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Ocular Drug Delivery System – A Review

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***Abstract*: *Background:* The ocular drug delivery is a one of the challenging approaches in novel drug delivery system. The eye is the important part of the human body but it sometimes suffers with diseases or disorders due to various reasons. Depending on the type and the severity of the disease problem arise ocular drug delivery system (with suitable dosage form) used to treat eye disease and disorders. *Main Body Abstract:* The surface of ocular drug delivery is restricted for only some areas and it requires lower dose than systemic circulation. Due to blood flow barriers in the eye, ocular disorders are treated with medication through topical application. For this reason, it is important to understand anatomy and physiology as the drug is administered via several ways. *Conclusion:* In the grow up population, scientists are designing nano and micro formulation drug release to boost the bioavailability and to overcome the barriers. They are like as liposomes, nanoparticles, nano-wafers, micro-needles etc.**

***Keywords*: Ocular drug delivery system, eye, ocular diseases.**

1. Background

Eye is an important part of the body for the vision and locomotion for the human. The various infections are caused to the eye such as Glaucoma, Conjunctivitis, Corneal ulcer, Dry eye, Macular degeneration, Diabatic retinopathy.

For the ocular drug delivery system firstly need to study human eye anatomy. The two eyeballs are situated in the orbit, where they each occupy approximately one-fifth of the orbital volume. The extraocular muscles, fascia, fat, blood vessels, nerves, and the lacrimal gland occupy the remaining area [1]. The parts of eye are iris, sclera, pupil, lacrimal caruncle as shown in Figure 1. It has exclusive structure that connects to the entire body by its vascular grid and nerve fibers [2] as shown in Figure 2.

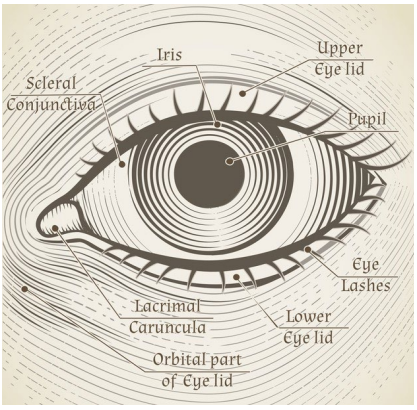

Fig. 1. Human eye (External anatomy)

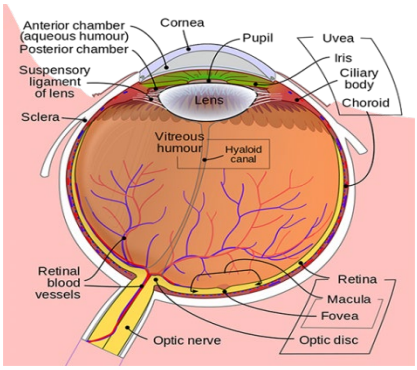

Fig. 2. Human eye (Internal anatomy)

Two barriers like as static and dynamic affects in the ocular drug delivery system. First, the static barrier, which involved the cornea, sclera, retina, and other barriers connected to the retina, involved the various eye parts. Second one is dynamic static it involves choroidal and conjunctival blood flow, lymphatic clearance, tear dilution. These two ways of barriers effects on the bioavailability of drug [3].The main aim of any ocular drug delivery reach to the optimum concentration of a drug at the active site for the suitable time. Ocular disposition and elimination of therapeutic agent is dependent on its physiochemical effects as well relevant ocular anatomy and physiology. Various approaches that have been tried to increase bioavailability and the duration of the therapeutic action. The ocular drug delivery system is divided into two types they are as follows:

1. Based on the sustained drug delivery system, it offers continuous and controlled ophthalmic drug delivery.
2. Using the benefits of corneal drug absorption and minimizing pre-corneal drug loss [4].

2. Introduction

Structure of eye: In compact structure of eye, it consists of following parts in Anterior and posterior. As shown in Figure 3. The posterior eye parts are for the systemic function of the eye, whereas the anterior eye parts protect the extracellular layer of the eye.

- Anterior parts of the eye they are as follows:
    1. Cornea
    2. Lens
    3. Iris
    4. Ciliary body

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- Posterior parts of eye they are as follows:
    1. Retina
    2. Optic nerve
    3. Choroid
    4. Sclera
    5. Fovea
    6. Vitreous [5].

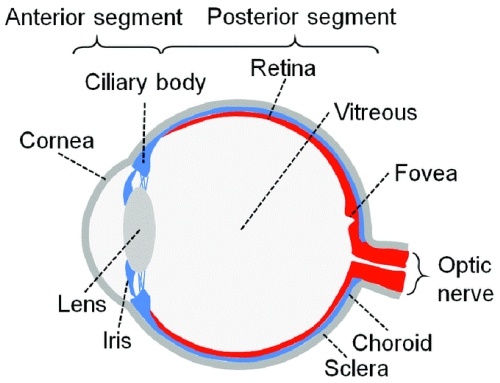

Fig. 3. Anterior & posterior parts of eye

Anterior parts of eye:

1. *Cornea:* In the anterior of the eye, there is a prominent, transparent bulge called the cornea. The adult cornea's surface has a radius of about 8mm [6]. Cornea is upper part of eye, in obverse of the iris and pupil. The cornea of human has horizontal diameter upto 11.5mm and vertical is 10.5mm. There are five layers of human cornea: epithelium, Bowman's membrane, laminar stroma, Descemet's membrane, endothelium membrane. The shell of the cornea is field with the tear film. The tear film "safeguards" it protects from chemical, toxic material and from microbial infection [7].
2. *Lens:* The eye lens is biconvex, translucent, and avascular structure [8]. Lens purpose is to transmit and focus light onto the retina. The lens is the primary controller of the eye and it has the highest protein and tissue content. The collagenous capsule that surrounds the lens serves as a barrier to diffusion and aids in accommodating the lens by giving the lens its shape. [9]. The collagen capsule molds the flexible lens into more spherical shape with greater refractive power process known as accommodation [8].
3. *Iris:* Iris is located behind the cornea and in front of lens. It controls the size of pupil [10]. In the structure iris it having four layer they are: anterior border layer, stroma, anterior epithelium, posterior pigmented epithelium [11]. Iris is the color part of the eye and they have the different shades like as green, blue, brown, hazel or grey [4].
4. *Ciliary body:* Ciliary body is present behind the iris. From the exterior view the ciliary body is not seen. It is constructed from the inner wall's tissue ring [12]. The ciliary body is built of the tissue, so the function is tissue interactions that occurs at certain stage in the normal development of eye [13].

Posterior part of eye:

1. *Retina:* Retina is located at the backside of the eye [4]. Retina is connected to the optical nerve [11]. Cover the inner portion of the posterior two-third globe of the eye wall. In the structure of retina there is the rods and cones present which is of purplish-red color. The rods are made up of Rhodopsin, derivatives of vitamin A, this are the visual pigment of the rods. The rods and cones are same, but only the protein moiety is different [8].
2. *Optic nerve:* The optic nerve is composed of 1 million nerve fibers [14]. This are in charge for the transmitting nerve signal from the eye to the brain. The signal is responsible for the image which is imagine or signal by the nerve to the brain. The topical surface of the nerve, which is visible upon the retina, is called the optic disk [4]. The optic nerve is made of visual fibers [80%] and afferent pupillary fiber [20%] [8].
3. *Choroid:* Choroid layer is existed behind the retina and it nourishes the retinal quantities also absorbs unused radiations. In the structure of the choroid there is maximum blood flows [14].
4. *Sclera:* The first layer of the eye, which is the white part of the eye, is called the sclera. It is a hard sheath. The tough fibrous membrane does this to preserve the form of the eye [4].
5. *Fovea:* The fovea is most critical portion of the retina. The fovea works as high visual acuity and color vision [15].
6. *Vitreous:* vitreous is present in the center of the retina and lens. The vitreous is in the transparent form like gel and that conquers the inner most part of the eye. The function of the vitreous is to provide the support and proteins to the retina from the ciliary body. The vitreous is attached to the optic disc, detachment caused non-vison threatening [11].

Eye disease: The disease of eye is caused by the different foreign body's like as bacteria, fungi and viruses. The disease affected either one or both eye parts. The common eye disease are as follows:

- Glaucoma
- Conjunctivitis
- Corneal ulcer
- Dry eye
- Macular degeneration
- Diabatic retinopathy

Routes of administration of ocular drug delivery system: There are several routes of administration as shown in Figure 4. This are depended on the targeted drug administration to the active site. The name of routes of administration are as shown in figure 5.

1. *Topical administration:* Mainly the topical drug administration is by the eye drop. They only have short contact time on the surface of eye [4]. This type of drug administration covers all type of anterior segment

disease related to the eye [16]. The design of the formulation can increase the contact and, thus, the duration of the pharmacological action [e.g. gels, ointments, and inserts] [4]. By making a hydrophilic layer that flows over the glycocalyx of the ocular surface and clears debris and pathogens, mucin found in the tear film has a protective function [17].

2. *Intra-vitreal administration:* the vitreous and retina is continent to direct drug administration into the vitreous. However, it should be highlighted that the problem with exploiting the RPE [Retinal Pigment Epithelium] barrier makes conveyance from the vitreous to the choroid more complicated. Small molecules can diffuse quickly inside the vitreous, while massive molecules, especially ones that are strongly charged, have limited mobility [14].
3. *Conjunctival administration:* The drug is infused into the IV at advanced stages of the uvea in pill form. [16]. The conjunctival epithelial barrier, which is a rate-limiting barrier for the penetration of water-soluble medicines, is removed by subconjunctival injection. The cornea-conjunctiva barrier is thus bypassed by the transscleral pathway. However, a number of metabolic, static, and dynamic obstacles prevent drugs from reaching the posterior section. Conjunctival blood and lymphatic circulation are examples of dynamic barriers [17].
4. *Intracameral administration:* compared to topical steroid administration, reduces systemic and corneal adverse effects; high drug concentration in the anterior chamber. Patients are at serious risk from toxic anterior segment syndrome and toxic endothelial cell destruction syndrome. Treatment for the intracameral disease swelling, endophthalmitis prophylaxis, inflammation, and dilated pupils [3].
5. *Scleral administration:* The sclera has recently come into focus as a potential drug delivery vector for the posterior segment because of its huge surface area, accessibility, and relatively high permeability to macromolecules. Scleral drug delivery has been attempted using a variety of techniques, including scleral plugs and implants, sub-tenon injection, and injection into the conjunctiva of the sun. Medication trans-scleral administration is a viable therapeutic approach for the management of several posterior segment diseases [16].
6. *Systemic/oral administration:* The blood retinal barrier creates it difficult to transfer drugs to the vitreo-retinal tissues by systemic administration. The vitreous humor only achieves 1% to 2% of the plasma drug concentration; as a result, repeated dosing is necessary to maintain therapeutic drug levels. This form of delivery may also produce systemic cytotoxicity and non-specific drug binding to other organs [16]. In comparison to injection delivery, oral delivery was investigated as a potential noninvasive and patient-favored method of treating chronic retinal disorders. Therefore, while bidding to achieve a therapeutic response in the eye following oral delivery, factors including safety and toxicity need to be taken into account [17].

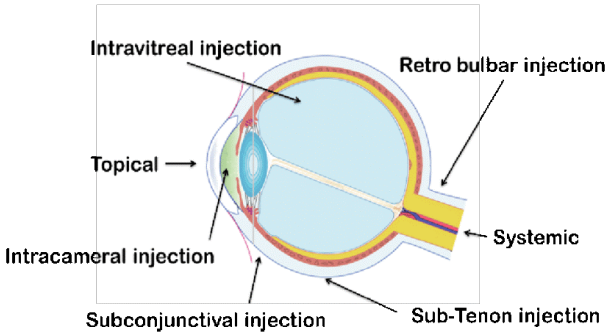

Fig. 4. Routes of administration of ocular drug delivery system

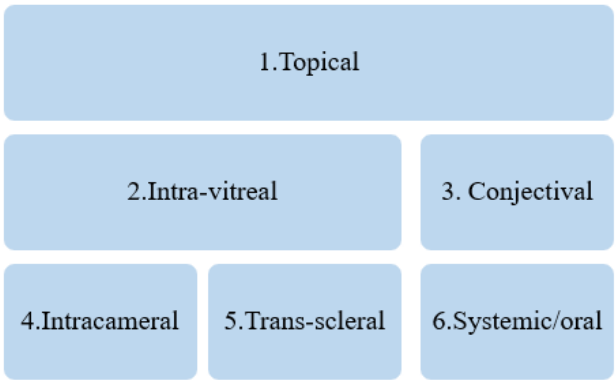

Fig. 5. Routes of administration of ocular drug delivery system

Drug delivery to eye: The delivery of the drug to different routes of administration in the different formulation. There are various types of formulation of ocular drug delivery. The formulation either in the form of solid, liquid or semisolid dosage form [18]. While formulating the dosage there are some factors are considered solubility, ocular toxicity, pH, tonicity, buffer capacity, viscosity, compatibility with other ingredients of ophthalmic formulations [19]. The formulation are as follows:

- *Eye drops:* The eye drops are in the form of solution, and emulation suspension [18]. The pH of the eye drops is similar to the pH of the eye as 4-8hat its eye can accurately tolerated [20]. The easiest, safest, fastest acting, patient-compliant, non-invasive, and most convenient method of administering ocular medications is by topical drops. After topical drop instillation, an eye drop solution offers a rapid medication penetration, after which its concentration rapidly falls. Drug concentration drop kinetics may roughly follow a first order. Consequently, in order to increase drug contact time, penetration, and ocular bioavailability. In the formulation of eye drops several additives are added to increases the bioavailability. The additives include surface active agents, preservatives, chelating agents, viscosity enhancers, and permeation enhancers, cyclodextrin among others.

The viscosity enhancer is sodium carboxy methyl cellulose, hydroxy ethyl cellulose, hydroxy methyl cellulose, etc. The permeation enhancer for the ocular formulation is sodium taurocholate, polyoxyethylene glycol ethers [lauryl, stearyl and oleyl], ethylenediaminetetra acetic acid sodium salt, benzalkonium chloride, saponins.

The solubility and bioavailability of pharmaceuticals can be enhanced via an emulsion-based formulation strategy. Oil in water [o/w] and water in oil [w/o] emulsion systems are the two forms of emulsions that are commercially used as carriers for active medicinal ingredients. O/w emulsion is a popular and well-liked drug delivery method for use in the eye over w/o systems. Less irritability and improved ocular tolerance of o/w emulsion are some of the causes.

Another category of non-invasive ocular topical drop medication carrier systems are suspensions. Suspension is the dispersion of finely divided insoluble API in an appropriate suspending and dispersing agent-containing aqueous solution. In other words, API is dissolved in a saturated solution in the carrier solvent system. Drug contact time and duration of effect are increased in comparison to drug solution thanks to suspension particles' retention in the precorneal pocket. The length of the drug's activity in suspension depends on the particle size. The medication absorbed into the ocular tissues from the precorneal pocket is replenished by smaller size particles [15]. The marketed eye drops with brand name such as Azithromycin [Azasite] for bacterial conjunctivitis, Betazolol [Betoptopic S] for glaucoma,Omega-3 fatty acids[Remogen omega] for Dry eye disease [3].

- *Eye ointments:* In order to create ophthalmic ointments that can melt at the physiological temperature of the eye [34 °C] and are non-irritating, solid hydrocarbon and semisolid mixes are typically used. The hydrocarbons are selected based on biocompatibility. The bases for the ointments can be either simple or compound, with simple bases forming a continuous phase and compound bases a two-phase system. Therapeutic agent addition can be done using a solution or a powdered form that has been finely ground. The ointments dissolve into droplets after application and remain as a depot in a cul-de-sac for a long time. Meanwhile, there are certain disadvantages to using ointments, like vision blurring and eyelid mating, which limits its use [2].
- *Gels:* Users are primarily used as tear substitutes in the treatment of dry eyes because gel eye drops have numerous drawbacks that restrict their use for the administration of pharmaceutical eye drops. Gel eye drops are straightforward viscous formulations that do not undergo any changes after their administration. Gel eye drops can result in blurred vision, crusting on the eyelids, and tears. They also make it difficult to accurately and consistently administer medications [21].

Advanced drug delivery system to eye: For the treatment of eye disease, several approaches have been used in recent years. One of the approaches currently being pursued for both anterior and posterior segment drug administration is nanotechnology-based optical formulations. A system based on nanotechnology that has the right particle size can be designed to assure reduced irritancy, adequate bioavailability, and compatibility with ocular tissue. For ocular medication administration, a variety of nanocarriers including nanoparticles, nanosuspension, liposomes, Nano-micelles, contact lenses, microneedles, *in situ* thermosensitive gels, dendrimers and nano-wafers have been created. Some of them have produced encouraging results in terms of enhancing ocular bioavailability [22].

- *Nanoparticles:* The sized of Nanoparticles less than micro, preferably smaller than 500 nm, solid distributed particles that can be polymers. Nanoparticles can be produced as nanospheres or Nano-capsules depending on the preparation methods utilized There are many different kinds of nanoparticles, including magnetic, bio-adhesive, gold, silver, solid lipid and self-aggregating ones[23]. In-vivo biodistribution of nanoparticles can be altered, and their propensity to combine with biological molecules can be diminished. The nanoparticles can have longer residence periods on the ocular surface if they are coated with a muco-adhesive or charged polymer [16]. A number of drugs, including eye medications, have been found to be latently delivered to the eye using liposomes, such as Penicillin G as well as Tropicamide Depending on how big and how they are constructed [24] Although there are many different preparation techniques, they can be grouped into two categories: those that involve the polymerization of monomers and those that involve the precipitation of polymers [25].
- *Nanosuspension:* Less than 1 m-sized water-insoluble particles are colloidally dispersed in water as nanosuspensions [according to some articles, less than 600 nm]. For these systems to remain stable, a surfactant, polymer, or both are required [23]. As soon as instillation, the microscopic particles cling to the tissues of the eye, forming a depot that will eventually release the medicine. The larger surface area of the nanoparticles also enables an appropriate rate of drug release and preserves a constant drug concentration in order to achieve the required bioavailability. Additionally, hydrogels and ocular implants contain nanosuspension for a specified amount of time for sustained action [2]. In the year of 2017 research done on the Econazole and the result of this study is When compared to the suspension formulation's 4 hour drug release, the nanosuspensions formulation performed better, releasing the drug over a period of 7-8 hours [23].
- *Liposomes:* Liposomes are a promising way to administer drugs for the eyes since they have a cell-like membrane made of natural phospholipids and excessive biocompatibility. Liposomes can bind to the hydrophobic corneal epithelium when given topically,

where they release the bound medication content constantly while enhancing pharmacokinetics and reducing harmful side effects. Fluconazole-loaded liposome was administered to the rabbit keratitis models, with fluconazole solution serving as a control. Results after 21 days of monitoring revealed that liposomal fluconazole medication was more effective than the control treatment at curing infection. Positively charged liposomes have been demonstrated to have a higher affinity for attaching to the corneal surface than neutral or negatively charged vesicles [26].

- *Nano-micelles:* Due to their smaller size, hydrophilic corona, ability to stay in the systemic circulation for a longer period of time, and ability to accumulate in sick tissues through the EPR effect, topical drops based on nonmicellar technology are attracting interest as a non-invasive drug delivery method. In order to help this nonmicellar technology distribute medications to both the front and posterior part of the eye, the selection of surfactant and polymer should be optimal [2].
- *Contact lenses:* The newest approach to ocular medication administration involves contact lenses. In this system, contact lenses are drug-saturated and put in the eye. These lenses take a very long time to release the medication. extensively used hydrophilic contact lenses. They drank drug solvent and absorbed the substance [water soluble drugs]. In the human eye, fluorescein is delivered by means of bionite lenses, which contain the hydrophilic polymer 2-hydroxy ethyl methylacrylate. They increase the Fluorescein drug's rate of penetration [24].
- *Microneedles:* The development of microneedles and the use of the tools to treat glaucoma are both related to microvascular injection. It is made out of a blunt needle attached to a flexible, tapered tube that has a microneedle or micropipette at the end for inserting into small blood arteries [19]. The sclera or the small region between the sclera and choroid known as the "suprachoroidal space" can both be treated with these needles to deposit a medication or carrier system [SCS] [15].
- *In situ thermosensitive gels:* In situ gels are easily injected as solutions into the conjunctival sac, where they undergo a transformation into gels with their preferred residence times. The physiological environment causes a chemical/physical alteration that leads to the sol-gel transition. The benefit of a solution being patient-friendly and the favorable residence time of a gel for increasing ocular bioavailability are combined in this form of gel [4]. There are several adaptive polymers that can gel in different ways. A mixture of these polymers may produce superior outcomes to a single polymer. For usage as an ocular in situ gel-forming system, however, a mixture of sodium alginate and HPMC was developed for the current study. A natural polymer derived from brown sea algae is called alginate. When specific divalent cations found in tear secretion, such as Ca2+, Sr2+, and Ba2+, are present in small amounts, the substance produces stable hydrogels. The polymer sodium alginate, which is very hydrophilic and biocompatible, is used in drug delivery. It undergoes osmotically induced gelation, in which the injection of fluid is made to gel by a change in ionic strength. [6].
- *Dendrimers:* Macromolecules called “dendrimers” are composed of a central core and a network of branches. Due to their nanoscale, ease of fabrication, functionality, and capacity to affix numerous surface groups, they are an acceptable solution vehicle for the administration of ocular drugs. [17]. PAMAM dendrimers are frequently used in the administration of ophthalmic drugs. Conjugates of modified PAMAM dendrimers with glucosamine [DG] and glucosamine 6-sulfate [DGS] were created to have anti-angiogenic and immunomodulatory effects, respectively, in order to prevent the formation of scar tissue during glaucoma filtration surgery. These modified conjugates were subconjunctival injected into rabbits after glaucoma filtration surgery. This significantly inhibited pro-inflammatory and pro-angiogenic reactions, which in turn led to less scar tissue formation. The experiment's findings suggested that the clinical application of DG and DGS to the eyes could be efficient and secure in preventing the formation of scar tissue following glaucoma filtration surgery [15].
- *Nano-wafers:* The ocular surface is coated with Nano-wafers as in Figure 5, which are tiny circular discs or rectangular membranes carrying a variety of drug-filled Nano-reservoirs. They extend the time of medication release, which boosts therapeutic effectiveness. The nano-wafers melt and disappear throughout the medication release process [27]**.** Corneal fluorescein staining was used to examine how Axi-5-NW affected the corneal wound healing procedure. According to the results of this investigation, the Axi-5-NW treatment had no effect on the corneal wound healing, and a typical healing pattern was seen. Complete corneal surface healing was seen by the ninth day, and the rate of epithelial closure of the corneal surface was nearly the same in both the Axi-5-NW and Axe-eye drop treated groups [1].

Barriers in ocular drug delivery system: So many membrane barriers, such as those in the cornea, conjunctiva, iris-ciliary body, and retina, where epithelial and/or endothelial cells are sealed by the tight junctional elements, must be crossed by drugs in order to achieve the desired target sites after passing through the tear film and lacrimal fluid [28].

- *Lacrimal fluid barrier:* drug absorption from the lacrimal fluid into the eye is restricted by the corneal epithelium. The corneal epithelial cells generate tight junctions that prevent drug diffusion into the

paracellular cells. Therefore, compared to hydrophilic medicines, lipophilic medications often have corneal permeability that is at least an order of magnitude higher. The conjunctiva has a surface area that is about 20 times higher than that of the cornea and is often a leakier epithelium than the cornea [6].

- *Blood-ocular barrier:* Blood-ocular barriers defend the eye from xenobiotics in the blood stream. Blood-aqueous and blood-retina barriers are the two components of these barriers. Endothelial cells in the uvea, or middle layer of the eye below the sclera, make up the anterior blood-eye barrier. The iris, ciliary body, and choroid make up this structure. This barrier limits the penetration of hydrophilic medicines from plasma into the aqueous humor as well as the access of plasma albumin to the aqueous humor. Retinal pigment epithelium [RPE] and the dense walls of retinal capillaries make up the posterior barrier separating the blood supply from the eye. The choroid vasculature, in contrast to retinal capillaries, has a large blood flow and leaky walls [6].

Advantages of ocular drug delivery system:

- Offer sustained and controlled drug delivery system.
- Some formulations are directly added by the patients like as eye drops, eye ointments.
- This type of formulation has enhanced patient obedience.
- There are some products reduced dose frequency [29].

Disadvantages of ocular drug delivery system:

- The bioavailability of the drug duration time is very less on the eye surface.
- There are some limitations of administration of drug to the eye.
- While administrating the ophthalmic ointment there is the interferes in the vision.
- Some drug causes eye irritation [29].

3. Conclusion

There has been a lot of research done recently on nanotechnologies for ocular medication delivery systems. the Nanotechnology based technologies include dendrimers, nano-wafers, nanoparticles, nanosuspension, liposomes, nano-micelles, contact lenses, microneedles, and in situ thermosensitive gels. It is necessary to study the anatomy of the eye for this formulation. However, there are some barriers that affect the system for delivering drugs to the eyes.

List of Abbreviations

RPE (Retinal Pigment Epithelium)
IV (Intra vascular)
pH (Potential of Hydrogen)
(O/W) Oil in water
(W/O) water in oil
API (Active Pharmaceutical Ingredients)
SCS (suprachoroidal space)
PAMAM (Polyamidoamine)
DG (glucosamine)
DGS (glucosamine 6-sulfate)
Axi-5-NW (Axitinib-5-Nano wafers)

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