Available Online through
www.ijpbs.com (or) www.ijpbsonline.com

IJPBS |Volume 4| Issue 2|APR-JUN|2014|162-173

Review Article
Pharmaceutical Sciences

CURRENT TRENDS FOR OPHTHALMIC DRUG DELIVERY: A REVIEW

Sachin Pathak* and Himansu Chopra

Faculty of Pharmacy, Guru Ram Das (PG) Institute of Management and Technology,
214 Rajpur Road, Dehradun (248009)

***Corresponding Author Email:** sachinpathakgrd@gmail.com

ABSTRACT

Controlled and sustained delivery of ophthalmic drugs continues to remain a major focus area in the field of pharmaceutical drug delivery with the emergence of new, more potent drugs and biological response modifiers that may also have very short biological half-lives. The present review was conducted on drug delivery to the ocular route. Polymers with suitable rheological properties can facilitate the absorption of poorly absorbed drugs by increasing the contact time of the drug. Ocular drug delivery has been a major challenge for scientists due to its unique anatomy and physiology which contains various types of barriers such as different layers of cornea, sclera and retina including blood aqueous and blood–retinal barriers, choroidal and conjunctival blood flow etc. These barriers cause a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment of the eye. In this review we emphasized on the anatomy, physiology of eye along with the various formulation approaches reported in the literature and recent research conducted on these formulations and their efficacy.

KEY WORDS

Controlled delivery, Sustained delivery & ophthalmic delivery

ANATOMY AND PHYSIOLOGY FEATURE OF THE EYE

The eye is a unique organ, both anatomically and physiologically, containing several widely varied structures with independent physiological functions that render the organ highly impervious to foreign substances[1]. The eye is a unique organ for drug delivery. Many of its anatomical and physiological features interfere with the fate of the administered drug[2]. First and foremost are blinking; tear secretion, and naso lacrimal drainage. Lid closure upon reflex blinking protects the eye from external aggression[3]. Tears permanently wash the surface of the eye and exert an anti-infectious activity by the lysozyme and immune globulins they contain[4]. Ophthalmic control drug delivery system have been mainly prepared as gels, ointments, liposomes, micro and nanoparticles, microspheres and ocular mini tablets (MT) or films[5]. Ocular administration is primarily associated with a need to treat ophthalmic diseases,not regarded as a means for gaining systemic circulation[6.] It is important if the drug is not intended to act on the external surface of the eye, then the active ingredient has to enter the eye. There is consensus that the most important route is transcorneal; however, a noncorneal route has been proposed and may contribute significantly to ocular bioavailability of some ingredients, e.g., Timolol and inulin[7]. In addition, the sclera has also been shown to have a high permeability for a series of ß-blocking drugs [8]. Schematically, the cornea is a sandwich comprising a hydrophilic layer, the stroma, between two lipophilic layers, the epithelium and the endothelium[9]. The epithelium is composed of five to six layers of cells, whereas the endothelium is single-layered on the inner side of the cornea. In humans, the corneal thickness measures slightly more than 0.5mm at the center and thickens a little at the periphery[10].

PHYSIOLOGICAL OVERVIEW

Human eye is spherical in shape with a diameter of 23 mm, structural component of the eye are divided into three parts, first; outermost coat comprises of clear transparent cornea and white opaque sclera, second; middle layer comprises of iris, ciliary body, choroid posteriorly, third; inner layer is retina which is a extension of central nervous system[11]. Fluid systems in eye are aqueous humor and vitreous humor.

Detailed description:-

The Eye composed of following layers (**Figure 1**: structure of human eye)

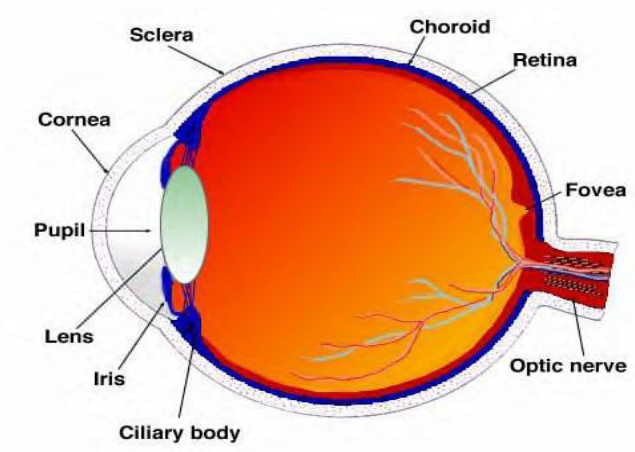

Figure1: Section through the human eye

1. Cornea:-The cornea is the transparent front part of the eye that covers the iris, pupil and the anterior chamber. The cornea with the anterior chamber and lens refracts light, with the cornea accounting for approximately two third of the eyes total optical power[12,13]. The refractive power of the cornea is approximately 43 dioptres[14].
2. Sclera:-The sclera also known as the white of the eye is the opaque fibrous part protective outer layer of the eye containing collagen and elastin fiber[15].
3. Retina: - Retina is the only part of the central nervous system that can be visualized non-invasively. The retina is a layered structure with several layers of neurons interconnected by synapses [16].
4. Fovea:- Fovea is a part of the eye located in the center of the macula region of the retina[17,18], Fovea size is relatively small to the rest of retina, but fovea is only area of the retina where 20/20 vision is attainable and very important for see fine detail and colour[19,20].
5. Optic nerve:- The optic nerve is the second of twelve paired cranial nerves but is considered to be a part of the central nervous system[21], each human optic nerve contain between 770,000 and 1.7 million nerve fibres[22]. The functional component carried in the optic nerve include SSA means special somatic afferent, which carries the sensory modility of vision[23].
6. Ciliary body: - Ciliary body is the circumferential tissue inside the eye composed of the ciliary muscle and ciliary processes[24], it is triangular in horizontal section and is coated by a double layer, the ciliary epithelium, this epithelium produces the aqueous humor[25].
7. Iris:-The iris a thin circular structure in the eye, responsible for controlling the diameter and size of the pupil and thus the amount of light reaching the retina[26].
8. Lens: - The crystalline lens is a transparent biconvex structure in the eye that along with the cornea[27], helps to refract light to be focused on the retina, in humans; the refractive power of the lens in its natural environment is approximately 18 dioptres[28].
9. Pupil:-The pupil is a hole located in the center of the iris of the eye that allows light to enter the retina[29].

10. Cornea consists of epithelium - stroma-endothelium which means fat-water-fat structure, penetration of non polar compounds through cornea depends on oil/water partition coefficient of drug (**Figure 2**: section through the cornea).

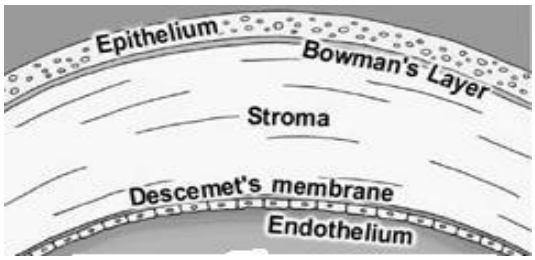

Figure 2: Section through the cornea

BLOOD OCCULAR BARRIER

There are two types of Blood ocular barrier

1. Blood aqueous barrier consist of two parts first; ciliary epithelium and second; capillaries of the iris
2. Blood retinal barrier they are non fenestrated capillaries of retinal circulation and tight junctions between retinal epithelial cells.[30]

DRUG ELIMINATION FROM LACRIMAL FLUID

Most of the instilled volume of liquid dosage form like solution, suspension; liposome is either drained from conjuctivital sac into nasal lachrymal duct or cleared from pre corneal area resulting in poor bioavailability of drug.[31]

PRECORNEAL CONSTRAINTS INCLUDE (Figure 3: Fate of ophthalmic drug delivery system)

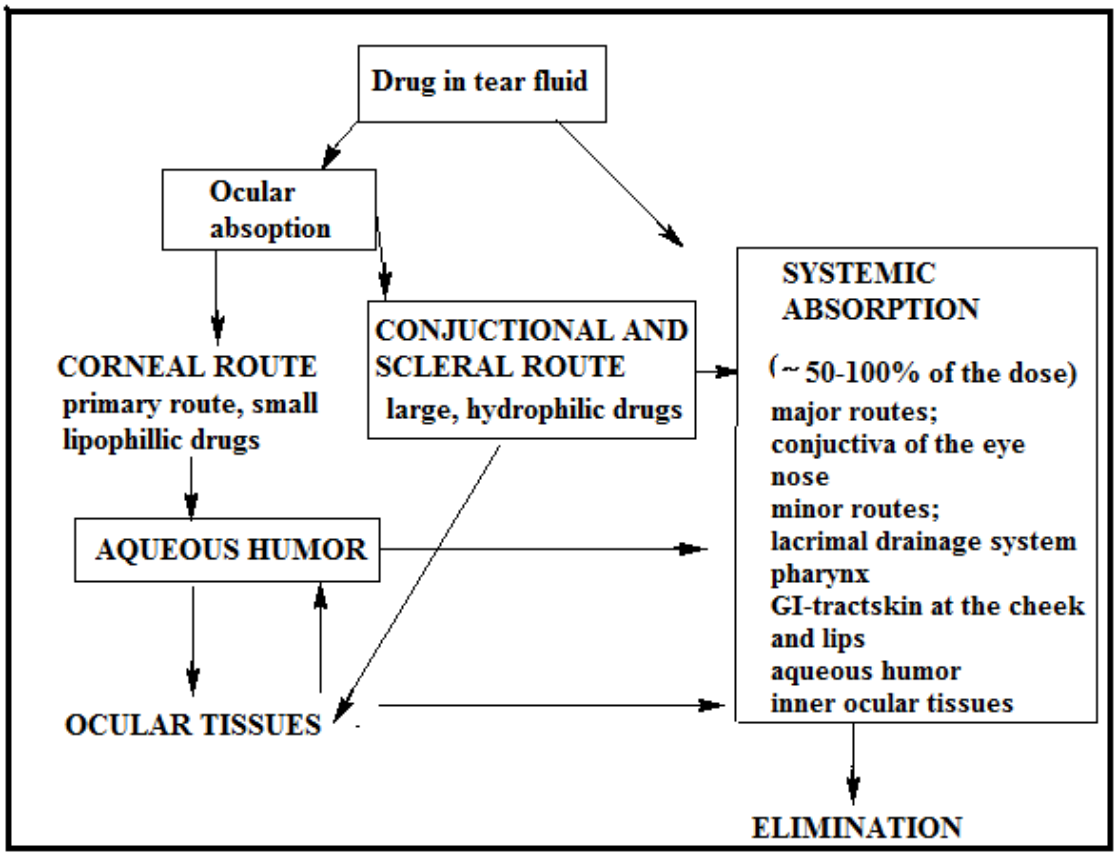

Figure3: Fate of ophthalmic drug delivery system

1. **Spillage of drug by overflow:-**Normal volume of tear is 7ml, without blinking human eye can accommodate 30 ml, with estimated drop volume of 50 ml, 70 % of dose is expelled from the eye by overflow.
2. **Dilution of drug by tear turn over:-**Remove the drug solution from conjuctivital cul de sac, Tear turnover is 16% per minutes, stimulated by many factors such as drug entry, pH, tonicity, formulation adjuvant.
3. **Nasolacrimal drainage: -** Most of the administered drug is lost through nasolacrimal drainage immediately after dosing, drainage allows drug to be systematically after dosing, drainage allows drug to be systematically absorb across the nasal mucosa and gastrointestinal tract.
4. **Conjuctivital absorption:-** Drug absorption into pulpebral and bulbar conjunctiva with concomitant removal of drug from the ocular tissue by peripheral blood stream.
5. **Enzymatic metabolism:-** May occur in Precorneal space or in cornea, physiological barrier restraining the entry of drug into eye restricting the bioavailability to 1-3% of the instilled dose.[32]

Following characteristics are required to optimize ocular drug delivery system:-

- Good corneal penetration.
- Prolong contact time with corneal tissue.
- Simplicity of instillation for the patient.
- Non irritative and comfortable form (viscous solution should not provoke lachrymal secretion and reflex blinking)
- Appropriate rheological properties and concentrations of the viscous system.

CLASSIFICATIONS OF OCULAR DRUG DELIVERY SYSTEMS

A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follows:

1. **Liquids:** Solutions, suspensions, sol to gel systems, sprays
2. **Solids:** Ocular inserts, contact lenses, corneal shield, artificial tear inserts, filter paper strips
3. **Semi-solids:** Ointments, Gels
4. **Miscellaneous:** Ocular iontophoresis, vesicular systems, mucoadhesive dosage forms, particulates, Ocular penetration enhancers.

1. Liquids

Liquids are the most popular and desirable state of dosage forms for the eye. This is because the drug absorption is fastest from this state. The slow release of the drug from the suspended solids provides a sustained effect for a short duration of time.

A. Solutions and Suspensions

Solutions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. The drug in solution is in the dissolved state and may be immediately active. This form also have some disadvantages; the very short time the solution stays at the eye surface, its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage), the instability of the dissolved drug, and the necessity of using preservatives. A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability. This rapid elimination is due to solution state of the preparation and may be influenced by the composition of the solution. The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume. Extensive work has been done to prolong ocular retention of drugs in the solution state by enhancing the viscosity or altering the pH of the solution[33].

B. Sol to gel Systems

The new concept of producing a gel in situ (e.g. in the cul-de-sac of the eye) was suggested for the first time in the early 1980s. It is widely accepted that increasing the viscosity of a drug formulation in the precorneal region will leads to an increased bioavailability, due to slower drainage from the cornea. Several concepts for the in situ gelling systems have been investigated. These systems can be triggered by pH, temperature or by ion activation. An anionic polymeric dispersion shows a low viscosity up to pH 5. 0, and will coacervate in contact with tear fluid due to presence of a carbonic buffer system which regulates the pH of tears. In situ gelling by a temperature change is produced when the

temperature of polymeric dispersion is raised from 25 to 37°C. Ion activation of polymeric dispersion occurred due to the presence of cations in the tear fluid.

C. Sprays

Although not commonly used, some practitioners use mydriatics or cycloplegics alone or in combination in the form of eye spray. These sprays are used in the eye for dilating the pupil or for cycloplegic examination.

2. Solids

The concept of using solids for the eye is based on providing sustained release characteristics.

A. Ocular inserts

Ocular inserts are solid dosage form and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions and ointments are replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system. The eye drops provided pulse entry pattern of drug administration in the eye which is characterized by transient overdose, relatively short period of acceptable dosing, followed by prolonged periods of under dosing. The ocular inserts maintain an effective drug concentration in the target tissues and yet minimize the number of applications consonant with the function of controlled release systems. Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications, and to occasional therapeutic failures (e.g. unnoticed expulsion from the eye, membrane ruptures etc.). A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, no erodible and hydrogel inserts[34].

B. Contact lenses

Contact lenses can absorb water soluble drugs when soaked in drug solutions. These drug saturated contact lenses are placed in the eye for releasing the drug for long period of time. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs. In humans, the bionite lens which was made from hydrophilic polymer (2-hydroxy ethyl methacrylate) has been shown to produce a greater penetration of fluorescein.

C. Corneal shield

A non cross-linked homogenized, porcine sclera collagen slice is developed by a company (Bicorn Bausch and Lomb pharmaceuticals). Topically applied antibiotics have been used in conjunction with the shield to promote healing of corneal ulcers. Collagen shields are fabricated with foetal calf skin tissue and originally developed as a corneal bandage. These devices, once softened by the tear fluid, form a thin pliable film that confirms exactly to the corneal surface, and undergoes dissolution up to 10, 24 or 72 hours. Collagen film proved as a promising carrier for ophthalmic drug delivery system because of its biological inertness, structural stability and good biocompatibility. Gussler et al investigated the delivery of trifluoro thymidine (TFT) in collagen shields and in topical drops in the cornea of normal rabbits and corneas with experimental epithelial defects. It was found that highest drug concentrations were found in the eyes treated with shields as compared to eye drops.

D. Artificial tear inserts

A rod shaped pellet of hydroxyl propyl cellulose without preservative is commercially available (Lacrisert). This device is designed as a sustained release artificial tear for the treatment of dry eye disorders. It was developed by Merck, Sharp and Dome in 1981[35].

E. Filter paper strips

Sodium fluoresce and rose bengal dyes are commercially available as drug impregnated filter paper strips. These dyes are used diagnostically to disclose corneal injuries and infections such as herpes simplex, and dry eye disorders.

3. Semi-solids

A wide variety of semisolids vehicles are used for topical ocular delivery which falls into two general categories: simple and compound bases. Simple bases refer to a single continuous phase.

These include white petrolatum, lanolin and viscous gels prepared from polymers such as PVA, carbopol etc. Compound bases are usually of a biphasic type forming either water in oil or oil in water emulsions. A drug in either a simple or compound base provide an increase in the duration of action due to reduction in

dilution by tears, reduction in drainage by way of a sustained release effect, and prolonged corneal contact time. The most commonly used semisolid preparation is ointments consisting of dispersion of a solid drug in an appropriate vehicle base. Semi-solids dosage forms are applied once or twice daily and provide sustained effects. The primary purpose of the ophthalmic ointment vehicle is to prolong drug contact time with the external ocular surface. But they present a disadvantage of causing blurring of vision and matting of eyelids. Ophthalmic gels are similar in viscosity and clinical usage to ophthalmic ointments. Pilopine HS is one of the ophthalmic preparations available in gel form and is intended to provide sustained action of pilocarpine over a period of 24 hours. Semi-solids vehicles were found to prolong the ocular contact time of many drugs, which ultimately leads to an enhanced bioavailability[36].

4. Recent developments in ophthalmic drug delivery

Most conventional ophthalmic dosage forms are simplistic. It is usual that water-soluble drugs are delivered through topical administration in an aqueous solution, and water-insoluble drugs are administered topically as an ointment or aqueous suspension. The major deficiencies of these conventional dosage forms include poor ocular drug bioavailability, pulse-drug entry after topical administration, systemic exposure because of nasolacrimal duct drainage, and a lack of effective systems for drug delivery to the posterior segment of ocular tissue. Poor ocular drug bioavailability is the result of ocular anatomical and physiological constraints, which include the relative impermeability of the corneal epithelial membrane, tear dynamics, nasolacrimal drainage, and the high efficiency of the blood–ocular barrier [37]. It is standard for only 1% or less of a topically applied dose to be absorbed across the cornea and thus reach the anterior segment of the eye[38]. Pulse entry is a common, and yet highly undesirable, pharmacokinetic characteristic associated with eye drops. The initial high drug concentration found in tears, followed by a rapid decline, poses a potential risk of toxicity, and suggests a requirement for frequent dosing. Attempts to overcome the toxicity associated with the high initial concentration without a requirement for frequent dosing form a challenging task, particularly in the case of potent drugs. Nasolacrimal drainage is the major factor for precorneal drug loss that leads to poor ocular bioavailability. It is also the major route of entry into the circulatory system for drugs that are applied through topical administration. For potent drugs, the systemic exposure through nasolacrimal drainage after topical administration can be sufficiently high to cause systemic toxicity. A recognized example is timolol, systemic toxicity has been reported for the ophthalmic solution of timolol following topical administration[39].

NANOPARTICLE FOR OCCULAR DRUG DELIVERY

The most application of drug loaded ophthalmic delivery system are for glaucoma therapy, especially cholinergic agonist like Pilocarpine. The short half life of aqueous eye drops (due probably due to lachrymal drainage) can be extended from a very short time (1-3min) to prolonged time (15-20min) using nanoparticles, which have biodegradable properties, these include, poly alkyl cyano acrylate nanoparticles, poly-e-carolactone, polyesters nanoparticles. It has been demonstrated that nanoparticles adhere to the inflamed tissue in a more quantitative manner as compared to the healthy tissue, thus these could also be used for targeting of anti-inflammatory drugs to inflamed eye. Various advantages are proposed for the polyalkylcyanoacrylate nanoparticles specially PHCA nanoparticles including their biodegradability, tissue adhesion and increased elimination half life of their drainage coupled with a slow clearance. It was found that Pilocarpine and betaxolol loaded polyalkylcyanoacrylate nanoparticles could prolong and maintain the reduced the intraocular pressure in rabbits for more than 9 hours. The polymers methylcellulose, polyvinyl alcohol and hydroxyl propyl methylcellulose possessed mainly viscosity enhancing properties whereas hyaluronic acid, mucin, sodium carboxy methylcellulose and Carbopol 941 were chosen because of their bioadhesive properties. The coating of albumin nanoparticles with viscosity imparting polymers however, failed in bringing an additive effect. However, with the bioadhesive polymer an additional improvement in miotic response and intra ocular pressure reduction compared to both. The pure nanoparticles and the

pure polymer vehicle were observed after coating the particles. The coated particles seem to adhere to conjunctival mucin thus prolonging the residence time for the drug-loaded particles in the precorneal area[40].

Review of research work conducted in recent years in ophthalmic drug delivery

1. Mohamed Ali et al (2013)[41] formulated and evaluated betamethasone sodium phosphate loaded nanoparticles for ophthalmic delivery ,an ion tropic Gelation technique was used, they reported that an initial burst release of the drug followed by slow sustained release over 24,48 and 72 hours.
2. Son joy Mandel et al (2013)[42] formulated and evaluated in situ gel forming ophthalmic formulation of moxifloxacin using gelling technique they reported sustained release of drug from a formulation over a period of 10 hours thus increasing residence time of the drug.
3. Sandeep Kumar et al (2013)[43] formulated Tropicamide loaded tamarind seed xyloglucan nano aggreates for ophthalmic delivery using ion tropic gelation technique. They reported that significant synergistic effect on two dependent variables particle size and encapsulation efficiency and higher corneal permeation.
4. Sandeep Kuma et al (2012)[44] studied carboxy methyl tamarind kernel polysaccharide nanoparticles for ophthalmic drug delivery developed by ionotropic gelation technique they reported that *ex vivo* bioadhesion and ocular tolerance was increased.
5. Jovita Kanoujia et al (2012)[45] formulated a novel pH-triggered in situ gelling ocular system containing Gatifloxacin using in-situ gelling technique they reported that controlled release ocular formulation for treatment of keratitis and conjunctivitis.
6. Ging-hu-hsuie et al (2011)[46] formulated poly 2-hydroxy ethyl methacrylate film as a drug delivery system for pilocarpine developed by polymerization technique they reported that drug is continuously released for 24 hour and therefore reduce the intra ocular pressure.
7. Himanshu Gupta et al (2011)[47] formulated biodegradable levofloxacin nanoparticle for sustained ocular delivery developed by using nano precipitation technique they reported that extended release and prolonged retention with better tolerability at corneal site.
8. Rahul Nair et al (2011)[48] formulated and evaluated solid lipid nanoparticles of water soluble drug isoniazid developed by solvent injection technique they reported that drug release can be sustained and may lead to the avoidance of frequent drug administration
9. Ashish Pandey et al (2010)[49] formulated levobunolol hydrochloride in situ gel for glaucoma treatment using in situ gelling technique they reported that the formulation can enhance bioavailability through its longer precorneal residence time and ability to sustain drug release and decreased frequency of administration.
10. Graemekay et al (2010)[50] studied gel formulations for treatment of the ophthalmic complication in cystinosis developed by in situ gelling technique they reported that the formulated gel can increase the residence time on the ocular surface, enhance the quality of life for cystinotic patients with ocular complications
11. G .Giammona el al (2009)[51] formulated polyhydroxy ethyl Aspartamide based micelles for ocular drug delivery developed by capillary electrophoresis and they reported that they have ability to enhance drug permeability across ocular epithelia.
12. Jinsong Hao et al (2009)[52] formulated electrically assisted delivery of macromolecules into the corneal epithelium developed by iontophoresis and electroporation methods they reported that the successful delivery of dextran up to 70 kd by a nodel iontophoresis suggests the feasibility of electrically facilitated corneal delivey of macromolecules
13. Fatima Sanjeri et al (2008)[53] formulated and evaluated a novel in situ gum based ophthalmic drug delivery linezolid was developed by in situ gelling technique, they reported that pH of *in situ* gel was found to be 7.4, the formulation undergo a rapid sol to gel transition.
14. Wei-san.pa et al (2008)[54] studied a controlled release ocular delivery system for ibuprofen based on nano structured lipid carriers developed by melted ultrasonic methods they reported that corresponding apparent permeability coefficient were 1.28 and 1.36 times more than that of the control preparation and

AUC of the formulation was 3.99 times more than that of ibuprofen eye drops.

15. Nayyar Parvez et al (2007)[55] formulated gellan based systems for sustained ophthalmic delivery of Ofloxacin developed by freeze drying technique they reported that the gel formed showed sustained release over an 12 hr period, dosage form were stable for a period of 3 months.

16. Yifan et al (2006)[56] formulated solid lipid nanoparticles for enhancing vinpocetine bioavailability using an ultrasonic solvent emulsification technique they reported that a poorly aqueous soluble drug vinpocetine was successfully incorporated into solid lipid nanoparticle and long term stability was investigated.

17. M. D et al imitries (2005)[58] studied a novel drug delivery system based in polymeric thermo responsive hydro gel nanoparticles developed by inverse emulsion polymerization technique; they reported that colloids with an average size of 170 nm with internal peg-rich hydrophobic regions encapsulation provided sustained release for up to 1 week in vitro.

18. Angela et al (2004)[58] studied chitosan nanoparticles as new ocular drug delivery system, fluorescent nanoparticles were prepared by ionotropic gelation method they reported that fluorescent nanoparticles are able to interact and remain associated to the ocular mucosa for extended period of time

19. Jayanta Kumara et al (2003)[59] studied in vitro and in vivo evaluation of the gel rite gellan gum based ocular delivery system for indomethacin the formulated system provided sustained release of the drug over an 8 hour period.

Table: Research work conducted in recent years in ophthalmic drug delivery

S.No.	Researcher	Year	Drug Used	Technique Used	Polymer Used
1.	Mohamed Ali Attia Shafie Hadeel Hamdy Mohammed Fayek (41)	2013	Betamethasone	Ion tropic Gelation technique	Sodium alginate, Lactic acid, Tween 80
2.	Sonjoy Mandal, Manjunath KMJ Thimmasetty, GL Prabhushankar, Geetha MS (42)	2013	Moxifloxacin	Gelling technique	Sodium alginate, Hydroxyl Propyl methyl cellulose, Berzalconium chloride
3.	Neeraj Dilbaghi, Harmanmeet Kaur, Munish Ahuja, Sandeep Kumar (43)	2013	Tropic amide	Ion tropic Gelation technique	Poloxamer-407,Mucin, Schiff reagent
4.	Sandeep Kumar , Dilbaghi Neeraj, Kaur Harmanmeet, Ahuja Munish (44)	2012	Tropicamide	ion tropic Gelation technique	Dioctyl sodium sulfosuccinate, Mucin, Schiff reagent
5.	Jovita Kanoujia, Kanchan Sonker, Manisha Pandey, Koshy M. Kymonil, Shubhini A. Saraf (45)	2012	Gatifloxacin	In situ gelling technique	Hydroxyl propyl methyl cellulose, Hydroxyl propyl methyl cellulose K15M, Carbopol 940
6.	Ging-hu-hsuie ,Jan-An Guu, Chin-Chen Cheng (46)	2012	pilocarpine	polymerization	Ethylene glycol, dimethacrylate Trimethylpropane trimethacrylate

7.	Himanshu Gupta, M. Aqil, R. K. Khar, Asgar Ali, Aseem Bhatnagar and Gaurav Mittal (47)	2011	Levofloxacin	Nanoprecipitation technique	Poly lactic glycolic acid, Poly vinyl alcohol,
8.	Rahul Nair K.Vishnu priya, K.S.Arun Kumar, T.Md.Badivaddin, Sevukarajan M (48)	2011	Isoniazid	Solvent injection technique	Phospholipon, R 80 H, tristerain
9.	Ashish Pandey, Prashant Y. Mali, Dinesh Sachdeva, Dhruval Kumar Patel and Ravda Ramesh (49)	2010	Levobunolol hydrochloride	In situ gelling technique	Carbopol 940, Hydroxy propyl methyl cellulose , Benzalkonium chloride , Sodium chloride
10.	Barbara Buchan, Graeme Kay, Anne Heneghan, Kerr H. Matthews, Donald Cairns (50)	2010	Aminothiol	In situ gelling technique	Carbomer 934 Cysteamine Trifluroacetic acid
11.	C. Civiale a, M. Licciardi b, G. Cavallarob, G. Giammonab, M.G. Mazzone (51)	2009	streptomycin	Capillary electrophoresis	Hydrocortisone, Bovine insulin , l-glutamine
12.	Jinsong Hao a, S. Kevin Li a, Chia-Yang Liu b, Winston W.Y. Kao b (52)	2009	-	iontophoresis and electroporation methods	Sodium chloride, Fluorescien isothiocynate dextran
13.	Fatima sanjeri dasankoppa ,Shivanand Swami (53)	2008	Linezolid	In situ gelling technique	Hydroxylethyl cellulose, Carbopol, Sodiumalginate Xanthum gum cyclodextrin
14.	wei-san pa , Xiang Li a, Shu-fang Niea, Jun Kongb, Ning Li (54)	2008	ibuprofen	Melted ultrasonic methods	Miglyol 812, Stearylamine, LM-10 micro dialysis probe
15.	Nayyar Parvez , Farah Siddiqui, M. Abul Kalam (55)	2007	ofloxacin	Freeze drying	Gelrite, Propyparaben, Methylparaben, cyclodextrin
16.	Yifan luo, Da wei chen (56)	2006	vinpocetine	ultrasonic solvent emulsification technique	Glyceryl monosterate Soya lecithin Polyoxy ethylene Castor oil

					Tween 80 dichloromethane
17.	M. dimitries (57)	2005	Doxorubicin	inverse emulsion polymerization technique	Pluronic f 127 Polyethylene glycol, Polypropylene glycol
18.	Angela m.de campos (58)	2004	Chitosan sea cure	ionotropic gelation method	Sodium tripolyphosphate Sodium fluorescien
19.	Jayanta kumara (59)	2003	Indomethacin	In situ gelling technique	Gellan gum, Bovine serum albumin, Lysozyme, y-globulin

CONCLUSION

There was extensive work reported in ocular drug delivery in recent years. It has been intend, to extend the residence time of topically applied drugs in the corneal and conjunctiva section. Some new approaches such as nanoparticles, liposome, contact lenses, ocular inserts, *in situ* activated gel formation, non corneal route of ocular drug diffusion, and nanoparticles-based polymeric solutions and gels are being developed by the pharmaceutical sciences. The novel advanced delivery systems offer more protective and effective mean of therapy for the nearly inaccessible diseases or syndromes of eyes. Progress in the field of ocular drug delivery has been established recently with controlled loading and sustained release. The modern approaches make it possible to achieve better therapeutic efficacy of ophthalmic route.

ACKNOWLEDGEMENT

It is my immense pleasure to acknowledge with gratitude with the help, guidance and encouragement rendered to me by a host of people, to whom I owe a substantial measure for the successful completion of this review article. It gives me fathomless pleasure to place on record my profound sense of appreciation and indebtedness for my project guide, Mr. Himansu Chopra, Asst. Professor , College of Pharmacy, GRD(PG)IMT, Rajpur Road, Dehradun (U.K).I express my thankfulness to our Director, Dr. Lakshmayya Director, (dept. of Pharmacy), GRD(PG)IMT, Rajpur Road, Dehradun (U.K). I take this pleasant opportunity to express my regards and gratitude to Shri Raja Singh, Chairman and Founder of Guru Ram das Educational Trust, for his constant encouragement and providing the required facilities that enabled me to complete my work. I also wish to put on record my sincere thanks to all Faculty Members, for their ever inspiring attitude.

REFRENCES

1. Kumar M, Kulkarni.GT Recent advances in ophthalmic drug delivery system. Int J Pharm Pharm Sci 2012; 4(1):387-394.
2. Lee VHL Precorneal, corneal and post corneal factors In Ophthalmic Drug Delivery Systems. New York: Marcel Dekker 1993; (P) 59–81
3. Tang NEML, Zaire PL, Prado RD, Keizer RJW, Van Best JA Re. ex lacrimation in patients with glaucoma and healthy control subjects by uorophotometry. Invest Ophthalmol Vis Sci. 2000; 41: 709–714.
4. White WL, Glover AT, Buckner AB. Effect of blinking on tear elimination as evaluated by dacryoscintigraphy. Ophthalmology1991; 98: 367-369.
5. Prajapati PA, Poddar SS, Patel MM, Der Pharmacia Lettre2010; 2 (1) 467-474.
6. Vyas SP, Khar Roop, Controlled drug delivery concepts and advances, 1 edition; new Delhi 2005
7. Ahmed I, Patton TF. Importance of non-corneal absorption route in topical ophthalmic drug delivery. Invest Ophthalmol Vis Sci. 1985; 26: 584–587.
8. Schoenwald RD, Deshpande GS, Rethwisch DG, Barfknecht CF. Penetration into the anterior chamber via the conjunctival scleral pathway. J. Ocul. Pharmacol. ther 1997; (13): 41–59.
9. Geroski DH and Edelhauser HF. Transscleral *drug* delivery for posterior segment disease. Adv. Drug Del. Rev. 2001; 52: 37-48.

10. Mishima S, Gasset A, Klyce SD, Baum JL. Determination of tear volume and tear flow. Invest Ophthalmol 1966; 5: 264.
11. Ding S. Recent developments in ophthalmic drug delivery. Pharm. Sci. Technol. Today 1998; 328–335.
12. Cassin b, Solomon s. dictionary of eye terminology gainsville, florida triad publishing company 1990
13. Goldstein, E. Bruce sensation and perception. 7 edition; Canada 2007.
14. Najjar, dany. Clinical optics and unreliable medical source refraction.
15. Cassin b and Solomon s dictionary of eye terminology. Gainesville.florida triad publishing company 1990.
16. Provis et al prog retin eye res vol35: 63-81.
17. Simple anatomy of the retina webvision, university of Utah, retrieved 2011;(09) 28.
18. Masayuki iwasaki,hajime inomora relation between superficial capillaries and foveal structures in the human retina.J investigate ophthalmology and visual sciences 1986 ;27 : 1698-1705
19. Gregory s, Hageman Age related macular degeneration retrieved December 11,2013.
20. Manuel c, Groove j, and Plazonet b. A novel ion activated in situ gelling polymer for ophthalmic vehicles Effect on bioavailability of Timolol. Int. J. Pharm. 1989; 163–168.
21. Dyce, sack and Wensing textbook of veterinary anatomy .4th edition dyce.
22. Jonas, Jost. Human optic nerve fiber count and optic disc size. J investigate ophthalmology and visual sciences 1992; (33) 6.
23. Cassin b Solomon s dictionary of eye terminology .gainisville, florida triad publishing company1990.
24. Lang g ophthalmology a pocket textbook atlas .2ed; Germany: 2007 :(P) 207.
25. Eye human .encyclopedia Britannica from encyclopedia Britannica ultimate refrence suite dvd 2006.
26. Equator of lens-definition from biology-online .org. retrieved 2012.
27. forrester john, dick Andrew, mcmenamin paul ,lee William. The eye basic sciences in practice. w,b saunders company ltd1996; isbn 0-7020-1790-6:29.
28. Cassin b, Solomon s dictionary of eye terminology .gainsville ,florida :triad publishing company1990.
29. Arto Urtti Ocular drug delivery Advanced Drug Delivery Reviews .2006; 58:1129-30.
30. Rathore KS, Nema RK An Insight into Ophthalmic Drug Delivery System. IJPSDR2009;1(1) 1-5.
31. Barathi A, kumar Santhosh. Advanced ocular drug delivery systems .Pharma buzz 2007;2:21-32.
32. Krishna N, Brown F. *Am. J. Ophthalmol*.1964; 57: 99.
33. Lerman S, Davis P, Jackson W B. *Can. J. Ophthalmol*. 1973; 8: 114-118.
34. Vasantha R, Sehgal P K, Rao P. *Int. J. Pharm*. 1988; 47:95 - 102.
35. Kyyronen K, Hume L, Benedetti L, Urtti A., Topp E, Stella V. *Int. J. Pharm*. 1992; 80:161-169.
36. Peyman, GA and Ganiban, GJ Adv. Drug Deliv. Rev, 1995; 16:107–123.
37. Lee VHL and Robinson, JR J. Ocul. Pharmacol. Ther 1986; 2: 67–108.
38. Urtti A, Salminen L. Surv. Ophthalmol.1993; 37:435–456.
39. Vyas S.P, Khar R.k targeted and controlled drug delivery novel carrier system .1 edition; New Delhi 2005:374-375.
40. Ali Mohamed Attia Shafie, Fayek Hadeel Hamdy Mohammed .Formulation and Evaluation of Betamethasone Sodium Phosphate Loaded Nanoparticles for Ophthalmic Delivery. J Clin Exp Ophthalmol 2013; 4:2.
41. Mandal Sonjoy, Thimmasetty manjunath kMJ, Prabhushankar GL, Geetha MS. Formulation and evaluation of an in situ gel-forming ophthalmic formulation of moxifloxacin hydrochloride .int jrnl .2013; 115-148.
42. Dilbaghi Neeraj,Kaur Harmanmeet, Ahuja Munish, Kumar sandeep. Evaluation of tropicamide-loaded tamarind seed xyloglucan nanoaggregates for ophthalmic delivery Carbohydrate Polymers 2013; 286– 291.
43. Dilbaghi Neeraj,Kaur Harmanmeet, Ahuja Munish, Kumar sandeep. Carboxymethyl tamarind kernel polysaccharide nanoparticles for ophthalmic drug delivery International Journal of Biological Macromolecules 2012; 50: 833– 839.
44. Kanoujia jovita, Kanchan sonker , pandeyManisha , Koshy M. Kymonil, saraf A.Shubhini, Formulation and characterization of a novel pH-triggered *in-situ* gelling ocular system containing Gatifloxacin. International Current Pharmaceutical Journal 2012; 1(3): 43-49.
45. Ging-hu-hsuie ,Jan-An Guu, Chin-Chen Cheng Poly(2-hydroxyethyl methacrylate) film as a drug delivery system for pilocarpine Biomaterials 2011;22: 1763-1769.
46. Gupta Himanshu, M. Aqil, Khar R. K, Ali Asgar , Bhatnagar Aseem and Mittal Gaurav. Biodegradable levofloxacin nanoparticles for sustained ocular drug delivery Journal of Drug Targeting. 2011; 19(6): 409–417
47. Nair Rahul, Vishnu priya k, Kumar K.S.Arun , BadivaddinT.Md, Sevukarajan.Formulation and Evaluation of Solid Lipid Nanoparticles of Water

Soluble Drug Isoniazid. J. Pharm. Sci. & Res. 2011; 3(5):1256-1264.

48. Pandey Ashish ,Mali prashant , Sachdeva Dinesh, kumar patel Dhruval and Ravda Ramesh.
49. Development and Optimization of Levobunolol Hydrochloride *In-situ* Gel for Glaucoma Treatment International Journal of Pharmaceutical & Biological Archives 2010; 1(2): 134 – 139.
50. Barbara Buchan, Graeme Kay, Anne Heneghan, Kerr H. Matthews, Donald Cairns.Gel formulations for treatment of the ophthalmic complications in cystinosis. International Journal of Pharmaceutics 2010; 392: 192–197.
51. C. Civiale a, M. Licciardi b, G. Cavallarob, G. Giammonab, M.G. Mazzone. Polyhydroxyethylaspartamide-based micelles for ocular drug delivery International Journal of Pharmaceutics 2009; 378:177–186.
52. Jinsong Hao a, S. Kevin Li a, Chia-Yang Liu b, Winston W.Y. Kao b. Electrically assisted delivery of macromolecules into the corneal epithelium Experimental Eye Research 2009; 1–8.
53. Fatima sanjeri dasankoppa ,Shivanand Swami Formulation and Evaluation of a Novel *In Situ* Gum Based Ophthalmic Drug Delivery System of Linezolid Sci Pharm. 2008; 76: 515–532.
54. wei-san pa , Xiang Li a, Shu-fang Niea, Jun Kongb, Ning Li. A controlled-release ocular delivery system for ibuprofen based on nanostructured lipid carriers International Journal of Pharmaceutics 2008; 363:177–182.
55. Nayyar Parvez, Farah Siddiqui, M. Abul Kalam. Gellan based systems for sustained ophthalmic delivery of ofloxacin Continental J. Pharmaceutical Sciences 2008; 2:1-14.
56. Yifan luo, Da wei chen Solid lipid nanoparticles for enhancing vinpocetine's oral bioavailability Journal of Controlled Release. 2006; 114: 53–59.
57. M.dimitries. development of a novel drug delivery systems based on polymeric, thermoresponsive, hydrogel nanoparticles THÈSE NO 3362 2005.
58. Angela m.de campos Chitosan Nanoparticles as New Ocular Drug Delivery Systems in Vitro Stability, in Vivo Fate, and Cellular Toxicity Pharmaceutical Research May 2004; 21:1-4.
59. Pandit jayanta kumari In vitro and in vivo evaluation of the Gelrite® gellan gum-based ocular delivery system for indomethacin Acta Pharm. 2003; 53:251–261.

***Corresponding Author:**
Sachin Pathak
Faculty of Pharmacy
214-Rajpur Road
Dehradun-248009
Email:sachinpathakgrd@gmail.com