International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

An Overview on Ocular Drug Delivery System : Past , Present and Future Perspective

Mr. Karpe Shubham C*., Prof. Mali Shubhangi R.

Department of Novel Drug Delivery System. Pratibhatai Pawar College Of Pharmacy , Shrirampur, Maharashtra ,India.

ABSTRACT:

The objective of this review is to present an update on the current knowledge within this field of Ocular drug delivery systems (ODDS). The unique anatomy of the eye makes it a protected organ and structure restrict entry of the drug in to the site of action. There is a lots of route of choice for drug delivery but the ODDS's becomes the most compelling and attractive attempt in front of pharmaceutical scientist. Different techniques in ODDS's have been developed to enhance the bioavailability and to increase the contact time of topically applied drugs to the eye. In an ophthalmic dosage form the reduced bioavailability is due to different Ocular barriers. The different Nano formulations have been introduced for anterior as well as posterior segment of Ocular drug delivery. These novel devices or formulations are easy to formulate, no irritating, high peroneal residence time, and enhance Ocular bioavailability of therapeutic. In this review the various new drug delivery systems applied in the eye such as nanoparticles, Nano suspension, liposome, noisome and viscosity enhancers etc. are discussed.

Keywords: Ocular delivery, Bioavailability, ophthalmic, nanoparticles, Liposomes

Introduction:

The eye is a complex organ and unique both anatomically and physiologically. Novel approachdrug can be installed on the cull-de sac or conjunctival cavity of eye is known as ODDS (1). The normal volume of tear fluid in the cul-de sac is about 7-8 micro liter. Ophthalmic formulation or preparation are specialized sterile preparation of dosage form. Drug can be installed on to the external surface i.e. topical, administered inside i.e. intraocular or adjacent i.e. periocular to the eye. the one of the most interesting and challenging task of ODDSis faced by the pharmaceuticals and researchers. the characteristics structure of the eye restricts the entry of the drug molecule at the specific site of action (2). in ODDS most commonly used administered dosage form are suspension, solution & ointment. poor bioavailability of drug can occur due to peroneal loss factors which includes lacrimation, solution drainage, tear dilution, tear turnover, conjunctival absorption, transient residence time in the cull-de sac or conjunctival cavity, and the major challenges are relative impermeability of the corneal epithelial membrane. Various approaches that have been assaying to increase the bioavailability as well as duration of therapeutic action of Ocular drug i.e. ocular insert, Nano suspension, micro emulsion, liposomes, noisome, nanoparticles and dendrimers etc. this review will provide an overview on advantage and disadvantage of ODDS, various barrier to drug permeation, drug selection criteria for Ocular drug delivery and novel approach (3).

- **Important factor has to be considered when attempting Drug delivery system to the eye:**

(1) How the blood- eye barrier (systemic to ocular) or cornea (external to ocular) is crossed by the drug to reach the site of action.

(2) How to prolong the duration of drug such as frequency of drug Administration can be reduced.

(3) How to localize the pharmacodynamics action at the eye and minimize drug action on other tissue (4).

Advantages of ODDS:

1. it provides controlled drug delivery systems.
2. better shelf life and no preservatives.
3. it increases the bioavailability of drug by increasing the corneal contact time.
4. it provides better patient compliance and reduced administration frequency.
5. Increase in shelf life due to absence of water.
6. The make self- administration of drug is possible.
7. They bypass the protective ophthalmic barriers, such as drainage, conjunctival absorption and lacrimation.
8. It provides targeting within the Ocular globe so as to prevent the loss to other ocular tissue.
9. It has less visual and systemic side effects. (5).

Disadvantages of ODDS:

1. Some devices are difficult to insert and remove.
2. It is difficult to handle.
3. It is expensive.
4. There is occasional loss while rubbing eyes.
5. In emergency dosage form cannot be terminated.
6. Feeling movement around the eye.
7. Instability for dissolved drug. (12)
8. Feeling foreign body sensation.
9. A very short time solution stays at the surface of eye.
10. A very short time the solution stays at the surface of the eye.

❖ **Anatomy of eye**

The human eye is unique and complex organ with its uncommon anatomy and physiology. the eyeball is spherical in shape. the size is about 1 inch across .it has many structures and functions that work together to facilitate sight. The structure of the eye is composed of two segments,

(a) anterior segment

(b) posterior segment.

The anterior segment consists of front one-third part of the eye that includes pupil, cornea, iris, ciliary body, aqueous se while the posterior segment consists of the back two-third part of the eye that includes vitreous humour, retina choroid, macula and optic nerve (6).

Sclera: the sclera is a white portion of the eye. it is tough white sheath and forms an outer - layer of the eye ball. it is a firm fibrous membrane which maintain the shape of the eye .it is approximately globe shaped (5).

Conjunctiva: the conjuctiva is a thin transparent mucous epithelial membrane lines the inside of the eyelids and covers the anterior one - third part of the eyeball. the conjuctiva consist of two-layer outer epithelium and stroma. The surface of the eye includes conjuctiva and cornea with tear film.

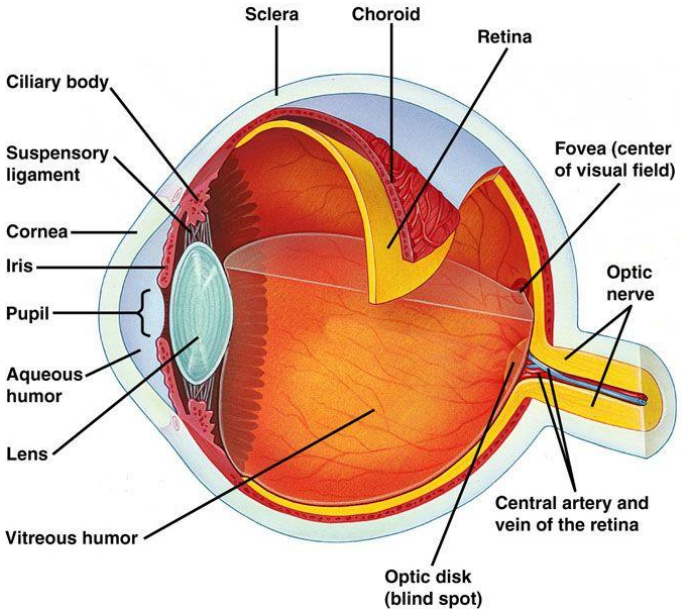

Figure :1 Anatomy of eye

Iris: iris is a colored part of the eye that helps to regulate the amount of light that enters in to the eye. the iris is a thin circular present in front of the lens but, just behind the cornea. the function of iris is to adjust the size of the pupil to regulate the amount of light enter in to the eye (5).

Ciliary body: it is a ring of striated smooth muscle in the eye. it presents in middle layer that control accommodation for viewing object at varying. after the contraction and relaxation of ciliary muscle by alter the curvature of the lens.

Choroid: choroid is located behind the retina and absorb unutilized radiation and nourishes to the outer portion of the retina it is vascular, thin membrane that is dark brown in color and it contains a pigment that absorb excess light and prevent blurred vision (5).

Optic nerve: the optic nerve connects from eye to the brain and carries impulses generated by retina to the visual cortex of the brain. the work of optic nerve is responsible for transmission nerve signal from eye to the brain. these nerve impulses contain information on an image for processing by the

brain. (5)

Pupil: the dark aperture in the iris is known as pupil that determines how much light is let in to the eye. the pupil generally appears to be the "darkcentre" of the eye (5).

Physiology of light:

Light waves travel at a speed of 300000 Km (186000 miles) per second. Light is reflected in to the eye by object within the field of vision. White light is a combination of all the colors of a visual spectrum (rainbow) i.e. Red, orange, yellow,green,blue,indigo and violet. This is indicated by passing white light through a glass prism which bends the rays of the different colors to a greater or lesser extent, depending on their wavelength. The main function of the eye is to receive the light which is converted in to visual image on the retina from where it is translated in to a correct picture by the involvement of visual center in the brain. In each hemisphere of the brain of optic nerve fibers from the eyes reach the optic lobe which contains the visual center. Impulses in the neurons in these lobes resister the image. when light falls on the rhodopsin containing cells of retina, the rhodopsin molecules split in to separate retinene and opsin components and a nerves impulse is produced at the same time. In the darkness of the eye ball and with the help of respiratory energy, retinene and opsin recombine again. this recombination generates the image. (1)

- **Commonly caused eye infection**:

Bacteria are the causative for a large number of eye infection. Also virus, fungus, and protozoa cause eye infection(7). The commonly caused disease are mentioned below

1) conjunctivitis
2) Glaucoma
3) iritis
4) keratitis/corneal ulcer
5) endophthalmitis

- **Barriers for Ocular delivery:**

Drug loss from the ocular surface: After instillation the flow of lacrimal fluid removes instilled compound from the surface of the eye. the lacrimal turnover rate is only about and microliter/min. The excess volume of the instilled fluid is flow to the nasolacrimal duct rapidly in minutes. Another source of non-productive drug removal it's systemic absorption instread of ocular absorption systemic absorption take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity (6).

Lacrimal fluid-eye barrier: corneal epithelium limit drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junction that limit the par acellular drug permeation lipophilic drug have typically at least on order of magnitude higher permeability in the cornea than the hydrophilic drug (6).

Blood – Ocular barrier: the eye is protected from xenobiotic in the blood stream by blood – Ocular barrier. there are two part of these barrier: blood-aqueous barrier and blood – retinal barrier. The anterior blood -eye barrier is consisting of the endothelial cell.

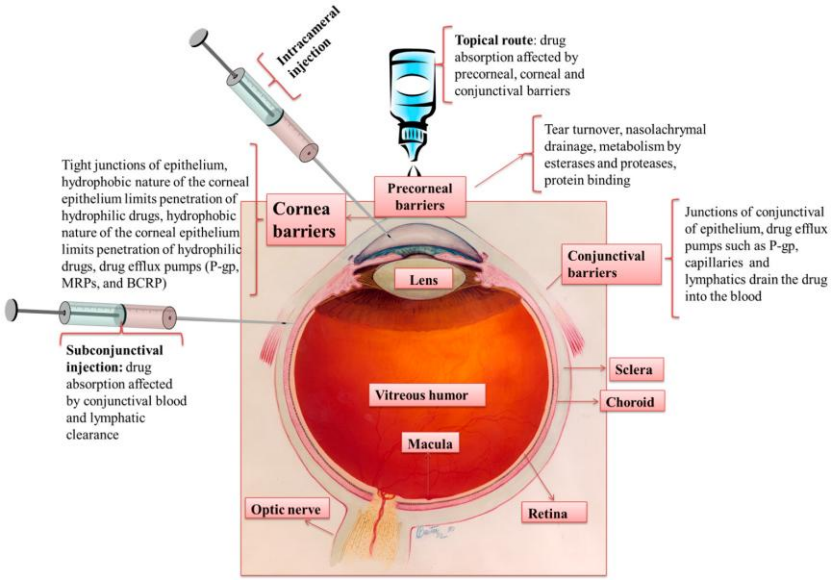

Figure 2: Ocularbarrier

Drug selection criteria for Ocular drug delivery systems

Gels	**Injection**	**Ointment**	**Suspension**	**Solution**	**Oral**
Drug : long duration required	Drug : target site accessibility onset of response	Drug : long duration required	Drug : insoluble drug potent	Drug : soluble less potent	Drug : impermeable topically few systemic side effects
Low bioavailability	-	Low bioavailability	-	Required high concentration	-
Intermediate cost	Required physician	Low cost	Low cost	Low cost	Low to moderate cost
Some blurring	-	Severe blurring	Little blurring	Little blurring	-
Selection : simple administration reduced frequent administration.	Selection : alternative surgical application.	Selection : slight threatening.	Selection : convensent accepted some extend duration.	Selection : convensent accepted	Selection : drug design not optimised
Safety	Safety	Safety	Safety solutions cloudy	Safety	Safety

Table 1 : Drug selection criteria for Ocular drug delivery systems

❖ **Novel approaches for Ocular drug delivery:**

In a last few days, various approaches have been utilized for the treatment of Ocular disease (7). nanotechnology based ophthalmic formulation or preparation are one of the most important approaches which is currently being designed for both anterior as well as posterior segment drug delivery (7). nanotechnology based system with a relevant particles size can be design to ensure adequate bioavailability, low irritation and Ocular tissue affinity. Several nanotechnologies based Nano carriers such as nanoparticles, Nano suspension, liposome, nanomicelles and Dendrimers have been developed for Ocular drug delivery systems (7). some of them have shown a better result for improving ocular bioavailability.

Nanoparticles:

The size of nanoparticles ranges of 10 to 1000 nm. For ophthalmic drug delivery. Nanoparticles are generally consisting of lipids, protein, natural or synthetic polymers like albumin, sodium alginate, chitosan, poly (lactide -co- glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Drug contain nanoparticles can be nanocapsule or nanospheres (3).in nanocapsule drug is enclosed inside the polymer shell. In nanospheres, drug is distributed uniformly throughout polymeric matrix. From past few days, nanoparticles have learned attention for Ocular drug delivery and a few reasearchers have loaded nanoparticles for delivery to both anterior and posterior segment of occular tissue (3). Chitosan coating is most widely investigated nanoparticle for improving precorneal residence. The chitosan is positively charged and hence it binds to negatively charged corneal surface. Thereby improve precorneal residence and decrease clearance. For example, kanamycin loaded chitosan nanoparticles exhibited high ocular bioavailability at reduced dosing frequency in rabbit eye as compared to marketed suspension (3).

Nanoparticles have also been successfully selected as an alternative strategy for long term drug delivery to the posterior segment ocular tissue. For posterior segment delivery, the deposition of nanoparticles depends on the size and surface property of that nanoparticles (3).

PLA nanospheres colloidal suspension it containing acyclovir provided a marketed sustained drug release in the aqueous humour. Remarkably higher level of acyclovir as compared to the free drug formulation (4).

Nano suspension:

The colloidal dispersion of submicron drug particles stabilized by polymer or surfactant is called as nano suspension (3). it is emerged as good strategy for delivery of hydrophobic drug .in Ocular drug delivery systems, it provides various advantages such as sterilization, less irritation, of eye drops preparation, increase precorneal residence time and increase ocular bioavailability of drug which are insoluble in tear fluid. The potency of nanosuspension in improving Ocular bioavailability of glucocorticoid has been demonstrated in various research studies (3). the polymeric nanosuspension are being formulated using inert polymeric resins, which can be used as important drug delivery vehicle, having the capacity to increase drug release and bioavailability (8). the carriers having such type of property can be used as inert carrier in ophthalmic drug, because they do not cause any irritation to the iris, cornea or conjuctiva. example: polymeric nanoparticles suspension having flurbiprofen (FLU) as active ingredient and eudragit RS 1001 and RL 1001 are polymer used (8).

Nanosuspension had an onset of action and increase dose proportionality. nanosuspension also alter the pharmacokinetics parameter, enhance safety and efficacy of the drug formulation like poloxamers lecithin's, Pondoes, polylobate etc. (9). in nanosuspension solvent used is water soluble solvent like butyl acetate, benzyl alcohol, and other pharmaceutical solvent. surfactant act as wetting agents. ethanol glycofurol, isopropanol etc. can be used as

co-surfactant. buffer salt, osmogene is used as additives in nanosuspension preparations (19).

liposomes:

liposome is biodegradable and nontoxic in nature (10). they are lipid vesicles with one or more phospholipid bilayer enclosing an aqueous core. the size of liposome is approximately range from 0.08 to 10.00 micrometer (3). liposome can be classified in three types i.e. small unilamellar vesicle (10-100 nm), large unilamellar vesicle (100-300 nm) and multilamellar vesicle (contain more than one bilayer) (3). for ophthalmic formulation, liposome represent ideal characteristics system due to excellent biocompatibility, cell like structure and ability to encapsulate both hydrophilic and hydrophobic drugs. Liposome have exhibited good effectiveness for both anterior and posterior segment of Ocular delivery is several research studies (3). Liposome can be prepared by sonication of dispersion of phospholipid reverse phase evaporation, solvent injection and calcium induced fusion method. these formulations are composed of phosphatidylcholine and other constituent like cholesterol and lipid conjugated hydrophilic polymer (18). phospholipids are used phosphatidylcholine, phosphatidic acid, sphingomyelin. liposome can attach closely on the eye surface to increase the residence time and increase bioavailability (17).

Niosomes:

noisome are chemically stable, bilayerd Nano carriers made up of nonionic surfactant .it is used as carriers for both hydrophilic and hydrophobic drugs (8). niosomes have lots of advantages including that they are biocompatible, biodegradable and nonimmunogenic which make them increase the contact time between the drug and cornea, thereby increasing bioavailability of drug (8). niosomes developed to avoid the limitations of liposome as they are chemically entrapping both hydrophilic and hydrophobic drug(12). a modified form of niosomes is discosome. discosome also act as carriers for ophthalmic drug. this gives a benefit of not allowing it to enter in the general circulation and its disc shape provide better fit in to the conjunctival cavity (8). the advantages of niosomes is to provide better patient compatibility and also a better therapeutic effect than conventional.

Dendrimers:

Dendrimers are nanosized, highly branched, star shaped polymeric system. this system is available in different molecular weight with terminal end amine, hydroxyl or carboxyl functional group. the terminal functional group utilized to conjugate targeting moieties. dendrimers are used as carrier's system in drug delivery. selection of molecular weight, surface charge, molecular geometry and functional group are critical to deliver drug. the structure of dendrimers is highly branched its allow incorporation of wide range of drug, hydrophilic as well as hydrophobic (12).

Use of viscosity Enhancers:

Viscosity increasing polymers are preferred additive in the ophthalmic preparation due to their properties of increasing viscosity and thereby imparting benefit to the penetration of the drug in to the anterior chamber of the eye .by decreasing the elimination rate from the preocular area , resulting in increase in precorneal residence time and transcrenial penetration, but having very limited effect of increasing bioavailability in human being .example of polymer are polyvinyl alcohol (PVA) ,polyvinylpyrrolidone(PVP),hydroxymethylcellulose ,hydroxypropyl methylcellulose (HPMC) & hydroxypropyl cellulose (19).

- **Past Perspective :**

The interest continues today, increasing level of research and investment in to the novel drug delivery systems. Despite the long history, multiple companies are joined in development efforts for sustained drug delivery for both anterior and posterior segment. Although glaucoma is a disease that affect optic nerve, we continue to view glaucoma for anterior segment disease. Pharmacological treatment for glaucoma is carried out through the anterior segment route. a multi companies are investigating sustained release technology for glaucoma treatment.

In 1970's the first company to launch a drug delivery device for eye was Alza Corporation. Ocusert was an implant placed in the conjunctival sac for the delivery of pilocarpine over a period of 1 week. It was failed because it caused patient discomfort, so it was the first effort in modern era to develop long lasting drug delivery to the eye (18).

It wasn't until 20 year later, in 1995, Chiron vision launched vitrasert, this is a word's first intraocular drug delivery implant vitrasert delivered ganciclovir to the back of the eye treatment of orphan disease cytomegalovirus retinitis, an opportunistic infection associate with HIV.This was the first time surgeons could put an implant into the posterior segment of the eye that could deliver a drug for 4 to 6 months, a major breakthrough for patients. The product was launched with a price of $4,500—a shock at the time—but the price was accepted given the fact that the device could deliver drug for such a length of time for this unmet medical need (20).

It was almost another 10 years before the next intraocular implant appeared. In 2005, Bausch + Lomb launched Retisert (fluocinolone acetonide 0.59 mg). The company had acquired Chiron Vision's technology, and Retisert used the same technology as Vitrasert but was smaller. It was labeled by the FDA for the treatment of the orphan disease noninfectious posterior uveitis, and it could deliver treatment for more than 32 months. The posterior segment pharmacologic landscape changed dramatically in 2006 with the introduction of the anti-VEGF drug ranibizumab (Lucentis, Genentech). This large-molecule biologic drug is indicated for treatment of neovascular age-related macular degeneration, DME, and macular edema following retinal vein occlusion. A second novel large-molecule anti-VEGF biologic, aflibercept (Eylea, Regeneron), was introduced a few years later (21).

With the appearance of this second product, companies began to recognize the potential of developing implants as vehicles for drug delivery to the back of the eye. In 2009, Allergan launched Ozurdex (dexamethasone implant 0.7 mg), which was different from the preceding implants in that it did not

require a trip to the OR. This was another breakthrough; the first time a drug delivery implant could be injected in the clinic. In 2011, Alimera Sciences launched Iluvien (fluocinolone acetonide implant 0.19 mg), containing the same steroid as Retisert but even smaller and able to be injected rather than implanted. Iluvien is indicated for treatment of DME.

In 2018, Ocular Therapeutic announced the FDA approval of Dextenza (dexamethasone ophthalmic insert 0.4 mg) to treat ocular pain following ophthalmic surgery. The intracanalicular insert delivers drug to the ocular surface for up to 30 days (22).

❖ **Present Perspectives :**

Punctum Plugs Punctum plugs are biocompatible devices inserted in the tear ducts to block tear drainage. These are also known as occludes or lacrimal plugs which have a size of 2-5 mm. Punctum plugs are noninvasive and can provide controlled drug release to the anterior segment of the eye. Construction of such ocular inserts is possible from non-biodegradable and biodegradable materials. Non-biodegradable punctum pug delivery system (PPDS) are made from silicone, polycaprolactum and hydroxyethyl methacrylate, which intends to provide controlled drug release up to 180 days. After this period, the insert is removed. Recently, a PPDS (SmartPlug®) was developed from a thermosensitive hydrophobic acrylic polymer for the treatment of dry eye disease. The thermosensitive PPDS undergoes modification from rigid solid to a soft gel like structure after insertion into the eye (Weber W).

Subconjunctival/Episcleral Implants Ocular implants can be inserted into the anterior segment of the eye for controlled drug delivery for a prolonged period. Such implants can be surgically inserted in the sub-conjunctival region, aqueous humor and the episcleral region. These implants provide the advantage of sustained localized drug delivery and higher patient compliance as compared to topical eye drops. An insertion is made on the conjunctiva for the insertion of the implants. While some inserts are implanted in the junction between the conjunctiva and the sclera (Nicoli, Ferrari et al. 2009), others are inserted into the aqueous humor (Molokhia, Thomas et al. 2013). Surodex® is an example of an anterior segment insert, which is inserted into the anterior ocular segment post cataract surgery to alleviate post-surgery inflammation. Surodex® is a rod shaped biodegradable insert consisting of drug dexamethasone using polymers like PLGA (poly lactide-co-glycolide) and hydroxypropyl methyl cellulose allowing sustained drug release for 7-10 days

The cul-de-sac of the eye is a pocket like depression where the bulbar and palpebral conjunctiva meet in the upper or lower eyelid. Ocular devices like Lacrisert® and Ocusert® are examples of cul-de-sac implants designed for drug delivery to the anterior segment of the eye. These devices are safer and less invasive than the conjunctival and the episcleral implants, since these are the exterior inserts into portion. Lacrisert® (Bausch & Lomb) is a hydroxypropyl cellulose implant inserted into the inferior cul-de-sac. The implant is suitable for patients with moderate to severe dry eye disease (McDonald, D'Aversa et al. 2009). Lacrisert® decreased corneal sensitivity, recurrent corneal erosions and exposure to keratitis. It is also effective for the treatment of conjunctival hyperemia (MERCK & CO. 1988) Lacrisert® releases cellulose, allowing maintenance of tear film integrity.

Drug Eluting Contact Lenses Drug Eluting Contact lenses (CLs) are light-transparent corneal dressings acting as drug reservoir and sustain drug discharge near the post-lens tear fluid for the treatment of anterior ocular disorders. Drug loaded soft contact lenses is an innovative drug delivery system to not only prolong and sustain drug release but also enhance drug penetration across the corneal epithelium as compared to conventional eye drops. Contact lenses can increase bioavailability of the drug by increasing the contact time of the drug (Mandal, Bisht et al. 2017). Various soft contact lenses have been developed for antifungal agents which can prolong drug delivery up to 21 days (Phan, Subbaraman et al. 2014). A clinical trial was conducted for evaluation of safety and efficacy of drug eluting contact lenses for the management of glaucoma. The contact lenses are loaded with timolol maleate and dorzolamide HCl along with vitamin E as an additive for achieving sustained drug release (NCT02852057). Various technologies have been utilized to load drugs on contact lenses, instead of just soaking the lens with the drug.

❖ **Challenges and future perspectives:**

The shortcomings of the current ocular drug delivery system like lower drug bioavailability for topical administered drugs and invasive nature of posterior implants creates challenges allowing novel technologies to rise with superior and effective treatment for ocular disorders. Ocular disorders like cataract, dry eye disease, wet and dry AMD, glaucoma, DR and DME are predicted to escalate with the next two decades. For a majority of the anterior segment disorders, eye drops are regarded as the safest and the most convenient dosage form. Eye drops face a challenge of having low drug bioavailability at the target tissue. Controlled drug delivery with the help of Nano formulations like nanomicelles, nanoparticles, liposomes, dendrimers, Nano wafers and microneedles can achieve high bioavailability of drugs at the anterior tissues like conjunctiva and cornea. Currently all treatments for back of the eye disorders are invasive in nature. Frequent intravitreal injections can lead to retinal detachment, hemorrhage and discomfort to the patients (23). Design of noninvasive sustained drug delivery system for the posterior segment is challenging to ocular drug delivery scientists. Thus, an urgent need for the development novel noninvasive drug delivery systems that can overcome ocular barriers, sustain drug release and maintain effective drug levels at the back of the eye.

❖ **Conclusion:**

Ocular drug delivery systems provide local as well as systemic delivery of the drug with increasing the residence time of an ophthalmic formulation on the corneal surface enhancing the drug bioavailability. Therefore, reduces frequency of drug administration. Treatment of Ocular diseases in an effective manner is a challenge for scientists who is working in the field of Ocular drug delivery because of the nature of the unique structure of the eye and barrier present in the system. Particularly the posterior Ocular segment make a system inaccessible. Effective and safe delivery of therapeutic agent to the Ocular tissues, mainly posterior segment tissue, is a demanding for the formulation scientist due to the presence of some physiological barriers. Various approaches have been studied to attain therapeutically effective concentrations of drugs in to Ocular tissue. Therefore, it could be concluded that modern technology seems to be consistent examined in various ways over the conventional approaches.

❖ **Reference:**

1) Sapna Rawat, Dinesh Sharma, Poonam Joshi; Ocular drug delivery systems: approaches to improve Ocular bioavailability;IJHCR. 2020, 3(1):25-33.

2) K.P. Sampath Kumar, Debjit Bhowmik, G. Harish, S. Duraivel, B. Pragathi Kumar; Ocular insert: A novel controlled drug delivery system ; J.Pharm.Innov.2013, vol.1 no.12, ISSN: 2277-7695

3) Ashaben Patel, Kishore Cholkar, Vibhuti Agrahari and Ashim K Mitra; Ocular drug delivery systems: an overviewWorld J. Pharmacol. 2013, 2(2): 47-64

4) Palani S, Nisha Mary Josheph, Goda C.C., Anish Zachariah and Zelalem Ayenew ; Ocular drug delivery; a review ; Int.J.Pharm.Sci.Res. (2010), volume 1, issue 3. ISSN:0975-8232

5) Kumar, Sonia Pahuja, Ranjit Sharma: Ocular drug delivery systems – A review: ijddt , 2019; 9(2); 114-119.

6) Ramaiyan Dhanapal and J. Vijaya Ratna; Ocular drug delivery systems- a review, Int.J.pharm.Sci.Res. 2012, volume 2, issue 1.

7) Vishal Kumar Raj, Rupa Mazumder, Monika Madhra: Ocular drug delivery system: challenges and approaches: ijap,2020, volume 12, issue 5. ISSN-0975-7058

8) Meetali Mudgil, Nidhi Gupta, Manju Nagpal, Pravin Pawar: Nanotechnology: a new approach for Ocular drug delivery system: ijpps, ,2012, volume 4, issue 2. ISSN-0975-1491.

9) Nikhil Gulati, Vanya Dwivedi: Review on Ocular drug delivery system and its devices: International journal of drug regulatory affairs; 2014, 2(3),79-82.

10) Yolanda D, Miguel J, Victoria S, Edison LSC, Maria O, Margarita C, Begona S and Maria JA: Ocular drug delivery by liposome-chitosan nanoparticles complexes (LCS-NP), Biomaterials 2007; 28(8):1553-1564.

11) Arpita Bhattacharjee, Pranab J Das, Piya Adhikari, Daphisha Marbaniang, Paulami Pal, Subhabrata, Pranab j. Das and Bhaskar Mazumder: novel drug delivery systems for Ocular therapy: with special reference to liposomal ocular delivery, European Journal of Ophthalmology 2019, volume 29(1) 113-126.

12) Neslihan Ustundag Okur, Emre Sefik Calgar and Panorama I. Isaak: novel Ocular drug delivery systems: an update on micro emulsions: Journal of Ocular pharmacology and therapeutics volume 36, number 6,2020.

13) Aakashsinh Vaghela, Dr. Pragneshpatni: newer approaches of the Ocular drug delivery system: an overview: ISOR journal of Pharmacy and Biological Science (ISOR-JPBS) e-ISSN:2278-3008, p-ISSN:2319-7676.Volume 14, Issue 4 Ser.II (jul-Aug 2019), PP 18-21.

14) Karbhari Vilas N. And Warad T. A: current trends on Ocular drug delivery system: Word Journal of Pharmacy and Pharmaceutical Sciences, Volume 5, issue 10, 2016 ,1248-1258.

15) Accompanied by prof.dr. Amiyakanta Mishra: Ocular drug delivery system.

16) Macha S. Mitra Ak. Ophthalmic drug delivery systems; second edition revised and expanded. Chapter 1, overview of Ocular drug delivery, p 1-3.

17)Mundada as, Avari JG, Mehta SP, Pandit SS, Patil AT. recent advances in ophthalmic drug delivery systems. Pharma Rev., 6(1) 2008, 481-489.

18)Nagarwal RC, Kanti S, Singh PN, Maiti P, Pandit JK. Polymeric nanoparticulate system; a potential approach for Ocular drug delivery. (Control release 2009; 136 (1) :2-13.

19) Koteshwara KB, Reddy MS, Naha A, Nampoothiri M. Nanosuspension: a novel drug delivery approch. IJRAP 2011; 2(1);162-165.

20) Lang JC., Ocular drug delivery conventional Ocular formulations. Adv. drug delivery Rev 1995; 16:39-43.

21) Patel PB, Shastra PK, Sehlat PK, Shukla Ak. Ophthalmic drug delivery systems.: Challenges and approaches. systemic rev pharms 2010; 1:113-20.

22) Sultana Y, Jain R, Aqil M, Ali A. Review of ocular drug delivery. Curr drug delivery ;2006; 3:207-17.

23) Gaudana R, Jwala J, Boddu SH, Mitra AK. Recent perspectives in ocular drug delivery. Pharm Res. 2009; 26:1197–1216. Doi: 10.1007/s11095-008-9694-0.

24) Meqi SA, Deshpande SG. Ocular drug delivery: Controlled and novel drug delivery. New delhi: CBS Publishers; 2002, p 82-84.