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A Comprehensive Review on Non-Invasive Ocular Drug Delivery Systems

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ABSTRACT

Among the various routes of drug delivery, ocular drug delivery is one of the most interesting and challenging tasks. Administration of drugs to the ocular region with conventional delivery systems leads to short contact time of the drugs on the epithelium and fast elimination takes place. This transient residence time leads to poor bioavailability of drugs. Ocular dosage forms include eyedrops, suspensions, gels, ointments, implants, injections, lenses, and so on in which most of them are invasive. In this review, we briefly discussed non-invasive drug delivery systems to overcome this state of complexity. Non-invasive drug delivery systems include eyedrops containing novel drug delivery systems like nanoparticles, liposomes, nanosuspensions, cubosomes, niosomes, etc., and Iontophoresis. Hence, these produce a painless drug delivery involving prolonged drug delivery and increased drug bioavailability.

INTRODUCTION:

Administration of drugs to the ocular region with conventional delivery systems leads to short contact time of the formulations and fast elimination of drugs. This transient residence time involves poor bioavailability of drugs which can be explained by the tear production, non-productive absorption, and impermeability of corneal epithelium. 1- 5% of the active ingredient applied to the surface of the eye penetrates the cornea and sclera and reaches intraocular [1]. This is an advantage for ocular drug delivery in that once the drug is successfully delivered to the intraocular tissues the drug is not likely to be cleared to the systemic circulation, which may cause undesirable adverse effects [2]. A normal eyedropper delivers 25-56µL of the topical formulation with an average volume of 39µL. However, an eye can transiently hold up to 30µL, and the rest is lost either by nasolachrymal drainage or reflex blinking, significantly decreasing the overall drug available for therapeutic action [3]. The main objective of therapeutic ophthalmology is to increase the ocular residence time of the drug instilled in the ocular tissues and to decrease the frequency of administration. It should be easy to handle and manufacture, remain stable over the whole ocular surface, biodegradable and biocompatible, have a long shelf life, and be free of toxic side effects [1]. Alternative delivery methods such as intravitreal or periocular injections have been developed to improve the bioavailability of the therapeutic agents, but due to the invasive nature side effects are observed. The challenges affiliated with these conventional methods of ocular drug delivery have led scientists to contribute significant effort into developing advanced drug delivery systems that provide targeted therapy with increased bioavailability [3]. These efforts lead to the development of novel drug delivery dosage forms such as nanoparticles, liposomes, ocuserts, mucoadhesive formulations, emulsions, ointments, suspensions, aqueous gels, nano micelles, dendrimers, implants, microneedles, etc [4]. Targeted drug delivery and controlled release aim to manage better drug pharmacokinetics, pharmacodynamics, non- specific toxicity, immunogenicity, and biorecognition of systems in the quest for improved efficacy [5].

Delivery of drug via nanotechnology-based product fulfills mainly three objectives as follows:

a) Enhances drug permeation

b) Controls the release of drug

c) Targets drug [6]

These controlled drug delivery systems offer many advantages over conventional dosage forms in terms of improving drug bioavailability, reducing toxicity, and decreasing dosage frequency [7]. Applications of nanotechnology can be very exciting in the treatment of a gamut of diseases affecting the anterior as well as the posterior segment of the eye [8]. Upcoming of nanotechnologies like nanodiagnostics, nanomedicine, and nanoimaging can be utilized to explore the frontiers of ocular drug delivery and therapy [2].

Novel Drug Delivery Systems in Ocular Drug Delivery

To improve the bioavailability of topically administered drugs, novel drug delivery systems are being investigated which possess high precorneal residence time, sustain the drug release, and enhance the ocular bioavailability of therapeutics [9]. A novel drug delivery system needs to demonstrate sufficient shelf stability, preferably at least 18 months, to be commercially viable. Finally, as the human eye is a delicate organ, novel formulations or delivery devices aimed at improving bioavailability or patient compliance must not cause excessive irritation such as stinging, foreign body sensation, or vision blurring. Given these constraints, even though the science for drug delivery and ocular pharmacokinetics has advanced a great deal to allow the innovative design of new systems, improvement over the years has been incremental without breakthroughs [10]. Most of the formulation efforts aim at maximizing ocular drug absorption through prolongation of the drug residence time in the cornea and conjunctival sac, as well as to slow drug release from the delivery system and minimize precorneal drug loss [11]. Novel ophthalmic delivery systems propose the use of many excipients to increase the viscosity or the bio adhesion of the product. Nanocarrier delivery systems demonstrate enhanced drug permeation and prolonged drug release [12]. The most recent advancements of the ocular drug delivery systems provide the delivery of genes and proteins to the internal structures which were once inaccessible and thus are of great importance in treating the diseases which are caused due to genetic mutation, failure in normal homeostasis, malignancy but also maintaining the physiological function of the eye [13]. Several Novel drug delivery systems such as Microemulsions, Nanosuspensions, Nanoparticles, Liposomes, Niosomes, Discomes, Dendrimers, Implants, Nanomicelles, Cubosomes, Microneedles, Nano wafers, Aqueous gels, and Insitu thermosensitive gels came into existence [14].

Liposomes

Liposomes are small artificial vesicles that can be produced from natural non- toxic phospholipids and cholesterol [15]. Phospholipids commonly used are phosphatidylcholine, phosphatidylserine, phosphatidic acid, sphingomyelins, and cardiolipins [16]. Liposomes are spherical vesicles consisting of one or more concentric layers of about 25-10000nm in diameter which is biocompatible, biodegradable made of natural lipids [17]. Due to the biphasic nature of liposomes, these can encapsulate both hydrophilic and/or lipophilic therapeutic agents in each compartment.

Niosomes

Niosomes are bilayered, nanosized vesicles made up of amphiphilic nonionic surfactants that are biodegradable, biocompatible, and non- immunogenic. They are chemically stable with 10 to 1000nm in size and are capable of incorporating both hydrophilic and lipophilic drugs [18]. An *ex vivo* study of transcorneal permeability reveals that niosomes can provide sustained drug delivery and improved corneal permeation. Therefore, niosomes can be considered as a safe option for sustained transcorneal drug delivery [19]. In niosomes, an aqueous solution of solute is entirely enclosed by a membrane that resulted from the organization of surfactant macromolecules as bilayers [20]. These are chemically more stable, are less toxic because of the non-ionic nature of the surfactants are easier to handle without special precautions, can improve the performance of the drug via better bioavailability and controlled delivery at a specific site [21].

Discomes

Discomes are large structures about 12-16µm derived from niosomes by the addition of non-ionic surfactant, which is Solulan C24. Discomes, when prepared, cause the surfactant to partition into the lipid bilayer, forming a large disc-like structure. Discomes have a longer residence time in the cul-de-sac and less systemic drainage due to their large size [22]. Discomes may act as potential drug delivery carriers as they are released drugs in a sustained manner at the ocular site [23].

Dendrimers

Dendrimers are three dimensional, highly branched, and tree-structured macromolecules that have nanoscale sizes due to their well-organized synthesis strategy [24]. These are encapsulated hydrophobic drug molecules since they possess internal empty cavities. Dendrimers have better water- solubility, bioavailability, and biocompatibility [25].

Nanoparticles

Nanoparticles are colloidal drug carriers with a size ranging from 10 to 1000nm. Drug loaded nanoparticles with size ranging from 50-400nm are considered versatile for ocular delivery [26]. Drug loaded nanoparticles can be nanocapsules or nanospheres. In nanocapsules, the drug is enclosed inside the polymeric shell while in nanospheres drug is uniformly distributed throughout the polymeric matrix [27].

Nanosuspensions

Nanosuspensions are sub-micron colloidal dispersions of poorly water-soluble drugs in a dispersion medium stabilized by surfactants or polymers. These consist of pure, poorly water-soluble drugs, suspended in an appropriate dispersion medium. Nanosuspensions usually contain a colloidal carrier such as a polymeric resin, which is inert, for enhancing drug solubility and bioavailability [28].

Nanomicelles

Nanomicelles are colloidal structured carrier systems that range from 5 to 200nm in size. They are made up of amphiphilic surfactant molecules that may be anionic, cationic, or zwitterionic, or deblock polymers. Micelles could be spherical, cylindrical, or star-shaped, depending on the molecular weight of the core and corona forming blocks [29].

Microemulsions

A microemulsion is a dispersion of water and oil stabilized by surfactants or co-surfactants to reduce the interfacial tension. Microemulsions are clear in appearance and thermodynamically stable ensuring a very long shelf-life. The drop size is ranging about 10-150nm which is 100nm. An oil-in-water type of microemulsion in the presence of a

surfactant or co-surfactant can increase corneal membrane permeability [30]. These formulations often provide sustained drug release thereby reducing the frequency of the drug administration.

Implants

Implants have been widely employed to extend the release of drugs in ocular fluids and tissues, particularly in the posterior segment. The ocular implants are classified as biodegradable and non- biodegradable devices [31]. Non- biodegradable implants can provide more accurate control of drug release than biodegradable polymers. Earlier Non-biodegradable polymers were used but they needed surgical procedures for insertion and removal. Presently biodegradable polymers such as polylactic acid are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs [32].

Cubosomes

Cubosomes are defined as nanoparticles of a liquid crystalline phase with cubic crystallographic symmetry formed by the self- assembly of amphiphilic or surfactant-like molecules. One of the most common surfactants used to make Cubosomes is monoglyceride glycerol monoolein (MO) identified as a non- toxic, biodegradable, and biocompatible material. Cubosomes were able to improve the ocular residence time and bioavailability of the drug in ocular tissue [33].

Nanowafers

Nanowafers are tiny circular discs or rectangular membranes containing an array of drug-loaded nano reservoirs applied to the ocular surface using a fingertip. They release the drug over a longer period, thereby increasing the therapeutic efficacy. During drug release, the nanowafers dissolve and fade away [34].

Gels

Ophthalmic gels have gained popularity as a replacement for ointment formulations as more synthetic, biocompatible polymers become available. Depending on how the gels are packaged and administered, their viscosities can vary between 1000 and 100,000 centipoises [35]. A common method for prolonging the ocular residence time of drugs and thus

increasing intracorneal diffuse is to increase solution viscosity which is by polymeric gels.

There are two groups:

1. Classical preformed gels

2. In- situ forming gels

Preformed gels can be defined as simple viscous solutions, which do not undergo any modification after administration.

In- situ forming gels are viscous liquids which undergo a sol-gel phase transition after exposure to the physiological conditions in the cul-de-sac, forming a viscoelastic gel [36].

Complications of Invasive drug delivery systems [37, 38]

- The highest risk of ocular complications is with the invasive intraocular drug delivery.
- In the case of Intravitreal, Periocular and subconjunctival injections repeated injections can cause pain, discomfort, Intraocular pressure increases, Intraocular bleeding, clouding.
- The major complication for intravitreal injection is endophthalmitis, hemorrhage, retinal detachment, and poor patient tolerance.
- Insertion of implants is invasive associated with ocular complications like retinal detachment, astigmatism, and intravitreal hemorrhage.
- These implants require surgery for harvest and remove.
- Injections containing microparticles, nanoparticles, and liposomes cause risks like vitreous clouding.
- One of the major complications of intravitreal injection is of inducing the stimulation of pathogenic immune responses, resulting in photoreceptor degeneration.
- In some cases, the intravitreal route results in an increased risk of cataract development.

Non-Invasive Ocular Drug delivery systems

Introduction

Even though the various drug delivery systems mentioned above offer numerous advantages over conventional drug therapy, nonetheless, they are not devoid of pitfalls, including poor patient compliance and difficulty of insertion in case of inserts sometimes resulting in tissue irritation and damage. Options available include modifying the formulation by suspensions, emulsions, or by increasing tissue permeability by iontophoresis. Designing non-invasive sustained drug delivery systems and exploring the feasibility of topical application to deliver drugs to the posterior segment may drastically improve drug delivery in the years to come [39].

Drug delivery systems include the following:

A). Eye drops

Topical installation is the most widely preferred non-invasive route of drug administration to treat diseases affecting the anterior segment. Drugs that are active at the eye or eye surface are widely administered in the form of Solutions, Emulsions, and Suspension. Generally, eye drops are used only for anterior segment disorders as adequate drug concentrations are not reached in the posterior tissues using this drug delivery method. Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity, and instilled volume can influence the retention of a solution in the eye. Less than 5% of the dose is absorbed after topical administration into the eye [23]. A normal eyedropper delivers 25-56 µL of the topical formulation with an average volume of 39 µL. However, an eye can transiently hold up to 30 µL, and the rest is lost either by nasolachrymal drainage or reflex blinking (5-7 blinks/ min), significantly decreasing the drug available for therapeutic action [28]. However, precorneal elimination caused by nasolacrimal drainage and high tear fluid turnover remains the major drawback of these drug delivery systems for topical application. Over the last decade, numerous drug delivery systems have been explored to overcome the limitation of conventional dosage forms [40]. Although the conventional solution and suspension are still the most frequently used dosage forms, several controlled drug delivery systems have been introduced to minimize 'peak and valley' effects and maintain drug concentration at an effective level for a prolonged period. Novel formulations such as liposomes, nanoparticles,

dendrimers, nanosuspensions, nanoemulsions, and niosomes were developed to enhance drug bioavailability and to minimize adverse effects [41]. The nanocarrier-drug complex can be administrated as eye drop solutions, requiring less frequent administration due to the high retention of the drugs, reducing the cost of administration, and increasing patient compliance. Zimmer and Kreuter have suggested that the sizes of administered particles for ophthalmic applications must be less than 10 µm to avoid the sensation of scratching upon administration [42].

1). Liposomes

Liposomes are microscopic vesicles composed of lipid bilayers surrounding aqueous compartments. These are biocompatible and biodegradable particles consisting of membrane-like lipid bilayers composed mainly of phospholipids [43].

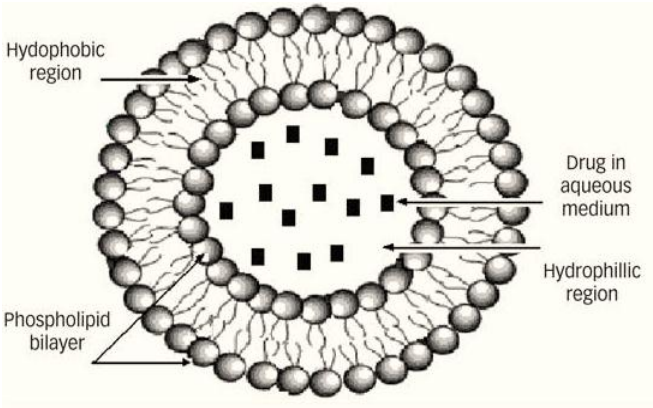

Figure No. 1: Diagrammatic representation of Liposomes

Phospholipids are amphiphilic having a hydrophilic head and a lipophilic tail. The major components of liposomes are lipids, water, drug, and electrolytes. It is one of the controlled drug delivery systems which are introduced to minimize **peak and valley effects** and maintain drug concentration at an effective level for a prolonged period. The behavior of liposomes as an ocular drug delivery system is because of their surface charge [41]. These liposomal formulations are favorable for the drugs having low solubility, low partition coefficient, high molecular weight, and poor absorption [44]. Positively charged liposomes are preferentially captured at the negatively charged corneal surface, compared to neutral or negatively charged liposomes. These positively charged liposomes are more effective in lowering intraocular pressure over a prolonged period [45]. The binding affinity of liposomes

to the cornea suggests that the liposome uptake by the cornea is greatest for positively charged liposomes, less for negatively charged liposomes, and least for neutral liposomes which states that the initial interaction between the corneal surface and liposomes is electrostatic. The findings suggest that liposomes enhance the corneal penetration of drugs which is adsorbed onto the corneal surface, with direct transfer of drugs from liposomes to epithelial cell membranes [46]. Habib et al. evaluated the clinical effect of a topical controlled release ophthalmic fluconazole liposomal formulation in rabbits, comparing its effect with fluconazole solution [47]. Although liposomes offer many advantages over eye drops and reduce the dosing frequency these possess short shelf-life, sterilization issues, and limited drug loading capacity which limit their use [2].

2). Nanoparticles

Nanoparticles are defined as particles with a diameter of <1 µm consisting of various biodegradable materials [48]. These nanoparticles can be divided into **nanospheres** in which the drug is uniformly and physically dispersed and **nanocapsules** are comprised of a central cavity surrounded by a polymeric membrane.

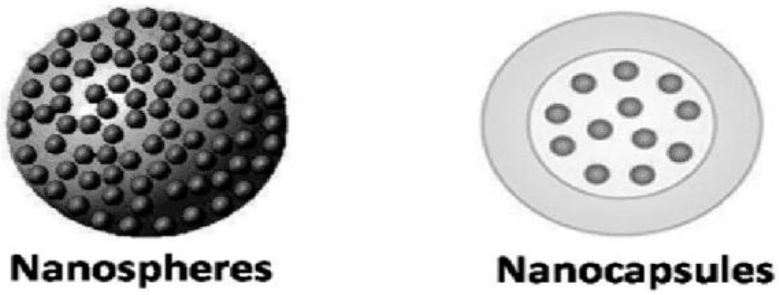

Figure No. 2: Diagrammatic representation Nanoparticles

Biodegradable polymers like Polylactides, polycyanoacrylate, natural polymers like Chitosan, gelatine, sodium alginate, and albumin can be used effectively for efficient drug delivery to the ocular tissues, which undergo hydrolysis in tears. Drug loaded nanoparticles with size ranging from 50 to 400 nm are stated as versatile for ocular drug delivery as they can pass through the physiological barriers and deliver the drug to specific cells, either by ligand-mediated or passive targeting mechanisms [26]. Nanoparticles loaded with Ibuprofen were able to improve the bioavailability of the drug in the aqueous humor of rabbit eyes comparatively with Ibuprofen aqueous eye drops [49]. These particles provide sustained

release and prolonged therapeutic activity when retained in a cul-de-sac and the drug which is entrapped must be released at an appropriate rate. Pre-clinical experiments demonstrated the presence of nanoparticles in retinal pigment epithelial (**RPE**) cells [50-51]. This is due to the phagocytic capacity of RPE indicating that nanoparticles could be used to treat the retinal disorders. Although nanoparticles provide a prolonged and comfortable ocular drug delivery system, their use also involves some problems such as tissue accumulation, an aggregation that blocks the lachrymal drainage punctum, and impairment of tear film recycling [52].

3). Dendrimers

Dendrimers are polymeric macromolecules with highly branched structures of a star shape. These are nano constructs with physical and chemical properties such as higher encapsulation ability, water-solubility, monodispersity, and surface functional groups. The ability to functionalize these surface groups makes them suitable to deliver both hydrophilic and hydrophobic groups [53]. Bioadhesive polymers such as poly (acrylic acid) are used to improve the ocular drug delivery by prolonging contact time for better absorption. But the blurring of vision and formation of the veil in the precorneal area, leading to vision loss, limits the use of the polymer [54].To overcome this limitation dendrimers consisting of poly (amidoamine) were introduced.

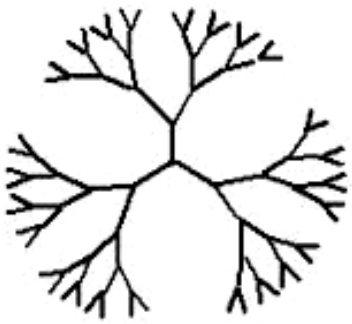

Figure No. 3: Diagrammatic representation of Dendrimers

PAMAM which is also known as poly (amidoamine) is one of the most widely used dendrimers for an ocular drug delivery system. Vandamme et al. studied the effect of tropicamide and pilocarpine nitrate using PAMAM dendrimers and found improved bioavailability due to better Bioadhesion and sustained drug release [55]. Some animal studies stated that a blurred vision was observed after the administration of dendrimers on the

ocular surface [56].

4) Nanosuspensions

Nanosuspensions are sub-micron colloidal dispersions of pure drug particles in an outer liquid phase. It has been recommended that particles less than 10μm minimize particle irritation to the eye, decrease tearing, and drainage of instilled dose resulting in increased efficacy of an ocular treatment [57]. These nanosuspensions are non-irritant and regarded as a desirable ocular drug delivery vehicle [28]. After being instilled into the eye, the nanoparticles tend to adhere to the eye tissues to form a depot and release drugs for the desired period. The inert carriers employed in nanosuspensions are non-irritating to the iris, cornea, and conjunctiva [2]. Nanosuspensions enhance the solubility and ocular bioavailability of drugs and increase the precorneal residence time. Flurbiprofen-loaded polymeric nanosuspension has been shown to prevent miosis during extracapsular cataract surgery. The positive charge on nanoparticles increases the adherence with the corneal surface which is negatively charged. The studies demonstrated that nanosuspensions are an alternative to conventional eye drops for ocular drug delivery.

Niosomes

Niosomes are bilayered structural vesicles made up of non-ionic surfactant which are capable of encapsulating both lipophilic and hydrophilic compounds. Niosomes reduce the systemic drainage and improve the residence time, which leads to an increase in ocular bioavailability [59]. Niosomes size ranges from 10 to 1000 nm which is biodegradable, biocompatible, and nonimmunogenic. Niosomal formulation of coated timolol maleate exhibited significant IOP lowering effect in rabbits as compared with timolol solution [60].

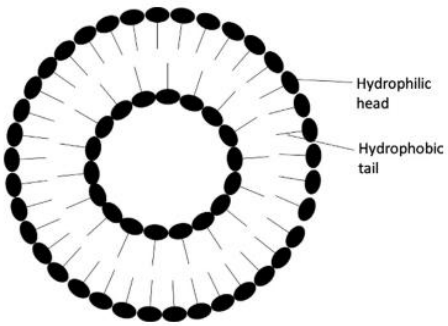

Figure No. 4: Diagrammatic representation of Niosomes

B). Iontophoresis

Iontophoresis is a non-invasive technique for ocular drug delivery and therefore avoids the complications of surgical implantation or frequent and high dose of intravitreal injections [61]. Ocular iontophoresis is classified into trans-corneal, corneoscleral or trans-scleral iontophoresis [62]. This method involves the transfer of ionized drugs through membranes with low current [63]. The drug is applied with a weak direct current (DC) that drives charged molecules across the sclera and into the choroid, retina, and vitreous. A ground electrode of the opposite charge is placed elsewhere on the body to complete the circuit. The drug serves as the conductor of the current through the tissue and moved across the membranes by two mechanisms- migration and electro-osmosis. In the rabbit iontophoresis of DEX phosphate, DEX levels in the cornea after a single transcorneal iontophoresis for 1 min (1 mA) were up to 30 fold higher compared to those obtained after frequent eyedrops instillation [61]. EyeGate Pharmaceutical, Inc. (Waltham, MA, U.S.) has begun to enroll for a pivotal Phase III study of EGP-437 for the treatment of dry eye syndrome [64]. EGP-437 is a DEX phosphate for delivery using the EyeGate II® Delivery System. The EyeGate II® Delivery System has been studied in many subjects and completed Phase II studies for the treatment of dry eye [65] and anterior uveitis [66]. Theoretically, iontophoresis is limited to drugs of small size, anionic nature, and with low molecular weight, and in the case of diffusion, treatment time is passively determined by the typically slow diffusion process rather than the therapeutic need. In many cases, existing drugs need to be reformulated to confer an electric charge so that they can be utilized within the system. To resolve these problems, Macroesis™ (Buckeye Pharmaceuticals, Beachwood, OH, U.S.) proposes using an alternating current instead of DC [66-67]. The iontophoretic technique is less invasive than the intraocular injections but its action is less prolonged when compared with the controlled delivery systems. The efficacy and patient acceptance are not yet known regarding clinical applications.

CONCLUSION:

Drug delivery to the ocular surface is challenging for formulation scientists owing to its anatomical barriers and the limitations of conventional ocular therapy. The conventional drug delivery formulations have proven their efficacy in the therapy of anterior eye part diseases, but are less powerful in the therapy of posterior eye part diseases, even after frequent dosing.

Application of nanoparticles in the ocular delivery of drugs allows overcoming existing barriers when it comes to formulating dosage forms, which then allows prolonged retention of a drug in the eye with the use of smaller doses and provides better drug effects and greater patients' compliance. Nanocarriers are designed to overcome the limitations associated with current ocular therapy and ensure targeted and controlled drug delivery. Topical administration to the ocular surface would be the safest delivery method, as it is noninvasive and painless compared with other delivery methods. Therefore, Non-invasive ocular drug delivery through nanocarriers can reduce the overall administration frequency of intravitreal injections, enhance the therapeutic efficacy, significantly reduce treatment costs, and improve the quality of life of ocular disease patients.

REFERENCES:

1. Djamila A, Kamel A, Philippe P, Veronique A. Recent advances in ocular drug delivery. Drug Development and Industrial Pharmacy, 2012 Nov; 39(11): 1599-617.
2. Sanjeeb KS, Fahima D, Krishnakumar S. Nanotechnology in ocular drug delivery. Drug Discovery Today, 2008 Feb; 13(3-4): 144-151.
3. Rinda Devi B, Pallabitha C, Zahraa HFA, Pradeep KK, Sai HSB. Ocular Drug Delivery Barriers- Role of Nanocarriers in the Treatment of Anterior Segment Ocular Diseases. Pharmaceutics, 2018; 10(1): 28.
4. Ramesh Y, Kothapalli CB, Reddigari JRP. A novel approaches on Ocular drug delivery systems. Journal of Drug Delivery and Therapeutics. 2017; 7(6): 117-124.
5. Richard TA. Ocular Drug Delivery Advances, Challenges and Applications. Springer International Publishing, 2016.
6. Akanksha T, Raj Kumar S. Novel ocular drug delivery systems: An overview. Journal of Chemical and Pharmaceutical Research. 2010; 2(3): 348-355.
7. Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, Bannerjee SK. Drug delivery systems: An updated review. International Journal of Pharmaceutical Investigation. 2012 Jan; 2(1): 2-11.
8. Ripal G, Jwala J, Sai HSB, Ashmin KM. Recent Perspectives in Ocular Drug Delivery. Pharmaceutical Research. 2009 May; 26(5): 1197-216.
9. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: An overview. World Journal of Pharmacology. 2013; 2(2): 47-64.
10. Vitthal S. Kulkarni. Handbook of Non-Invasive Drug Delivery Systems: Science and Technology. Elsevier, 2009.
11. Mundada AS, Avari JG, Mehta SP, Pandit SS, Patil AT. Recent advances in ophthalmic drug delivery system. Pharmacological Reviews. 2008; 6(1): 481-489.
12. Din FU, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S, Zeb A. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. International Journal of Nanomedicine. 2017 Oct; 12: 7291-7309.

13. Sanket KT, Shiv KG, Pramod S, Deepu P, Sohan Lal C. Current status and advanced approaches in ocular drug delivery system: Safety evaluation, future consideration. World Journal of Pharmaceutical Research. 2013 Aug; 2(5): 1440-1465.

14. Akanksha T, Raj Kumar S. Novel ocular drug delivery systems: An overview. Journal of Chemical and Pharmaceutical Research. 2010; 2(3): 348-355.

15. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, *et al*. Liposome: classification, preparation, and applications. Nanoscale Research Letters. 2013 Feb; 8(1): 102.

16. Laddha Umesh D, Kshirsagar Sanjay J. Ocular Drug Delivery System: Challenges and Opportunities. Research and Reviews: A Journal of Pharmaceutical Science. 2018; 9(3): 14–30.

17. Shehab Ebrahim MD, Gholam A. Peyman MD, Paul J. Lee MD. Applications of Liposomes in Ophthalmology. Survey of Ophthalmology. 2005 Mar; 50(2): 167-182.

18. Harini Chowdary V, Sevukarajan M. Niosomal Drug Delivery System: A Review. Indo American Journal of Pharmaceutical Research. 2012; 2(9).

19. Abdelkader H, Ismail S, Kamal A, Alany RG. Design and evaluation of controlled release niosomes and Discomes for Naltrexone hydrochloride ocular delivery. Journal of Pharmaceutical Sciences. 2011 May; 100(5): 1833-1846.

20. Dhruvi AS, Sheeraj S, Kaushik P. Innovation in Ocular Drug Delivery System. World Journal of Pharmaceutical Research. 2018; 7(1): 389-406.

21. Abdelbary G, El-Gendy N. Niosome-encapsulated Gentamicin for ophthalmic controlled delivery. AAPS PharmSciTech. 2008; 9(3): 740-747.

22. Kaur IP, Garg A, Singla AK, Aggarwal D. Vesicular systems in ocular drug delivery: an overview. International Journal of Pharmaceutics. 2004; 269(1): 1-14.

23. Patel V, Agarwal YK. Current status and advanced approaches in ocular drug delivery system. Journal of Global Trends in Pharmaceutical Sciences. 2011; 2(2): 131-148.

24. Abbasi E, Aval SF, Akbarzadeh A, *et al*. Dendrimers: synthesis, applications, and properties. Nanoscale Research Letters. 2014; 9(1): 247.

25. Sandeep CA, Nishan NB, Vikrant PW, Shrikant DP, Kiran KT. Current trends towards an Ocular drug delivery system: Review. International Journal of Pharmacy and Pharmaceutical Research. 2013; 3(1): 28-34.

26. Almeida H, Amaral MH, Lobao P, Silva AC, Loboa JM. Applications of polymeric and lipid nanoparticles in ophthalmic Pharmaceutical formulations: Present and Future considerations. Journal of Pharmacy and Pharmaceutical sciences. 2014; 17(3): 278-93.

27. Kim J, Chauhan A. Dexamethasone transport and ocular delivery from poly hydroxyethyl methacrylate gels. International Journal of Pharmaceutics. 2008 April; 353(1-2): 205-222.

28. Gaudana R, Jwala J, Boddu SHS, Mitra AK. Recent perspectives in ocular drug delivery. Pharmaceutical Research. 2008 Aug; 26(5): 1197-1216.

29. Vaishya RD, Khurana V, Patel S, Mitra AK. Controlled ocular drug delivery with nanomicelles. Wiley interdisciplinary reviews. Nanomedicine and Nanobiotechnology. 2014; 6(5): 422-437.

30. Ansari MJ, Kohli K, Dixit N. Microemulsion as potential drug delivery system: A review. PDA Journal of Pharmaceutical Science and Technology. 2008; 62: 66-79.

31. Bourges JL, Bloquel A, Thomas A, Froussart F, Bochot, *et al*. Intraocular implants for extended drug delivery: Therapeutic applications. Advanced drug delivery reviews. 2006 Nov; 58(11): 1182-1202.

32. Gray C. Systemic toxicity with topical ophthalmic medications in children, Paediatric and Perinatal Drug Therapy. 2006; 7(1): 23-29.

33. Gan L, Han S, Shen J, et al. Self-assembled liquid crystalline nanoparticles as a novel ophthalmic delivery system for dexamethasone: Improving preocular retention and ocular bioavailability. International Journal of Pharmaceutics. 2010 Aug; 396(1-2): 179-187.

34. Mehra NK, Cai D, Kuo L, Hein T, Palakurthi S. Safety and toxicity of nanomaterials for ocular drug delivery applications. Nanotoxicology. 2016; 10(7): 836-860.

35. James NC. Handbook of Non –Invasive Drug Delivery Systems. Recent Advances in Ophthalmic Drug Delivery. 2010; 165-192p.

36. Sultana Y, Jain R, Aqil M, Ali A. Review of ocular drug delivery. Current Drug Delivery. 2006; 3(2): 207-217.

37. Merodio M, Irache JM, Valamanesh F, Mirshahi M. Ocular disposition and tolerance of ganciclovir-loaded albumin nanoparticles after intravitreal injection in rats. Biomaterials. 2002; 23(7): 1587-1594.

38. Del Amo EM, Urtti A. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. Drug Discovery Today. 2008; 13(3-4): 135-143.

39. Wen H, Jung H, Li X. Drug Delivery Approaches in Addressing Clinical Pharmacology-Related Issues: Opportunities and Challenges. America Association of Pharmaceutical Scientists Journal. 2015; 17(6): 1327-1340.

40. Agrahari V, Mandal A, Agrahari V, *et al*. A comprehensive insight on ocular pharmacokinetics. Drug Delivery and Translational Research. 2016; 6(6): 735-754.

41. Cholkar K, Patel SP, Vadlapudi AD, Mitra AK. Novel strategies for anterior segment ocular drug delivery. Journal of Ocular Pharmacology and Therapeutics. 2013; 29(2): 106-123.

42. Zinmer A, Kreurer J. Microspheres and nanoparticles used in ocular delivery systems. Advanced Drug Delivery Reviews. 1995; 16: 61- 73.

43. Du Toit LC, Pillay V, Choonara YE, Govender T, Carmichael T. Ocular drug delivery - a look towards nanobioadhesives. Expert Opinion Drug Delivery. 2011; 8(1): 71-94. [PubMed]

44. Indu PK, Alka G, Anil KS, Deepika A. Vesicular systems in ocular drug delivery: an overview. International Journal of Pharmaceutics. 2004 Jan; 269(1): 1-14.

45. Hathout RM, Mansour S, Mortada ND, Guinedi AS. Liposomes as an ocular delivery system for acetazolamide: in vitro and in vivo studies. AAPS PharmSciTech. 2007; 8(1): 1.

46. Ehab IT, Magda HE, Ibrahim AE, Mohsen AB. Design of liposomal colloidal systems for ocular delivery of ciprofloxacin. Saudi Pharmaceutical Journal. 2013.

47. Habib FS, Fouad EA, Abdel-Rhaman MS, Fathalla D. Liposomes as an ocular delivery system of fluconazole: in-vitro studies. Acta Ophthalmologica. 2010 Dec; 88(8): 901-904.

48. Singh R, Lillard JW Jr. Nanoparticle-based targeted drug delivery. Experimental and Molecular Pathology. 2009; 86(3): 215-223.

49. Pignatello R, Bucolo C, Ferrara P, Maltese A, Puleo A, Puglisi G. Eudragit RS100 nanosuspensions for the ophthalmic controlled delivery of ibuprofen. European Journal of Pharmaceutical Sciences. 2002; 16(1-2): 53-61.

50. Bourges JL, Gautier SE, Delie F, *et al*. Ocular drug delivery targeting the retina and retinal pigment epithelium using polylactide nanoparticles. Investigative Ophthalmology and Visual Science. 2003; 44(8): 3562-3569.

51. Bejjani RA, David B, Cohen H, *et al*. Nanoparticles for gene delivery to retinal pigment epithelial cells. Molecular Vision. 2005 Feb; 11: 124-132.

52. Xu Q, Kambhampati SP, Kannan RM. Nanotechnology approaches for ocular drug delivery. Middle East African journal of ophthalmology. 2013; 20(1): 26–37.

53. Quintana A, Raczka E, Piehler L. *et al.* Design and Function of a Dendrimer-Based Therapeutic Nanodevice Targeted to Tumor Cells Through the Folate Receptor. Pharmaceutical Research. 2002; 19: 1310–1316.

54. Thomas FP, Joseph RR. Ocular Evaluation of Polyvinyl Alcohol Vehicle in Rabbits. Journal of Pharmaceutical Sciences. 64(8): 1312-1316.

55. Vandamme TF, Brobeck L. Poly (amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. Journal of Control Release. 2005; 102(1): 23-38.

56. Wadhwa S, Paliwal R, Paliwal SR, Vyas SP. Nanocarriers in ocular drug delivery: an update review. Current Pharmaceutical Design. 2009; 15(23): 2724-2750.

57. Patel VR, Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. Journal of Advanced Pharmaceutical Technology and Research. 2011; 2(2): 81-87.

58. Arora K, Singh S, Chaurasia L. Ophthalmic Drug Delivery System- A Concise Review on Its Conventional and Novel Approaches. Current Research in Pharmaceutical Sciences. 2019 Jan; 8(4): 263-9.

59. Prabu P, Chaudhari AA, Aryal S. *et al. In vitro* evaluation of poly (caporlactone) grafted dextran (PGD) nanoparticles with cancer cell. Journal of Materials Science: Materials in Medicine. 2008; 19: 2157–2163.

60. Aggarwal D, Kaur IP. Improved pharmacodynamics of timolol maleate from a mucoadhesive niosomal ophthalmic drug delivery system. International Journal of Pharmaceutics. 2005; 290(1-2): 155-159.

61. Elijarrat-Binstock E, Raiskup F, Frucht-Pery J, Domb AJ. Transcorneal and transscleral iontophoresis of dexamethasone phosphate using drug loaded hydrogel. Journal of Controlled Release. 2005; 106: 386-390.

62. Bejjani RA, *et al.* Electrically assisted ocular gene therapy. Survey of Ophthalmology. 2007; 52(2): 196-208.

63. Marvin EM, Donna MN, James MH. Recent progress in ocular drug delivery for posterior segment disease: Emphasis on transscleral iontophoresis. Advanced Drug Delivery Reviews. 2005; 57(14): 2063 – 2079.

64. Patane MA, Cohen A, From S, Torkildsen G, Welch D, Ousler GW 3rd. Ocular iontophoresis of EGP-437 (dexamethasone phosphate) in dry eye patients: results of a randomized clinical trial. Clinical Ophthalmology. 2011 May; 5: 633-643.

65. ClinicalTrials.gov Safety and efficacy study of EGP-437 (Dexamethasone phosphate formulated for ocular iontophoresis) to treat eye. Available online: http://clinicaltrials.gov/ct2/show/NCT01129856?term=EyeGate&rank=3 (Accessed on 18 October 2010).

66. ClinicalTrials.gov Safety and efficacy study of iontophoresis and dexamethasone phosphate to treat anterior uveitis. Available online: http://clinicaltrials.gov/ct2/show/NCT00694135?term=EyeGate&rank=4 (Accessed on 18 October 2010).

67. Singh RP, Mathews ME, Kaufman M, Riga A. Transcleral delivery of triamcinolone acetonide and ranibizumab to retinal tissues using macroesis. The British Journal of Ophthalmology. 2010 Feb; 94(2): 170-173.