroidal anti-inflammatory drugs, such as ibuprofen, are prescribed for pain relief. Also with oral medication containing corticosteroids and in some cases, antibiotics.
	Keratitis	Keratitis has multiple causes, one of which is an infection of a present or previous herpes simplex virus secondary to an upper respiratory infection, involving cold sores, *Staphylococcus aureus, Pseudomonas aeruginosa.* Some fungi, amoeba are also involved	inflammation of the cornea,	Levofloxaci, gatifloxacin, moxifloxacin, ofloxacin, Steroid containing medications should not be used for bacterial infections.
	Corneal ulcer / Corneal abrasion	loss of the surface epithelial layer of the eye's cornea caused by Staphylococcus aureus, Streptococcus viridans, Escherichia coli, Enterococci, Pseudomonas, Nocardia and many other bacteria. Some fungi and protozoa also cause	Extremely painful due to nerve exposure, and can cause tearing, squinting, and vision loss of the eye.	topical cycloplegics like atropine, homatropine Topical corticosteroids a n anesthetic.

		corneal ulcer.		
	Snow blindness / Arc eye	a painful condition caused by exposure of unprotected eyes to bright light Any intense exposure to UV light can lead to photokeratitis	pain, intense tears, eyelids, twitching, discomfort from bright light.	Non-steroidal anti-inflammatory drug (NSAID) eye drops
	Keratoconus	It might be possible due to genetic, environmental or cellular	the cornea thins and changes shape to be more like a cone than a parabola.	Contact lenses Corneal transplant
	Iritis	inflammation of the iris	Ocular and periorbital pain, Photophobia, Blurred or cloudy vision Reddened eye, especially adjacent to the iris, White blood cells seen as tiny white dots, and protein (resulting in a grey or near-white haze, clinically termed flare) leak into the anterior chamber.	Steroid, anti-inflammatory eye drop, Oral steroids prednisone, Subconjunctival steroid injections, Steroid-sparing agents methotreate
	Uveitis	Inflammatory process involving the interior of the eye; Sympathetic ophthalmia is a subset.	Redness of the eye Blurred vision, Sensitivity to light (photophobia), Dark, floating spots along the visual field and Eye pain	glucocorticoid steroids, c orticosteroids, atropine or homatropine, methotrexate, Infliximab etc
04.	**Disorders of lens:**			
	Cataract	the lens becomes opaque	Cataract becomes more opaque, clear vision is compromised. A loss of visual acuity is noted. Contrast sensitivity is also lost	Antioxidants (such as vitamins A, C and E), local anaesthetic etc
05.	**Disorders of choroid:**			

	Hypertensive retinopathy	burst blood vessels, due to long-term high blood pressure	decreased vision or Headaches. Hemorrhages, Edema, Papilledema, or optic disc edema, in patients with malignant hypertension, Visual acuity loss due to macular involvement	anti-hypertensive drug
	Diabetic retinopathy	damage to the retina caused by complications of diabetes mellitus,	Macular edema, which may cause vision loss more rapidly.	injection of triamcinolone in eye, kinase inhibitors and anti-VEGF) etc
07.	**Retinal disorders:**			
	Glaucoma	Ocular hypertension	Sudden onset of severe eye pain, Nausea and vomiting, Blurry vision, Rainbow halos around lights, Eye redness	Beta Blockers, Prostaglandin Analogs, Alpha-agonists, Carbonic Anhydrase Inhibitors
09.	**Disorders of ocular muscles, binocular movement, accommodation and refraction:**			
	Strabismus (Crossed eye/Wandering eye/Walleye)	a disorder of the brain in coordinating the eyes, or of one or more of the relevant muscles' power or direction of motion	the eyes do not point in the same direction	Botulinum Toxin

Table 02: FDA Approved Drugs for Ophthalmology [14]

Year	Drug	Formulation	Brand name	Industries	Treatment\purpose
November 2011	aflibercept		Eylea	Regeneron Pharmaceuticals	For the treatment of neo-vascular (wet) age-related macular degeneration
May 2010	gatifloxacin	ophthalmic solution	Zymaxid	Allergan	bacterial conjunctivitis

July 2009	ketorolac tromethamine		Acuvail	Allergan	pain and inflammation following cataract surgery
September 2009	bepotastine besilate	ophthalmic solution	Bepreve	Ista Pharmaceuticals	For the treatment of itching associated with allergic conjunctivitis
June 2009	besifloxacin	ophthalmic suspension	Besivance	Bausch & Lomb	For the treatment of bacterial conjunctivitis
June 2009	dexamethasone		Ozurdex	Allergan	For the treatment of macular edema following branch retinal vein occlusion or central retinal vein occlusion
September 2009	ganciclovir	ophthalmic gel	Zirgan	Sirion Therapeutics	For the treatment of acute herpetic keratitis
October 2008	lidocaine hydrochloride		Akten	Akorn	For anesthesia during ophthalmologic procedures
October 2008	azelastine hydrochloride	nasal spray	Astepro	Meda Pharmaceuticals	For the treatment of seasonal and perennial allergic rhinitis
June 2008	difluprednate		Durezol	Sirion Therapeutics	For the treatment of inflammation and pain associated with ocular surgery
April 2007	Azithromycin		AzaSite	InSite Vision	For the treatment of bacterial conjunctivitis
Year	Drug	Formulation	Brand name	Industries	Treatment\purpose
June 2006	Ranibizumab		Lucentis	Genentech	For the treatment of neovascular (wet) age related macular degeneration
December 2004	Pegaptanib		Macugen	Pfizer / Eyetech Pharmaceuticals	For the treatment of wet age-related macular degeneration.
December 2002	Cyclosporine	ophthalmic emulsion	Restasis	Allergan	For the treatment of low tear production
March 2001	Bimatoprost	ophthalmic solution	Lumigan	Allergan	For the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

March 2001	Travoprost	ophthalmic solution	Travatan	Alcon	For the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
March 2001	valganciclovir HCl		Valcyte	Roche	For the treatment of cytomegalovirus retinitis in patients with AIDS
February 2000			Betaxon	Alcon	For lowering IOP in patients with chronic open-angle glaucoma or ocular hypertension
August 2000	Levofloxacin	injection	Quixin	Santen	For treatment of bacterial conjunctivitis
August 2000	unoprostone isopropyl	ophthalmic solution 0.15%	Rescula	Ciba Vision	For the treatment of open-angle glaucoma or ocular hypertension
Year	Drug	Formulation	Brand name	Industries	Treatment\purpose
April 2000	Verteporfin	injection	Visudyne	QLT	For the treatment of wet age-related macular degeneration (wet AMD)
September 1999	pemirolast potassium	ophthalmic solution	Alamast	Santen	
July 1999			zaditor	Ciba Vision	Treatment for the prevention of itching of the eye
March 1998			Alrex	Bausch & Lomb, Pharmos	Treatment for seasonal allergic conjunctivitis
April 1998			Cosopt	Merck	Treatment for glaucoma or ocular hypertension
March 1998			Lotemax	Bausch & Lomb, Pharmos	Treatment for post-operative eye inflammation
February 1998		Tablets	salagen	MGI Pharma	Treatment for Sjogren's Syndrome
February 1998			Viroptic	King Pharmaceuticals	Treatment for inflammation of the cornea in children due to herpes simplex virus
August 1998		Injection	Vitravene	Isis Pharmaceuticals	Treatment for CMV in AIDS patients
January 1997	ketorolac tromethamine	solution 0.5%	Acular	Allergan	Treatment for postoperative inflammation in patients who have undergone cataract extraction

Year	Drug	Formulation	Brand name	Industries	Treatment\purpose
December 1997		Sterile Irrigating Solution	BSS	Alcon	Treatment during ocular surgical procedures

January 1996	naphazoline		AK-Con-A	Akorn	Over-the-counter combination vasoconstrictor/antihistamine product for opthalmic use
September 1996	brimonidine		Alphagan	Allergan	Treatment for open-angle glaucoma and ocular hypertension
May 1996	ofloxacin	opthalmic solution 0.3%	Ocuflox	Allergan	Treatment for corneal ulcers
January 1996			OcuHist	Pfizer	Over-the-counter antihistamine eye drop
June 1996	cidofovir		Vistide	Vistide	Treatment for cytomegalovirus (CMV) retinitis
March 1996		Implant	Vitrasert	Chiron	Drug delivery system for the treatment of cytomegalovirus
	Latanoprost	ophthalmic solution	Xalatan	Pfizer	topical medication used for controlling the progression of glaucoma or ocular hypertension by reducing intraocular pressure

Table 03: Research work on ophthalmic drug delivery system: [15-43]

Sl.No	Active Drug	Design of Dosage form	Drug category	Polymers used	Source of information
1	Pilocarpine	Ointment	Miotic agent	Petrolatum bases	15
2	Pilocarpine	Emulsion	Miotic agent	------	16
3	Pilocarpine	Sol to gel system	Miotic agent	Cellulose acetate phthalate	17
4	Pilocarpine	Matrices	Miotic agent	Hydroxyl propyl cellulose and Polyvinyl pyrrolidone	18
5	Pilocarpine	Hydrogel	Miotic agent	Polyacrylic acid and Polyacrylamide	19
6	Dexamethasone	Suspension	Anti-inflammatory	----	20
7	Dexamethasone	Ocular insert	Anti-inflammatory	Cellulose acetate phthalate, Eudragit RS. 100 and RL 100	20
8	Pilocarpine nitrate	Ocular insert	Miotic agent	Collagen	21
9	Pilocarpine nitrate	Ocular insert	Miotic agent	Mixtures of sodium salts of hyaluronic acid	22
10	Tropicamide	Ocular insert	Mydriatic agent	Mixtures of sodium salts of hyaluronic acid	22

11	Pilocarpine nitrate	Gel	Miotic agent	Polyacrylic acid	22
12	Timolol	Sol to gel system	Anti-glaucoma agent	Gelrite^{Ò}	23
13	Timolol Maleate	Ocular insert	Anti-glaucoma agent	Alkyl monoesters of poly vinyl methyl ether-maleic anhydride (PVM - MA)	24
14	Methyl Prednisolone	Films and Microspheres	Anti-inflammatory	Various esters of hyaluronic acid	25
15	Flurbiprofen	Gels	Anti-inflammatory	Pluronic F 127	26
16	Timolol maleate	Solutions	Anti-glaucoma agent	Polyacrylic acid	27
17	Penicillin G	Liposomes	Antibiotic	Phospholipids	28
18	Pilocarpine	Solution	Miotic agent	Hyaluronic acid sodium salt	29
19	Timolol maleate	In-situ forming gel	Anti-glaucoma agent	Hydroxy propyl methyl cellulose and Polyacrylic acid	30
20	Gentamicin, Tobramycin and Ciprofloxacin	Iontophoresis	Anti-infective agents	---	31
21	Gentamicin, Tobramycin and Ciprofloxacin	Corneal collagen shield	Anti-infective agents	Collagen	31
22	Sulphacetamide sodium and Trimethoprim	Solution	Anti-infective agents	---	32
23	Pilocarpine	Solution	Miotic agent		33
24	Piroxicam	Submicron emulsion	Anti-inflammatory	Poloxamer and Stearylamine as emulsifier	34
25	Indomethacin	Nanoparticles, Nanocapsules and Submicron emulsion	Anti-inflammatory	Poly-Î-caprolactone, Poloxamer	35
26	Hydrocortisone	Solution	Anti-inflammatory	Hydroxypropyl-b-cyclodextrin	36
27	Indomethacin	Nanocapsules	Anti-inflammatory	Chitosan and Poly-L-Lysine coated Poly-Î-caprolactone	37
28	Pilocarpine Hydrochloride	Gels	Miotic agent	Pluronic F127, Methyl cellulose, Hydroxypropyl methyl cellulose	38
29	Ciprofloxacin	Ocular insert	Anti-infective	Hydroxy propyl methyl	39

	Hydrochloride		agent	cellulose, Methyl cellulose, Ethyl cellulose and polyvinyl pyrrolidone	
30	Insulin	Ocular devices	Anti diabetic	Absorbable gelatin sponge	40
31	Tropicamide	Liposomes dispersed in gel.	Mydriatic agent	Polycarbophil	41
32	Indomethacin	Solution	Anti-inflammatory	PluronicÔF68 and F127	42
33	Ketorolac Tromethamine	Ocular Inserts	Anti-inflammatory	Hydroxy-propyl methyl cellulose, Polyvinyl Pyrrolidone, Methyl cellulose and Ethyl cellulose	43

A recent review indicated about the bioavailability of ocular drugs topically applied in eye-drops is very poor, with ocular drug absorption limited by protective mechanisms that promote proper functioning of the eye, as well as by a number of concomitant limiting factors related to the efficacy of drug application. [44] Drainage of an administered drug dose by the naso-lachrymal system can occur when the volume of fluid in the eye exceeds the normal lachrymal volume of about 7–10µl.

The application of one to two drops of a drug medication applied by an eye-dropper as the drug delivery device represents roughly 50–100µl. Much of dose is rapidly drained. The remaining applied drug solution is diluted by induced increased lachrymation and physiological tear turnover produced by the applied drug solution. Drug is subject to non-selective transcorneal adsorption. All these factors taken together can result in a loss of drug from that applied to the eye that can be 500–700 times greater than the rate of absorption of the drug into the anterior chamber.

Advanced technology based on the use of nanocarriers (nanoparticles, liposomes, and dendrimers) has been investigated recently with the aim of enhancing ocular drug delivery. [45][46] These systems are claimed to provide a prolonged residence time at the ocular surface, minimising the effect of natural eye clearance systems. It is assumed that when combined with controlled drug delivery, it should be possible to provide drug therapeutic levels for a prolonged time at the site of action. The use of nanoparticles for this purpose has been reported in many of research work. [47]

The choice of drug delivery system and route of drug administration is driven by patient acceptability, the properties of the drug access to a disease location, or effectiveness in dealing with the specific disease.

Nanoparticle in drug ocular delivery

Nanotechnology: Nanotechnology is the study of phenomenon and manipulation of materials at atomic, molecular and micro-molecular scales, where properties differ significantly from those at a larger scale.

Nanotechnology (nano + technology) words "Nano" is derived from the Greek word for Dwarf. It means "a billionth." A nanometer is a billionth of a meter, that is, about 1/80,000 of the diameter of a human hair, or 10 times the diameter of a hydrogen atom, and technology means involvement of scientific techniques study. The term "nanotechnology" was first used in 1974, when Norio Taniguchi, a scientist at the University of Tokyo, Japan, referred to materials in nano meters. [48]

Pharmaceutical nanotechnology embraces applications of nanoscience to pharmacy as nanomaterials, and as devices like drug delivery, diagnostic, imaging and biosensor.

Nanoparticles: Nanoparticles are often defined as particles of less than 100nm in diameter. Nanoparticles can be also defined as particles less than 100nm in diameter that exhibit new or enhanced size-dependent properties compared with larger particles of the same material. [48]

Particulate polymeric drug delivery systems include micro and nanoparticles. The upper size limit for microparticles for ophthalmic administration is about 5-10 mm. above this size, a scratching feeling in the eye can result after ocular application. Microspheres and nanoparticles represent promising drug carriers for ophthalmic application. The binding of the drug depends on the physicochemical properties of the drugs, as well as of the nano- or micro-particle polymer. After optimal drug binding to these particles, the drug absorption in the eye is enhanced significantly in comparison to eye

drops. Particulates such as nanoparticles, nano-capsules, submicron emulsions, nano-suspensions improved the bioavailability of ocularly applied drugs. [49][50]

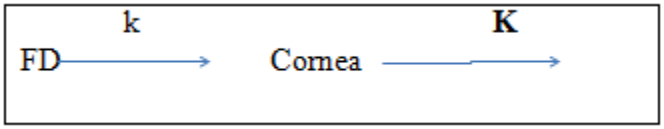
Advantages [51]

i. Drug carriers Controlled and sustained drug release at the site of action.
ii. Site specific targeting can be achieved.
iii. Particle size and surface characteristics of nanoparticles can be easily modified to achieve both passive and active drug target ocular dosage forming Reduced drug toxicity

Application of Nanoparticle

Nanoparticles are used as carriers for drugs as well as for vaccines. The drug or antigen entrapped in polymer matrix. In comparison to aqueous eye drop, elimination rate of nanoparticles from eye is considerably less. [52]

In last two decades ophthalmic pharmaceuticals has develop various dosage form include solution, suspension, ointment, gels, intraritreal injection, sub-conjunctival injection, iontophoretic system, collagen shields, ocular inserts. Pharmacokinetic /Pharmacodynamics models are used to estimates of the dynamic state of drug behavior in an actual clinical situation so which these new products are developed. The simplest pharmacokinetic model for eye is the single compartment model as shown in figure:



Equation for describing in the form of drug concentration is:-

$$C = (FD/V_d).\{k/(k-K)\}.(e^{-Kt} - e^{-kt})$$

Where F is the fraction of absorbed drug, D is dose, k and K are absorption and elimination rate constant respectively and Vd is the apparent volume of distribution. [53]

In ocular disease like choroidal neo-vascularization, diabetic retinopathy, central retinal vein occlusion and intraocular solid tumors, drug targeting can be affecting method for treatment. Ocular drug targeting has following objects:- [54]

a.Enhancement of drug permeation
b.Control release of drugs
c.Drug targeting

Significance of nanotechnology in ocular drug delivery:

Nanotechnology based drug delivery systems like Nano-suspensions, solid lipid nanoparticles and liposomes led to the solution of various solubility related problems of poorly soluble drugs.

Nanoparticles can be designed to be successfully used in overcoming retinal barriers.

Nanoparticles are also very efficient in crossing membrane barriers like blood retinal barrier.

Various nano-particulate drug delivery systems used in ophthalmic research are given in table:

Table no: 03. Drug with nanoparticulate delivery significance: [54]

S.No.	Drug	Nano-particulate system	Result
1.	Oligonucleotides	Liposomes	Better control of release rate
2.	Acetazolamide	Liposomes	Produced a marked decrease in intra ocular pressure
3.	Pilocarpine HCl	Liposomes	Increased miotic response and ocular bioavailability of the drug
4.	Inulin	Liposomes	Increased ocular concentration of the drug
5.	Timolol maleate	Discomes	Entrapped comparatively higher amount of drug than niosomes
6.	Amikacin	Nanoparticles	Improved delivery of drug to cornea and aqueous humor
7.	Flurbiprofen	Acrylate polymer nano-suspension	Obtained higher drug levels in the aqueous humor and inhibition of paracentesis-induced miosis
8.	Cyclosporin	Chitosan nanoparticles	Enhanced delivery to external ocular tissue

Table 04: U.S. Patents obtained for ocular drug delivery devices/strategies: [55-88]

S.No.	Patent No.	Title	Reference No.
1	U.S.4,952,581	Use of a prostaglandin in combination with an adrenergic blocking agent for reduction	55

		of intraocular pressure	
2	U.S.5,227,372	Method for retaining ophthalmological agents in ocular tissues	56
3	U.S.5,296,228	Compositions for controlled delivery of pharmaceutical compounds	57
4	U.S.5,480,914	Nonaqueous thixotropic drug delivery suspensions and methods of their use	58
5	U.S.5,578,638	Treatment of glaucoma and ocular hypertension with .beta.sub.3 -adrenergic agonists	59
6	U.S.5,705,194	Pharmaceutical compositions containing polyalkylene block copolymers which gel at physiological temperature	60
7	U.S.5,888,493	Ophthalmic aqueous gel formulation and related methods	61
8	U.S.6,242,442	Brinzolamide and brimonidine for treating ocular conditions	62
9	U.S.6,297,240	Method for treating ophthalmic disease through fast dispersing dosage forms	63
10	U.S.6,316,441	Brinzolamide and brimonidine for treating glaucoma	64
11	U.S.6,410,045	Drug delivery system for antiglaucomatous medication	65
12	U.S.6,416,740	Acoustically active drug delivery systems	66
13	U.S.20020071874	Compositions containing therapeutically active components having enhanced solubility	67
14	U.S.20020197300	Drug delivery system for anti-glaucomatous medication	68
15.	U.S.20030017199	Compositions having enhanced pharmacokinetic characteristics	69
16	U.S.5,837,226	Ocular microsphere delivery system	70
17	U.S.6,071,875	TGF.alpha. for the treatment of ocular hypertension and glaucoma	71
18.	U.S.6,154,671	Device for the intraocular transfer of active products by iontophoresis	72
19	U.S.6,217,896	Conjunctival inserts for topical delivery of medication or lubrication	73
20	U.S.6,319,240	Methods and apparatus for ocular iontophoresis	74

21	U.S.6,335,335	Prolonged-action eye drop	75
22	U.S.6,410,045	Drug delivery system for antiglaucomatous medication	76
23	U.S.6,539,251	Ocular iontophoretic apparatus	77
24	U.S.6,579,519	Sustained release and long residing ophthalmic formulation and the process of preparing the same	78
25	U.S.20020026176	Devices for intraocular drug delivery	79
26	U.S.20030147849	Topical formulations for delivery of interleukin-11	80
27	U.S.20020064513	Sustained release and long residing ophthalmic formulation and the process of preparing the same	81
28	U.S.20020114778.	Reversible gelling system for ocular drug delivery	82
29	U.S.20020119941	In-situ gel formation of pectin	83
30	U.S.20020197300	Drug delivery system for anti-glaucomatous medication	84
31	U.S.20030175324	Ocular therapeutic agent delivery devices and methods for making and using such devices	85
32	U.S.20030185892	Intraocular delivery compositions and methods	86
33	U.S.20030191426	Device for enhanced delivery of biologically active substances and compounds in an organism	87
34	U.S.20040037889	Stabilized, dry pharmaceutical compositions for drug delivery and methods of preparing same	88

Discussion

The eye is a unique organ, both anatomically and physiologically containing several widely varied structures with independent physiological function and various physiological barriers. For example, the cornea and the crystalline lens are the only tissues in the body besides cartilage that have no blood supply. The complexity of the eye provides unique challenges to drug delivery strategies. Pharmaceutical treatment and drug delivery methods for treating eye diseases and disorders vary considerably depending on the nature and extent of the disease or disorder. Drainage of an administered drug dose by the naso-lachrymal system can occur when the volume of fluid in the eye exceeds the normal lachrymal volume of about 7–10µl. In contrast, the application of one to two drops of a drug medication applied by an eye-dropper as the drug delivery device represents roughly 50–100µl. Much of this dose is wasted or rapidly drained. The remaining applied drug solution is diluted by induced increased lachrymation and physiological tear turnover produced by the applied drug solution. [89]

These factors and the corneal barrier limit the penetration of the topically administered drug into the eye. Only a few percentages of applied doses are delivered into intraocular tissue.

It is possible to conclude that nanoparticles offer great chances of solving these limitations, while still acting

benefiting from their topical administration as eye drops. Indeed, nanoparticles, depending on their composition, are significantly retained on the ocular mucosa, and from this location, they deliver the associated drugs for extended periods of time. This situation normally results in an enhanced and prolonged therapeutic response, and also in a decrease in the side effects.

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