



Short Review Article On Quality Control For Ophthalmic Prepration

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ABSTRACT

Because of its distinct anatomy and physiology, ocular medication administration presents difficulties, such as efflux pumps and static and dynamic barriers. The development of transporter- targeted medication delivery and the identification of influx transporters have accelerated. To maintain medication levels at the target region, several drug delivery techniques have been developed, including fibrin sealant-based methods and bioadhesive gels. Drug delivery may be enhanced by topical application for posterior segment administration and noninvasive sustained drug delivery methods. 90% of ophthalmic medicines are topical, and they are sterile liquid, semi- solid, or solid solutions utilized in the pharmaceutical and scientific domains to explain critical conditions. The research discusses sterility concerns, looks at the action of different preservatives, and investigates the physical and chemical elements affecting ophthalmic formulations. As ophthalmic preservatives, chlorocresol, chlorbutol, benzalkonium chloride, and chlorhexidine are recommended. For ophthalmic preparations to remain functional, they must be protected from physical, chemical, and biological alterations. When creating these preparations, chemists need to take into account variables including tonicity, pH, stability, viscosity, and sterility. The report suggests more research on preservation and sterility against microorganisms.

Keywords:- Topical ophthalmic , semisolid ophthalmic , solid ophthalmic , Ophthalmic delivery system.

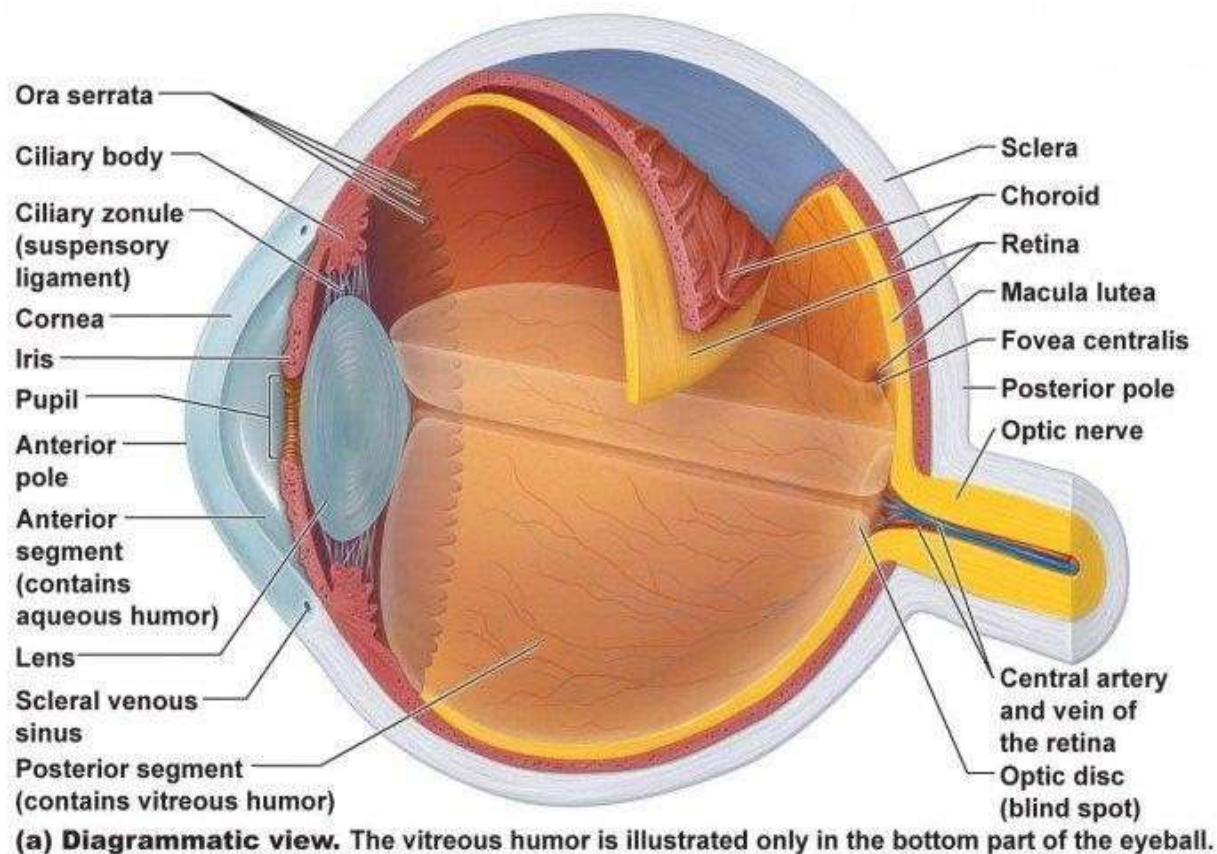
INTRODUCTION

The eye is a special organ with special medication disposition properties, topical administration is recommended for conditions affecting the eyes. This is because active components must first pass through precorneal barriers, which impede their entry into the eye through the tear film and conjunctiva, before they can pass through the cornea's anatomical barrier. Because of the decreased bioavailability of drugs after application, ophthalmic drug formulations have been a significant area of pharmaceutical study for decades. These problems are exacerbated by the eye's intricate anatomical structure, small absorptive surface, low corneal transparency, lipophilicity of the corneal epithelium, metabolism, enzymolysis, drug bonding with tear fluid proteins, and defense mechanisms like blinking, tear formation, and tissue flow through the nasolacrimal duct. 50–75µl of conventional ophthalmic solution is produced each drop, and the contact time is often less

than one to two minutes for implanted solutions. Ophthalmic drugs are available in a number of dosage forms, including as buffered solutions and suspensions. To optimize drug delivery, a variety of drug delivery systems (CDDS) are employed, including as erodible or non-erodible inserts, colloidal suspensions, viscous gels, and polymers. For small and medium-sized peptides, the cornea offers more resistance to negatively charged molecules than to positively charged ones. The most common topical dose forms for ophthalmic medications are eye drops, which can be buffered, isotonic, aqueous solutions, or suspensions. Gels, ointments, liposomes, micro and nanoparticles, microspheres, ocular minitables, films, or inserts are some of the several forms in which ophthalmic CDDS are manufactured. Polymers, viscous gels, colloidal suspensions, and erodible or non-erodible inserts can all be employed to maximize drug delivery. For small and medium-sized peptides, the cornea provides better resistance to negatively charged substances than to positively charged ones in bioadhesive systems such as suspensions of microparticles or polymeric solutions.

ANATOMY OF EYE

Cornea, conjunctiva, iris, ciliary body, aqueous humor, and lens make up anterior portion of the human eye, which is separated from the posterior section. The cornea, the most transparent membrane on the outside, is fed by limbal blood capillaries and aqueous fluid but lacks a blood supply. Pigmented epithelium cells and circular muscles make up iris, the colorful part of eye that controls light intake. Shape of the lens is controlled by ciliary body, ring-shaped muscle that is connected iris. Lens is a flexible, crystalline structure that is held aloft by zonules from the ciliary muscles. By producing mucus and sticking to the tear film, the conjunctiva, a transparent mucous membrane that borders interior of the eyelids, lubricates eye. Primary barrier protecting internal organs is the sclera, a white covering that envelops the eyeball. Photoreceptor cells in the retina are nourished by the highly vascularized choroid that sits between the sclera. A multilayered sensory, light-sensitive tissue called the retina absorbs light rays and transforms this into electrical impulses are sent to the brain through the optic nerve. Jelly-like material that lies between the retina and lens is called vitreous humor.



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Routes of Administration

Ocular barriers, that are specific to a ocular anatomy and physiology, provide difficulties for ocular medication administration. It is challenging to provide the right dosage at the right location because of these obstacles. Drugs cannot enter the systemic circulation by ophthalmic medication administration, which is intended to treat local eye diseases. Optimization of localized drug administration to the eye has advanced. Achieving an adequate medication concentration inside the target region is challenging due to the eye's extensive and unique defensive systems. Because of these processes, conventional ocular medication delivery methods, like eye drops, have low bioavailability. The eye is impervious to external substances due to its morphology and physiology, which includes lachrymation, drainage by the nasolacrimal system, blood-retinal barriers, corneal impermeability, and the incapacity of non-corneal organs to absorb chemicals. Although these natural barriers are useful for keeping out unwanted substances, infections, and particles, they make it difficult to administer medications to the eyes.

Topical administration

When treating illnesses of anterior portion , topical administration are the recommended approach. This is frequently done using eye drops, ointments, gels, or emulsions. other layers of the cornea, conjunctiva, sclera, and other anterior segment tissues including iris and ciliary body are usually where these medications work. However, the bioavailability of these formulations may be adversely affected by anatomical barriers and precorneal variables. Opening and closing , tear film, tear turn-over, solution drainage, and induced lachrymation are some of these variables. About 30 μL of fluid may be found in the cul-de-sac, while the amount of the human tear is believed to be 7 μL . underneath 5% of the administered dosage reaches the intraocular tissues due to the short contact time with the absorptive membranes. Cornea is the first layer of the eye, serves as a

mechanical barrier to shield ocular tissues and restrict the passage of foreign chemicals.

Systemic Administration

The Drug delivery to anterior and posterior portions of eye is hampered by a blood-aqueous and blood-retinal barriers. Transporting molecules via a choroid into deeper retinal layers is difficult due to the blood-retina barrier, which limits medication penetration even with optimal systemic administration. Consequently, specialized targeting systems are required.

Oral Administration

Although oral administration has been investigated for a treatment of chronic retinal disorders, systemic adverse effects may arise due to its large doses and restricted accessibility. Therapeutic concentrations in the posterior segment have not been achieved with topical administration alone. Although oral administration is thought to be a noninvasive and patient-favored method, safety and toxicity factors need to be taken into account to guarantee a therapeutic effect in a eye.

Periocular and Intravitreal Administration

To get around inefficiency of topical and systemic delivery to a posterior region, periocular route—which involve subconjunctival, subtenons, retrobulbar, and peribulbar administration—is utilized. Because it avoids the conjunctival epithelial barrier, this method is less invasive than the intravitreal one and produces large concentrations in the retina and vitrea. Because molecules a injected directly into the vitreous, intravitreal injection has the benefit of supplying the vitreous and retina with larger quantities. Larger molecules are constrained while tiny molecules spread quickly in the vitreous, resulting in nonuniform medication distribution. This distribution are also influenced by the drug molecular weight and pathophysiological state. Shape and surface charge of the nanoparticles also affect their mobility in the vitreous.

Drug Applied To The Eye

A critical requirement for product sterility and ocular tissue sensitivity to irritation is shared by all ophthalmic dosage forms.

Solutions

When topical ophthalmic solutions' corneal contact length is extended by up to 20 centipoises, it causes tears and blinking and decreases the frequency of medicine application. Viscosity enhancers include synthetic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, polyacrylic acid, and cellulose derivatives. Modern techniques employ polymers with a semisolid consistency enabling simple injection and durable permanency. However, patients may find it challenging to follow treatment regimens because to the drawbacks of viscous and mucoadhesive formulations, such as blurring and an uncomfortable sticky feeling in the eye.

Suspension

Solid preparations known as ophthalmic suspensions lengthen a drug's ocular contact duration, resulting in a longer-lasting effect. They are employed the active component are unstable in solution or insoluble in the intended vehicle. To stop corneal irritation or scratching, the insoluble medication is micronized and used to

make suspensions. They are typically made by dispersing powdered medication that has been micronized in an appropriate aqueous medium. Drug particles remain in the conjunctival sac and produce sustained-release effect, ophthalmic suspensions are regarded as appropriate delivery mechanisms, especially for steroids. However, because of their relative insolubility, suspensions have the drawback of being unable to control the concentration of dissolved medication. For ocular medication administration, particle size in suspensions matters because an increase in Ocular bioavailability is improved by particle size. Reflex tearing, however, might result with particles larger than 10 μm . Particle size reduction often increases patient comfort and suspension formulation acceptance. Sterilization and the presence of non-irritating particles that do not aggregate into bigger ones while stored are essential for ophthalmic solutions. They need to be designed to avoid clumping together. Because sterilization may cause morphological changes or deterioration, manufacturing sterile suspensions can be difficult. For medications that are not very stable in liquid form, sterile powders for reconstitution are helpful. These have a longer shelf life than solutions or suspensions and can be produced by lyophilization in separate containers. Usually, the sterile powder comes with a separately packed sterile diluent.

Ointments

Ophthalmic ointments, which can be made sterilely via aseptic or terminal sterilization processes, are used to preserve eye health. Compared to saline solutions, these ointments have a melting point that is close to body temperature and a longer period of ocular contact. They are more difficult to make than suspensions, though, and can result in visual impairment when the base melts and penetrates the lens.

Gel

Mucoadhesive polymers used to make ophthalmic gels lengthen the duration of a drug's interaction with biological tissues by delivering an active component to the eye through bioadhesion. This enhances the bioavailability of the eyes. For the kinetics of drug release, the polymer selection is essential. Sodium alginate, carboxymethylcellulose, carbopol, and polycarbophil are a few bioadhesive polymers with different mucoadhesive properties. The kinetics of drug release from dosage form are greatly influenced by the polymer selection.

Emulsion

In order to achieve a consistent oil-in-water emulsion, topical ophthalmic emulsions are made by dissolving active chemicals in an oil phase, adding emulsifying agents, and then combining with water. Prior to or while charging, every process is sterilized. By reducing oil droplet size to sub-micron size, high-shear homogenation can increase the physical stability of oil emulsions. Little oil droplets should be evenly suspended in the final dose form.

Strips

In situations of dry eye, the production of tears is measured using ophthalmic strips, which are constructed of filter paper. They can be separately packed for sterility and impregnated with drugs such as rose bengal, lissamine green, and fluorescein sodium. Rose bengal staining degenerating epithelium in mucous filaments and the outer cornea, fluorescein sodium diagnosing abnormalities in the corneal epithelium, and lissamine green staining dry patches and damaged cells. Hard contact lens fitting and applanation tonometry are two applications for these strips.

Injection

Instead than addressing injections as a dosage form, this article concentrates on the proper physical form, such as a solution or suspension.

Insert

Solid dose forms called ophthalmic inserts and ocular systems are inserted into the cornea, lachrymal punctum, or conjunctival fornix. They fall into one of two categories: nonerodible (insoluble) or erodible (soluble). These tools improve ocular bioavailability, prevent the need for preservatives, and enable precise dosage administration. Drugs are released from soluble inserts in two stages: slowly when a gel layer develops on the insert's surface and quickly once tear fluid enters the system. Blurred vision may result from the solubilized components, however. Soluble inserts include gelling polymers and collagen shields. Eroderible inserts that dissolve in 12 to 24 hours can be made from bioerodible polymers such as polyesters, hypromellose, poly vinyl alcohol, and crosslinked gelatin derivatives. High inter- and intraindividual variability results from the erosion rate's dependence on the physiological environment. In profiles of drug release. Insoluble inserts release medications over extended periods of time and feature a reservoir or matrix structure. The sense of a foreign thing in the eye, the significant danger of unintentional ejection, and handling challenges restrict their practical usage despite their therapeutic benefits.

Drug Product Quality Tests (Universal Test)

A qualitative description of the drug product, including its color, clarity, and look, is included in the manufacturer's specification. A quantitative process can be required if color changes while being stored.

- Identification
- Assay
- Impurities
- pH
- Tonicity
- Foreign Matter
- Sterilization & Antimicrobial Preservation
- Bacterial toxins
- Consistency Dosage Units
- Container material
- Container Integrity

Drug Product Quality Tests (Specific Tests)

- Thickness
- Antioxidative agents
- Redispersability
- Particle dimension
- Particle Size Dispersion

How to use of eye drops

➤ Lie down flat

- **Just one drop**
- **Close your eyes for 2-3 minutes**
- **After three minutes fully absorb in the eye**

Precautions using eye drops

1. Make sure to read the label's expiration date and adhere to the bottle's directions before using eye drops.
2. Use soap and water to wash your hands, then pat dry with a fresh towel.
3. If your doctor or the label instructs you to shake the bottle, do so.
4. Keep your fingertips away from the bottle's tip and place the top on a spotless surface.
5. One drop should be gently squeezed into the lower eyelid, and any extra fluid should be wiped away with a fresh tissue.
6. Because eye drops might harbor bacteria, avoid letting the tip come into contact with any area of your eye or lashes.
7. After applying the eye drop, softly close your eyes and push lightly on the inner corner of your eye for 30 seconds to stop fluid from leaking down the nasal canal and into your throat and nose.
8. Before using medicated eye drops, take out your contact lenses and wait fifteen minutes before putting them back in.
9. If you're using more than one kind of eye drop, wait ten minutes after the first drop before applying the second.
10. To avoid infection, avoid wiping the dropper tip with anything.
11. usage, screw it on firmly and replace the cap.
12. To get rid of any remaining medicine, wash your hands.
13. Sharing eye drops with other people might transmit infections and viruses.
14. Follow the label's storage instructions, or ask your doctor or pharmacist how long it's safe to use the bottle after opening.

EVALUATION OF OPHTHALMIC PRODUCTS

❖ **Sterility Test**

- Membrane filtration
- Culture media

❖ **Clarity test**

- Visual examination
- Instrumental method

❖ **Leakage test**

Conclusion

Improvements in drug delivery systems for the anterior and posterior eye segments over the last ten years have decreased dosage frequency, total drug loading, and side effects while increasing drug residence length, permeability, and bioavailability. Because of the anatomy of the eye, ocular medication delivery techniques are varied and intricate. Although topical eye drops are the most popular treatment method, they have disadvantages such as decreased patient compliance, limited corneal permeability, and tear drainage. Traditional ocular medication delivery methods, such as ocular emulsion, suspension, ointment, and polymeric gels, have been developed to increase therapeutic effectiveness. Furthermore, ocular inserts, liposomes, nanomicelles, and nanoparticles are being created to improve the safety and effectiveness of ocular medication administration. These systems still have a number of shortcomings, though. Future innovative solutions seek to address these problems while preserving patient compliance, safety, and efficacy. For ocular and formulation scientists, creating ocular drug delivery systems is still a major issue in spite of these obstacles.

REFERENCE

1. P. Pahuja, S. Arora, and P. Pawar, —Ocular drug delivery system: a reference to natural polymers,|| Expert Opinion on Drug Delivery, 2012; 9(7) : 837-861
2. S. Nisha and K. Deepak, —An insight to ophthalmic drug delivery system,|| International Journal of Pharmaceutical Studies Research, 2012; 3(2): 9–13.
3. R. Gaudana, J. Jwala, S. H. S. Boddu, and A. K. Mitra, —Recent perspectives in ocular drug delivery,|| Pharmaceutical Research, 2009; 26(5): 1197–1216.
4. A. Rajasekaran, K. S. G. A. Kumaran, J. P. Preetha, and K. Karthika, —A comparative review on conventional and advanced ocular drug delivery formulations,|| International Journal of PharmTech Research, 2010; 2(1): 668–674
5. P. Tangri and S. Khurana, —Basics of ocular drug delivery systems,|| International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011; 2(4): 1541–1552
6. International Conference on Harmonization, —Stability testing of new drug substances and products Q1A (R2),|| Federal Register, 2003; 68(225): 65717–65718.
7. Polish Pharmacopoeia, vol. 8, part 1, The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Warsaw, Poland, 2008.
8. S. Rathore and R. K. Nema, —An insight into ophthalmic drug delivery system,|| International Journal of Pharmaceutical Sciences and Drug Research, 2009; 1(1): 1–5.
9. United States Pharmacopeia (2013) USP 36–NF 31, Antimicrobial Effectiveness Testing 51, Rockville, MD: USP: 54–55.
10. Gaudana, R., Ananthula, H.K., Parenky, A., Mitra, A.K. Ocular drug delivery. AAPS J., 2010; 12(3): 348–360.
11. United States Pharmacopeial Convention. (2011) Pharmaceutical compounding— sterile preparations. In: U.S. Pharmacopeia 34/National Formulary 29. Rockville, Md: United States Pharmacopeial Convention.
12. Euradlex. (2014). The Rules Governing Medicinal Products in the European Community, Annex 1, published by the European Commission: Brussels.
13. Food and Drug Administration. (2004). Guideline on Sterile Drug Products Produced by Aseptic Processing FDA, Rockville, MD: USA.
14. United States Pharmacopeia (2012). General Chapter Microbiological Control and Monitoring of Aseptic Processing Environments, USP 35–NF 30, United States Pharmacopeia: Bethesda, MD: USA.
15. Aseptic Processing of Health Care Products (1997). 1 - General Requirements. ISO 13408-1, International Standards Organization: Geneva, Switzerland.

16. ISO 14698-1. (2003). Cleanrooms and associated controlled environments– Biocontamination Control: Part 1: _General principles and methods. Geneva, Switzerland, International Organisation for Standardisation: Geneva, Switzerland.
17. Patel, A. Ocular Drug Delivery Systems: An Overview. *World J. Pharmacol.* 2013, 2 (2), 47.
18. Agrahari, V.; Mandal, A.; Agrahari, V.; Trinh, H. M.; Joseph, M.; Ray, A.; Hadji, H.; Mitra, R.; Pal, D.; Mitra, A. K. A Comprehensive Insight on Ocular Pharmacokinetics. *Drug Delivery Transl. Res.* 2016, 6, 735–754.
19. Lang, J. C. Ocular Drug Delivery Conventional Ocular Formulations. *Adv. Drug Delivery Rev.* 1995, 16, 39–43.
20. Pal Kaur, I.; Kanwar, M. Ocular Preparations: The Formulation Approach. *Drug Dev. Ind. Pharm.* 2002, 28 (5), 473–493.
21. Le Boursais, C.; Acar, L.; Zia, H.; Sado, P. A.; Needham, T.; Leverge, R. Ophthalmic Drug Delivery Systems - Recent Advances. *Prog. Retinal Eye Res.* 1998, 17, 33–58.
22. Järvinen, K.; Järvinen, T.; Urtti, A. Ocular Absorption Following Topical Delivery. *Adv. Drug Delivery Rev.* 1995, 16, 3–19.
23. Gorantla, S.; Rapalli, V. K.; Waghule, T.; Singh, P. P.; Dubey, S. K.; Saha, R. N.; Singhvi, G. Nanocarriers for Ocular Drug Delivery: Current Status and Translational Opportunity. *RSC Adv.* 2020, 10, 27835–27855.
24. Souto, E. B.; Dias-Ferreira, J.; López-Machado, A.; Ettcheto, M.; Cano, A.; Espuny, A. C.; Espina, M.; Garcia, M. L.; Sánchez-López, E. Advanced Formulation Approaches for Ocular Drug Delivery: State-of-the-Art and Recent Patents. *Pharmaceutics* 2019, 11, 460.
25. Lallemand, F.; Daull, P.; Benita, S.; Buggage, R.; Garrigue, J.-S. Successfully Improving Ocular Drug Delivery Using the Cationic Nanoemulsion, Novasorb. *J. Drug Delivery* 2012, 2012, 1–16.
26. Khiev, D.; Mohamed, Z. A.; Vichare, R.; Paulson, R.; Bhatia, S.; Mohapatra, S.; Lobo, G. P.; Valapala, M.; Kerur, N.; Passaglia, C. L.; Mohapatra, S. S.; Biswal, M. R. Emerging Nano-Formulations and Nanomedicines Applications for Ocular Drug Delivery. *Nanomaterials* 2021, 11 (1), 173.
27. Reimondez-Troitino, S.; Csaba, N.; Alonso, M.J.; de la Fuente, M. Nanotherapies for the Treatment of Ocular Diseases. *Eur. J. Pharm. Biopharm.* 2015, 95 (Pt B), 279–293.
28. Yeu, E.; Silverstein, S.; Guillon, M.; Schulze, M.-M.; Galarreta, D.; Srinivasan, S.; Manoj, V. Efficacy and Safety of Phospholipid Nanoemulsion-Based Ocular Lubricant for the Management of Various Subtypes of Dry Eye Disease: A Phase IV, Multicenter Trial. *Clin. Ophthalmol.* 2020, 14, 2561.
29. Choradiya, B. R.; Patil, S. B. A Comprehensive Review on Nanoemulsion as an Ophthalmic Drug Delivery System. *J. Mol. Liq.* 2021, 339, 116751.
30. Solans, C.; Izquierdo, P.; Nolla, J.; Azemar, N.; Garcia-Celma, M. J. Nano-Emulsions. *Curr. Opin. Colloid Interface Sci.* 2005, 10, 102–110.
31. Gutiérrez, J. M.; González, C.; Maestro, A.; Sole, I.; Pey, C. M.; Nolla, J. Nano- Emulsions: New Applications and Optimization of Their Preparation. *Curr. Opin. Colloid Interface Sci.* 2008, 13, 245– 251
32. R.M.Mehta, *Pharmaceutics II Vallabh Prakashan, Ophthalmic Products*, page no. (273- 285)
33. D.K Tripathi —*Pharmaceutics Basic Principle and Formulation, Sterile Preparation in Ophthalmic Ointment*, page no.(286-304)
34. David Jones, —*FASTtrack, Pharmaceutics-Dosage Form and Design, Ocular dosage form*, page no.(135-150)
35. Gan L, Wang J, Jiang M, Bartlett H, Ouyang D, Eperjesi F, Liu J. Gan, Y. Recent advances in topical ophthalmic drug delivery with lipid-based nanocarriers. *Drug Discov. Today* 2013; 18, 290-297.
36. Le Boursais C, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems—Recent advances. *Prog. Retin. Eye Res.* 1998; 17, 33–58.
37. Achouri D, Alhanout K, Piccerelle P, Andrieu V. Recent advances in ocular drug delivery. *Drug*

Dev. Ind. Pharm. 2013; 39, 1599–1617.

38. Yellepeddi VK, Palakurthi S. Recent advances in topical ocular drug delivery. *J. Ocul. Pharmacol. Ther. Off. J. Assoc. Ocul. Pharmacol. Ther.* 2016; 32, 67–82.

39. Kalhapure RS, Suleman N, Mocktar C, Seedat N, Govender T. Nanoengineered drug delivery systems for enhancing antibiotic therapy. *J. Pharm. Sci.* 2015; 104, 872–905.

40. Sachin P and Himansu C. Current trends for ophthalmic drug delivery: A review. *International Journal of Pharmacy and Biological Sciences (IJPBS)*. 2014; vol 4, 2, 162–173.

41. Remington LA. *Clinical anatomy and physiology of the visual system*, 3rd ed.; Elsevier/Butterworth Heinemann: St. Louis, MO, USA, 2012.

42. Rathbone MJ, Hadgraft J, Roberts MS, Lane ME. *Modified-release drug delivery technology (Drugs and the pharmaceutical sciences)*, 2nd ed.; Informa Healthcare: New York, NY, USA, 2008; Volume 2, ISBN 978-1- 4200-4435-5.

43. Occhiutto ML, Freitas FR, Maranhao RC, Costa VP. Breakdown of the Blood-Ocular Barrier as a Strategy for the Systemic Use of Nanosystems. *Pharmaceutics* 2012; 4, 252– 275.

44. Cunha-Vaz J. The blood-ocular barriers. *Surv. Ophthalmol.* 1979; 23, 279–296.

45. Loftsson T, Ansson ES. Cyclodextrins in eye drop formulations: enhanced topical delivery of corticosteroids to the eye. 2002; *Acta Ophthalmologica Scandinavica*, vol.80, no.2, pp.144–150.

46. Patel, A. Ocular drug delivery systems: An overview. *World J. Pharmacol.* 2013, 2, 47. [CrossRef] [PubMed]

47. Pisella, P.J.; Fillacier, K.; Elena, P.P.; Debbasch, C.; Baudouin, C. Comparison of the effects of preserved and unpreserved formulations of timolol on the ocular surface of albino rabbits. *Ophthalmic Res.* 2000, 32, 3–8.

48. Van der Bijl, P.; van Eyk, A.D.; Meyer, D. Effects of three penetration enhancers on transcorneal permeation of cyclosporine. *Cornea* 2001, 20, 505–508.