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A Detailed Review of Occular Drug Delivery System

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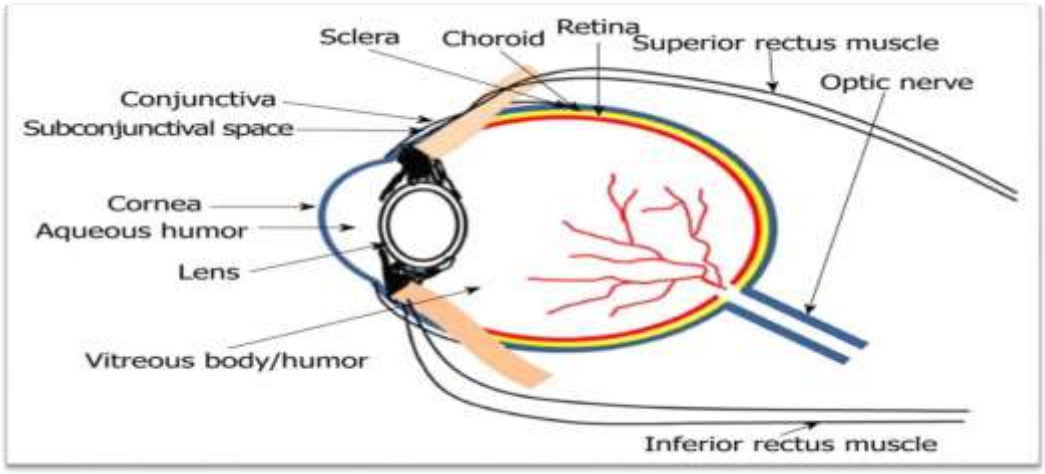
ABSTRACT: -

Ocular drug delivery systems are pivotal for treating eye disorders but face unique challenges due to the eye's protective anatomy and physiology, which limit the effectiveness of conventional delivery methods. This review synthesizes the latest advancements in the field, focusing on the design and implementation of innovative strategies to enhance drug bioavailability and therapeutic efficacy in the anterior and posterior segments of the eye. We discuss various delivery approaches, including topical solutions, intraocular injections, implantable devices, and nanotechnology-based systems, evaluating their potential to overcome traditional barriers such as ocular permeability and retention time. Particular attention is given to emerging trends such as stimuli-responsive systems and gene therapy vectors, which offer controlled and sustained drug release. Additionally, we highlight the importance of mucoadhesive polymers and encapsulation techniques that improve drug penetration and duration of action. The review also addresses the pharmacokinetic challenges, regulatory hurdles, and future directions for research and development in ocular drug delivery technologies. By providing an extensive overview of both established and novel delivery methods, this paper aims to assist researchers and pharmaceutical companies in developing more effective therapeutic solutions for a range of ocular diseases, ultimately aiming to enhance patient compliance and treatment outcomes

KEY FEATURES:- Anatomy and physiology, Cornea, Contact lens, Drug delivery, Eye, Emulsions, Formulations, Implants, Liposomes, Nanomicelles, Ointments, Retina, Suspensions

INTRODUCTION:-

The structure and physiology of the eye are distinct, making it a complex organ. The anterior segment and posterior segment are the two primary components of the eye's anatomy (Figure 1).



Structure of the eye.

About one-third of the eye is made up of the anterior segment, with the posterior section taking up the remaining space[1]. The anterior section is composed of tissues including the cornea, conjunctiva, aqueous fluid, iris, ciliary body, and lens. The choroid, neural retina, optic nerve, retinal pigment epithelium, sclera, and vitreous humor comprise the posterior portion of the eye.However, because of the eye's effective defense mechanisms, ophthalmic medicines have relatively low absorption[2]. Efforts such as blinking, baseline and reflex lachrymation, and drainage help eliminate foreign objects, such as medications, from the surface of the eye quickly Numerous conditions can damage the eyes, and blindness is one of them. As a result, there are numerous drug delivery methods for the eyes accessible. These medication delivery methods are divided into traditional and nonconventional (newer) categories[3]

A therapeutic agent's ocular disposition and excretion are influenced by both its physical-chemical characteristics and the pertinent anatomy and physiology of the eye. Because of this, a thorough understanding of the drug molecule and the limitations imposed by the ocular route of administration are necessary for the successful design of a drug delivery system[4]. The infected or inflammatory areas in the anterior and posterior segments of the eye are the active sites for the antibiotics, antivirals, and steroids. A variety of tissues are involved, and each one may present unique difficulties for the developer of ophthalmic delivery systems. As a result, the drug entities must be directed to numerous locations throughout the world[5].

CONVENTIONAL DRUG DELIVERY SYSTEM

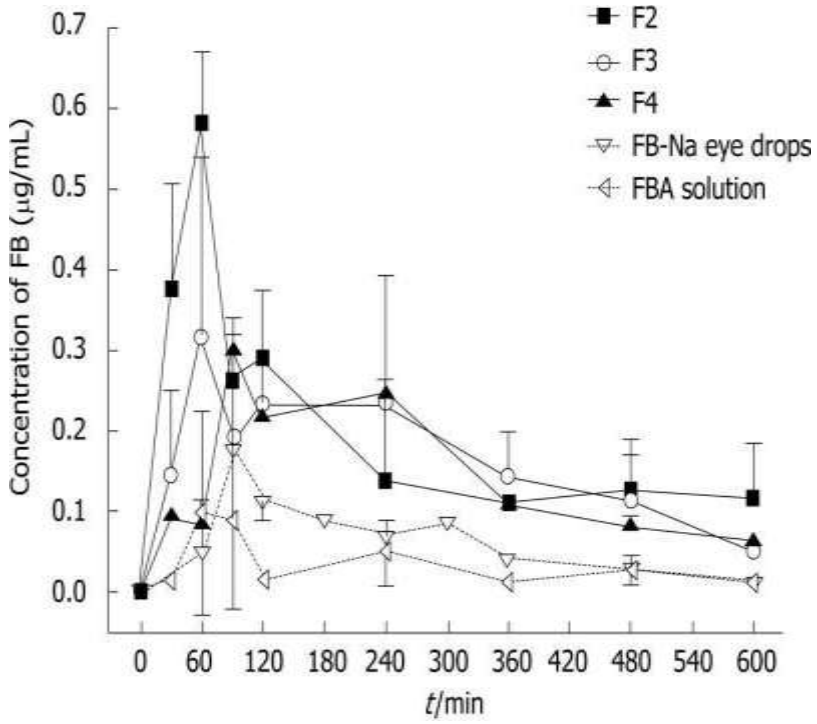
Administering medication via topical drop instillation into the lower precorneal pocket is a commonly suggested and patient-compliant method. However, only 20% (−7 μL) of the implanted dose remains in the precorneal pocket, with the majority of the topically applied dose

lost to reflux blinking[6]. Passive diffusion of the medication across the cornea is driven by its concentration in the precorneal region. On the other hand, prolonged drug cornea contact times and high corneal penetration are necessary for effective ocular medication administration with eye drops. Enhancing corneal penetration and precorneal residence duration has been the focus of several initiatives[7]. Approximately 70% of prescriptions for ophthalmic products involve traditional eye drops, despite the market offering a wide variety of items. The efficacy, stability, cost-effectiveness, high patient acceptability, and ease of bulk scale manufacturing could be the causes[8].

EMULSIONS :-

It is advantageous to use an emulsion-based formulation technique to increase a drug's solubility and bioavailability. The two forms of emulsions that are used in the pharmaceutical industry as carriers of active ingredients are water in oil (w/o) and oil in water (o/w) emulsion systems[9].

O/w emulsion is a common and generally favored method of ocular medication administration over w/o system. Less discomfort and improved ocular tolerance of the o/w emulsion are among the causes. Currently available ocular emulsions in the US include RestasiseTM, Refresh Endura® (a non-medicated emulsion for eye lubrication), and AzaSite[10]. Emulsions have been shown in numerous trials to be effective in prolonging drug release, increasing ocular bioavailability, and improving precorneal residence time and drug corneal permeation[11].Derivatizing active pharmaceutical ingredients (API) and enhancing its ocular bioavailability using an emulsion as a carrier system is another cutting-edge strategy. This tactic might lessen eye irritation and enhance the benefits of API. Shen et al.'s efforts to increase the flurbiprofen emulsion biocompatibility were made in order to test this theory. This study prepared an emulsion using castor oil, tween-80, and flurbiprofen axetil, a derivative of flurbiprofen. Four distinct emulsions, designated F1, F2, F3, and F4, were made with varied proportions of castor oil (0.1 wt%–2.5 wt%) and between 80 Pharmacokinetic investigations in aqueous humor revealed that F2 emulsion[12]



Flurbiprofen concentration-time profiles (in the aqueous humor following administration of FB-Na eye drops, flurbiprofen axetil emulsion F2-F4, and Flurbiprofen concentration-time profiles (in the aqueous humor following the administration of flurbiprofen axetil emulsion) F2-F4, flurbiprofen axetil-oil solution, and FB-Na eye drops in rabbits

Castor oil and tween-80 weight percentages are as follows: F1 = 0.1 weight percent; F2 = 0.5 weight percent; F3 = 1.0 weight percent; and F4 = 2.5 weight percent; tween-80 and glycerol weight percentage and flurbiprofen weight percentage, respectively. Reproduced from Shen et al with permission. FBA-EM: Flurbiprofen axetil emulsion; FB: Flurbiprofen[13].

SUSPENSIONS :-

Another type of non-invasive topical drug carrier method for the eyes is suspensions. A appropriate suspending and dispersing agent is combined with an aqueous solvent to create suspension, which is defined as finely split insoluble API suspended in the solvent. Stated otherwise, the saturated solution of API represents the carrier solvent system. In comparison to medication solution, suspension particles prolong drug contact time and duration of action by remaining in the precorneal pocket.[14] Other drawbacks of this form include the drug's instability when dissolved, the brief duration the solution remains at the eye's surface, its poor bioavailability (the majority, or 75%, is lost via nasolacrimal drainage), and the have to use preservatives. Using eye drops has several drawbacks, including the solution's quick removal and low bioavailability.[15] This quick removal is caused by the preparation's solution state, which may also be impacted by the solution's makeup. The viscosity, osmolality, injected volume, and hydrogen ion concentration all affect a solution's ability to stay in the eye. Many studies have been conducted to extend the time that medications remain in the ocular solution by increasing the viscosity or changing the pH of the solution.[16] After topical application, the safety and effectiveness of the suspension formulation were assessed in human subjects. In experiments using Lissamine green conjunctival staining and fluorescein corneal staining at two and four weeks, a dose-dependent response was seen for placebo, 1%, and 2% rebamipide solution. From week one to week four, there was no discernible variation in the baseline for tear production.

However, 1% and 2% rebamipide significantly changed the tear film break up time in comparison to the placebo. patients treated with suspension rebamipide formulation reported improvement in 64.1% and 54.9% of cases, respectively, compared with placebo-treated patients. After receiving placebo, 1%, or 2% suspension, respectively, dysgeusia, ocular irritation, and nasopharyngitis were the most common side effects reported in 27.2%, 29.1%, and 30.4% of patients.[17]

OINTMENTS :-

Another class of carrier systems designed for topical delivery are ophthalmic ointments. The ingredients of ocular ointment are a combination of solid and semisolid hydrocarbons, namely paraffin, which melts at the physiological temperature of the eyes, which is 34 °C. The biocompatibility of a hydrocarbon determines its choice. Ointments support and enhance the drug's sustained release and ocular bioavailability.

Methicillin and cephem-resistant Staphylococcus aureus (MRSA) as well as aerobic and anaerobic gram positive bacteria are all effectively combatted by the glycopeptide antibiotic vancomycin HCl (VCM). Despite VCM's increased activity, there was no suitable topical formulation on the market. Although improved ocular tissue permeability of VCM was not anticipated in a healthy eye, there have been some documented clinical effects of VCM solution in the treatment of ocular diseases.[18]

TOPICAL LIQUIDS/ SOLUTIONS EYE DROPS :-

The most practical, secure, instantly effective, patient-compliant, and non-invasive method of ocular medication administration is by topical drops. Following topical drop instillation, an eye drop solution offers a pulse medication penetration, after which its concentration quickly drops. There's a chance that the medication concentration drop kinetics will roughly follow first order. Therefore, several additives, such as viscosity enhancers, permeation enhancers, and cyclodextrins, may be added to topical eye drops in order to improve medication contact time, penetration, and ocular bioavailability. Through the enhancement of formulation viscosity, viscosity enhancers improve precorneal residence duration and bioavailability upon topical drop delivery. Hypermethyl cellulose, hydroxy ethyl cellulose, sodium carboxy methyl cellulose, hydroxypropyl methyl cellulose, and polyalcohol are a few types of viscosity enhancers.[19] By altering the cornea's integrity, permeability enhancers increase corneal uptake. Additional additions that have been investigated as potential permeation enhancers include chelating agents, preservatives, surface active agents, and bile salts. Examples of penetration enhancers being researched for better ocular administration include benzoalkonium chloride, polyoxyethylene glycol ethers (lauryl, stearyl, and oleyl), ethylenediaminetetra acetic acid sodium salt, sodium taurocholate, saponins, and cremophor EL.[20]

NOVEL OCCULAR DRUG DELIVERY SYSTEM

Numerous methods have been used in the last several decades to cure illnesses of the eyes. Pharmaceutical formulations based on nanotechnology are one of the strategies being investigated for drug delivery to the anterior and posterior segments of the eye. Systems based on nanotechnology that have the right particle size can be created to guarantee minimal eye tissue irritation, sufficient bioavailability, and compatibility. For the transport of drugs into the eyes, a variety of nanocarriers have been created, including liposomes, nanoparticles, nanosuspensions, nanomicelles, and dendrimers (Figure 3). A few of them have demonstrated encouraging outcomes in terms of enhancing ocular bioavailability.[21-22]

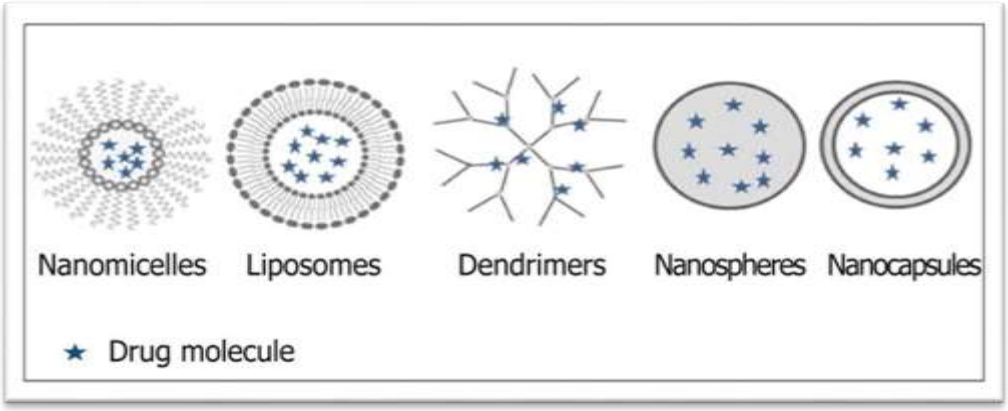


FIGURE 03 Nanocarriers for ocular drug delivery.

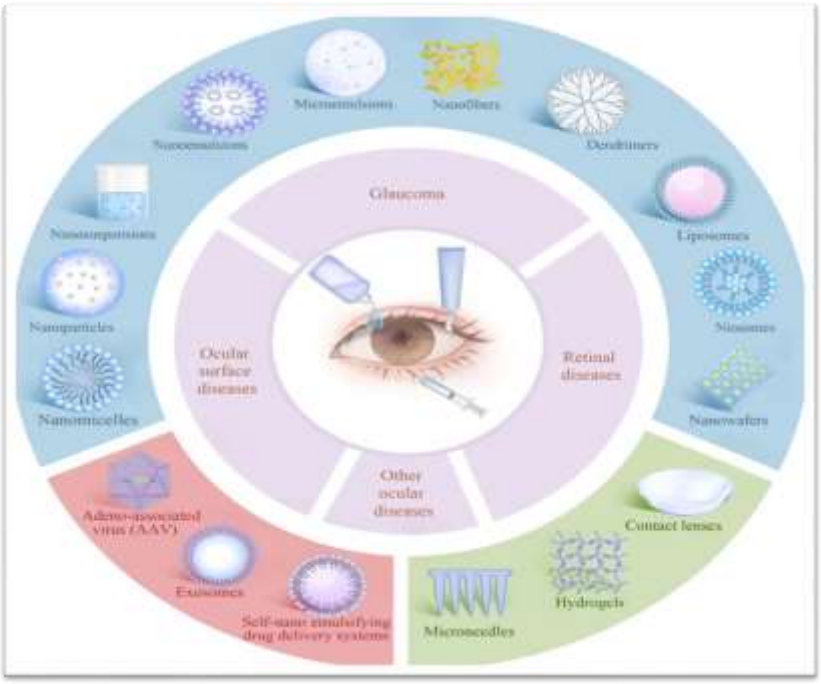


Figure 4 Graphical abstract.

NANOMICELLS :-

When creating therapeutic medicines in transparent aqueous solutions, nanomicelles are the most widely utilized carrier systems. Amphiphilic compounds are typically used to create these nanomicelles. These molecules could be polymeric or surfactant in composition. Recently, ocular barriers and the use of nanomicelles-based technology for ocular medication delivery have been thoroughly studied by Cholkar et al. At the moment, there is a lot of interest in developing nanomicellar formulation-based technology for the delivery of drugs into the eyes. Their high drug encapsulation capacity, simplicity in manufacture, compact size, and hydrophilic nanomicellar corona that produces aqueous solution could be the causes. Better therapeutic results may also result from micellar formulation, which increases the therapeutic medicines' bioavailability in ocular tissues. For example, using copolymers of polyhydroxyethylaspartamide [PHEAC(16)] and pegylated PHEAC(16) for anterior region administration, Civiale et al. [44] created dexamethasone loaded nanomicelles. Using aqueous humor sampling, in vivo dexamethasone concentration time patterns in rabbits were investigated and ascertained. The ocular bioavailability of dexamethasone-loaded PHEA micelles is higher than that of dexamethasone solution, according to the results. Compared to the control suspension, the dexamethasone micellar formulation's area under the curve was 40% larger. The findings indicate that topical ocular administration of small molecules can be achieved through the use of nanomicellar formulations. Nanomicelles have also been used by researchers to transfer genes into the eyes. Liaw et al.[45] attempted to transfer genes to the cornea using topical drop injection in a trial. The development of the copolymer poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPO-PEO)[23-24]

NANOPARTICLES (NP's) :-

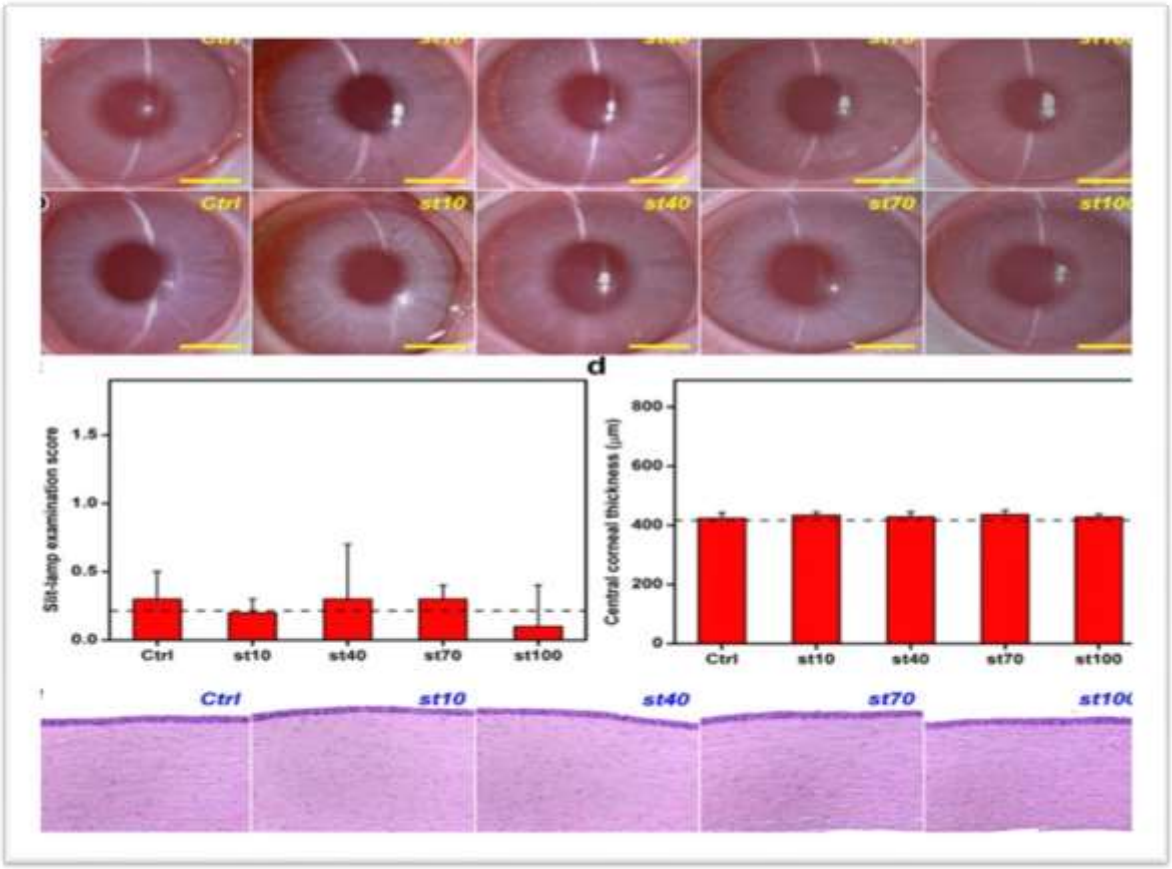
NPs are colloidal drug delivery systems ideally sized between 10 and 100 nm [. They are primarily separated into lipid and polymer NPs. Lipids, proteins, and natural or synthetic polymers such albumin, sodium alginate, chitosan, polylactide-coglycolide (PLGA), polylactic acid (PLA), and PCL make up NPs utilized in ocular preparations. Furthermore, the effective ocular absorption of NPs is significantly influenced by their surface charge. Catalytic nanoparticles (NPs) have a longer retention period on the ocular surface than anionic NPs because the surfaces of the cornea and conjunctiva are negatively charged.

With the following benefits, NPs have been widely employed to date to deliver medications to the targeted tissue in the eye:

1. smaller and less irritating;
2. sustained drug release to avoid repeated dosing; and
3. prevention of non-specific absorption.[25]

In one study, Bev, an anti-VEGF medication that is frequently used to treat DR, was delivered to the posterior chamber of the eye using chitosan-coated polylactide-glycolic acid nanoparticles (CS-PLGA NPs). With higher concentrations of Bev (above 22 ng/mL for 6 weeks) in the posterior ocular tissues, CS-PLGA NPs demonstrated superior permeability compared to the conventional drug solution, as demonstrated by pharmacokinetics and confocal laser scanning microscopy. When CS-PLGA NPs were injected subconjunctivally, as opposed to locally or intravitreally, the amount of VEGF in the retina was considerably decreased for a period of 12 weeks in the retinopathy model. As a result, CS-PLGA NPs may be utilized to target the retina for medication administration . Kim et al. used an iontophoretic technique to inject NPs containing latanoprost into the eye to treat glaucoma[26]Lipidic formulations are known to be less stable for sustained drug release compared to polymeric NPs. In an effort to improve the stability of nanocarriers, the addition of polymers to lipidic NP formulations has garnered significant attention recently [16]. Schnichels et al. studied lipid DNA NPs functionalized for brimonidine loading via hydrophobic interactions with double-stranded micelles and particular aptamers. In live animals, both NP kinds effectively decreased IOP. Compared to the mice treated with the original brimonidine (36%, SEM: ± 3%), an overall IOP reduction was found in 74% (SEM: ± 3%) and 54% (SEM: ± 1%) of the animals treated with two types of DNA NPs once daily for five weeks. Crucially, brimonidine-loaded NPs demonstrated increased efficacy and no harm. To sum up, these medication distribution methods.[27]

Figure05 ; The slit-lamp biomicroscope captured representative pictures of rabbit eyes following intracameral administration of BSS buffer (Ctrl group) or pilocarpine-loaded HPLA NP (st10, st40, st70, and st100) dispersions at 0 (a) and 56 (b) days. c Central corneal thickness at 56 days; d Slit-lamp examination scores at 56 days. e The histology of the corneal tissues after 56 day



NANO SUSPENSIONS:-

Only submicron colloidal dispersions of medication nanocrystals make up the nanosuspension. One of the most promising methods for delivering poorly soluble active components is to surround it with stabilizers. A carrier material is not necessary for nanosuspension, in contrast to traditional matrix-framed nano-systems. It is often stabilized by surfactants or polymers and includes only 100% pure medication NPs in the nanometer range . Increased residence time, prolonged drug release, and improved drug solubility are among its benefits.

Using an ion-pairing technique, Josyula et al. created an insoluble moxifloxacin–pamoate (MOX-PAM) complex, which was then developed into mucus-penetrating nanosuspension eye drops (MOX-PAM NS) to increase the bioavailability of moxifloxacin hydrochloride. When compared to the commercial formulation of Vigamox® in healthy rats, MOX-PAM NS markedly improved ocular medication absorption.[28]

Future aspects of Occular drug delivery system[29] :-

1. **Nanotechnology Enhancements**:
   - **Nano-sized drug carriers**: Utilization of nanoparticles, liposomes, and dendrimers to improve the penetration and retention of drugs in the ocular tissues.
   - **Solid lipid nanoparticles and nanostructured lipid carriers**: These offer advantages in terms of controlled release and enhanced stability of the drug within ocular environments.
2. **Biodegradable Implants**:
   - Longer-term drug release can be achieved through biodegradable polymeric implants that dissolve over time, reducing the need for frequent dosing and potentially improving patient compliance.
3. **Hydrogels**:
   - Hydrogels that respond to environmental stimuli (such as temperature and pH) can provide sustained and controlled drug release directly to the eye, improving the bioavailability and efficacy of treatments.
4. **Targeted Drug Delivery**:
   - Development of targeting ligands that can direct drugs specifically to diseased cells or tissues in the eye, thereby maximizing therapeutic effects and minimizing side effects.
5. **Gene Therapy**:
   - Techniques such as CRISPR and RNA interference could be utilized to correct genetic defects or to downregulate the expression of genes involved in ocular diseases, providing a foundational shift in how conditions like retinitis pigmentosa or age-related macular degeneration are treated.
6. **Smart Contact Lenses**:
   - Integration of sensors and drug reservoirs into contact lenses for on-demand drug release triggered by sensors that detect changes in tear fluid composition or eye movement patterns.
7. **3D Printing Technology**:
   - Customized ocular drug delivery devices, such as personalized ocular inserts or implants, can be fabricated using 3D printing technology to fit the specific anatomical requirements of individual patients.
8. **Mucoadhesive Systems**:
   - Development of mucoadhesive drops or films that can prolong the residence time of the drug on the ocular surface, enhancing drug absorption and effectiveness.
9. **Transscleral Delivery**:
   - Exploring non-invasive methods for delivering drugs across the sclera directly to the posterior segment of the eye to treat conditions like diabetic retinopathy and retinal vein occlusion.
10. **Electro-responsive Drug Delivery Systems**:
    - Devices that use electrical impulses to control the release of drugs, offering precise dosing capabilities and the potential to activate only when needed.
11. **Micro-Needles**:

- Minimally invasive patches equipped with tiny needles capable of delivering drugs into the ocular tissues with minimal discomfort and improved drug absorption profiles.

12. **Regulatory and Safety Aspects**:

- Enhanced focus on the regulatory pathways for approving advanced ocular drug delivery systems, ensuring theirsafety and efficacy through rigorous clinical trials

CONCLUSION[30] :-

For many years, ocular scientists have faced a significant obstacle in the form of drug delivery to specific ocular tissues. Using traditional formulations of medication solutions as topical drops had some disadvantages that led to the development of alternative carrier systems for ocular delivery. A great deal of work is being done in the field of ocular research to create innovative drug delivery systems that are safe and acceptable to patients. Researchers are working very hard right now to enhance traditional formulations' in vivo performance. On the other hand, ocular scientists are becoming increasingly interested in the novel methods, tools, and uses of nanotechnology in medication administration. Drug molecules are administered by invasive, non-invasive, or minimally invasive methods by being encased in nanoscale carrier systems or devices. Numerous nanotechnology-based carrier systems, including liposomes, nanoparticles, nanomicelles, nanosuspensions, and dendrimers, are being produced and extensively researched. Only a small number of them are used in clinical settings and are produced on a huge commercial basis. The body of the patient benefits from nanotechnology by experiencing less drug-induced toxicities and visual loss. Additionally, when targeting moieties are employed, these nanocarriers/devices improve specificity, prolong drug release, and assist in lowering dose frequency. However, after a non-invasive method of medication administration, a carrier system that could reach targeted ocular tissue—including the tissues in the rear of the eye—still has to be developed. A topical drop formulation that maintains a high precorneal residence time,

prevents non-specific drug tissue accumulation, and delivers therapeutic drug levels into targeted ocular tissue (both anterior and posterior) is anticipated as a result of the current pace of ocular research and efforts.

REFERENCES:-

1. Bourlais CL, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems--recent advances. Prog Retin Eye Res. 1998;17:33–58.doi: 10.1016/S1350-9462(97)00002-5
2. Gulsen D, Chauhan A. Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci. 2004;45:2342–2347. doi: 10.1167/iovs.03-0959.
3. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. AAPS J. 2010;12:348–360. doi: 10.1208/s12248-010-9183-3
4. 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
5. Gallarate M, Chirio D, Bussano R, Peira E, Battaglia L, Baratta F, Trotta M. Development of O/W nanoemulsions for ophthalmic administration of timolol. Int J Pharm. 2013;440:126–134. doi: 10.1016/j.ijpharm.2012.10.015.
6. Gunda S, Hariharan S, Mitra AK. Corneal absorption and anterior chamber pharmacokinetics of dipeptide monoester prodrugs of ganciclovir (GCV): in vivo comparative evaluation of these prodrugs with Val-GCV and GCV in rabbits. J Ocul Pharmacol Ther. 2006;22:465–476. doi: 10.1089/jop.2006.22.465.
7. Schoenwald RD. Ocular drug delivery. Pharmacokinetic considerations. Clin Pharmacokinet. 1990;18:255–269. doi: 10.2165/00003088-199018040-00001
8. Vaka SR, Sammeta SM, Day LB, Murthy SN. Transcorneal iontophoresis for delivery of ciprofloxacin hydrochloride. Curr Eye Res. 2008;33:661–667. doi: 10.1080/02713680802270945
9. Tirucherai GS, Mitra AK. Effect of hydroxypropyl beta cyclodextrin complexation on aqueous solubility, stability, and corneal permeation of acyl ester prodrugs of ganciclovir. AAPS PharmSciTech. 2003;4:E45. doi: 10.1208/pt040345
10. Meseguer G, Buri P, Plazonnet B, Rozier A, Gurny R. Gamma scintigraphic comparison of eyedrops containing pilocarpine in healthy volunteers. J Ocul Pharmacol Ther. 1996;12 :481–488. doi: 10.1089/jop.1996.12.481.
11. Gebhardt BM, Varnell ED, Kaufman HE. Cyclosporine in collagen particles: corneal penetration and suppression of allograft rejection. J Ocul Pharmacol Ther. 1995;11:509–517. doi: 10.1089/jop.1995.11.509.
12. J Ocul Pharmacol Ther. 1995;11:509–517. doi: 10.1089/jop.1995.11.509 Gebhardt BM, Varnell ED, Kaufman HE. Cyclosporine in collagen particles: corneal penetration and suppression of allograft rejection
13. van der Bijl P, van Eyk AD, Meyer D. Effects of three penetration enhancers on transcorneal permeation of cyclosporine. Cornea. 2001;20:505–508.doi: 10.1097/00003226-200107000-00013.

14. Burgalassi S, Chetoni P, Monti D, Saettone MF. Cytotoxicity of potential ocular permeation enhancers evaluated on rabbit and human corneal epithelial cell lines. Toxicol Lett. 2001;122:1–8. doi: 10.1016/S0378-4274(01)00261-2

15. Keister JC, Cooper ER, Missel PJ, Lang JC, Hager DF. Limits on optimizing ocular drug delivery. J Pharm Sci. 1991;80:50–53. doi: 10.1002/jps.2600800113.

16. Hornof MD, Bernkop-Schnürch A. In vitro evaluation of the permeation enhancing effect of polycarbophil-cysteine conjugates on the cornea of rabbits. J Pharm Sci. 2002;91:2588–2592. doi: 10.1002/jps.10258.

17. Kurz D, Ciulla TA. Novel approaches for retinal drug delivery. Ophthalmol Clin North Am. 2002;15:405–410. doi: 10.1016/S0896-1549(02)00034-2

18. Cabrera FJ, Wang DC, Reddy K, Acharya G, Shin CS. Challenges and opportunities for drug delivery to the posterior of the eye. Drug Discov Today. 2019;24(8):1679–84.

19. Jumelle C, Gholizadeh S, Annabi N, Dana R. Advances and limitations of drug delivery systems formulated as eye drops. J Control Release. 2020;321:1–22..

20. Ahmed S, Amin MM, Sayed S. Ocular drug delivery: a comprehensive review. AAPS PharmSciTech. 2023;24(2):66.

21. Al-Kinani AA, Zidan G, Elsaid N, Seyfoddin A, Alani AWG, Alany RG. Ophthalmic gels: past, present and future. Adv Drug Deliv Rev. 2018;126:113–26.

22. holizadeh S, Wang Z, Chen X, Dana R, Annabi N. Advanced nanodelivery platforms for topical ophthalmic drug delivery. Drug Discov Today. 2021;26(6):1437–49.

23. Onugwu AL, Nwagwu CS, Onugwu OS, et al. Nanotechnology based drug delivery systems for the treatment of anterior segment eye diseases. J Control Release. 2023;354:465–88

24. Kang-Mieler JJ, Rudeen KM, Liu W, Mieler WF. Advances in ocular drug delivery systems. Eye (Lond). 2020;34(8):1371–9

25. Vaneev A, Tikhomirova V, Chesnokova N, et al. Nanotechnology for topical drug delivery to the anterior segment of the eye. Int J Mol Sci. 2021;22(22):12368

26. Gupta A, Kafetzis KN, Tagalakis AD, Yu-Wai-Man C. RNA therapeutics in ophthalmology—translation to clinical trials. Exp Eye Res. 2021;205:108482.

27. Patel SR, Lin AS, Edelhauser HF, Prausnitz MR. Suprachoroidal drug delivery to the back of the eye using hollow microneedles. Pharm Res. 2011;28:166–176. doi: 10.1007/s11095-010-0271-y.

28. . Jiang J, Moore JS, Edelhauser HF, Prausnitz MR. Intra-scleral drug delivery to the eye using hollow microneedles. Pharm Res. 2009;26:395–403. doi: 10.1007/s11095-008-9756-3.

29. Del Amo EM, Urtti A. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. Drug Discov Today. 2008;13:135–143. doi: 10.1016/j.drudis.2007.11.002.

30. Heller J. Controlled drug release from monolithic systems. In: Saettone MF, Bucci G, Speiser P, editors. Ophthalmic Drug Delivery, Biopharmaceutical, Technological and Clinical Aspects, Fidia Research Sereis. Vol. 11. Padua: Liviana Press; 1987. p. 179- 89