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Ocular drug delivery system: A short review

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ABSTRACT: An ocular drug delivery system (ODDS) is a sterile dosage form, vehicle, or system intended for instilling, administering, or delivering a drug/medicine to the eye against any ailment or disorder involving or affecting vision. The ocular drug delivery system is one of the difficulties that scientists face today in formulations. Over the last twenty years, research on ocular drug administration has made significant progress in creating innovative, safe, patient-compliance. Ocular drug delivery is mainly used for enhanced precision in dosage administration to get around the negative effects of conventional systems pulsed dosing. Less than 5 % of medicine injected reaches the eye due to this consideration, alternative strategies like adding cyclodextrin or permeation enhancers and making the solution more viscous did not result in a discernible improvement. The anatomy of the eye consists of the iris, sclera, lens, retina, choroid, etc. It also entails creating custom topical applications like ointments, emulsions, and suspensions. A range of nano-formulations has been produced to facilitate drug administration to the anterior part of the eye. This review emphasized the importance of ocular drug delivery systems and their effective formulations to reach a maximum therapeutic effect. The extensive literature review and research works will help in the ocular drug delivery system and its various formulations in drug delivery to produce effective therapeutic responses.

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INTRODUCTION:

The structure and physiology of the eye are distinct, making it a complex organ. There are two primary components to the eye's structure: the anterior and posterior segments. About one-third of the eye is made up of the anterior segment, with the posterior section taking up the remaining space. The anterior section is composed of tissues including the cornea, conjunctiva, aqueous fluid, iris, ciliary body, and lens. The choroid, neural retina, optic nerve, retinal pigment epithelium, sclera, and vitreous humor comprise the posterior position of the eye [1]. Numerous conditions that pose a threat to eyesight affect the anterior and posterior segments of the eye. The anterior segment is impacted by several diseases, such as cataracts, allergic

conjunctivitis anterior uveitis, and glaucoma. On the other hand, the two most common conditions affecting the posterior portion of the eye are diabetic retinopathy and Age-related Macular Degeneration (AMD) [2]. On the other hand, eye drops comprise more than 90 % of the marketed ophthalmic formulations. These formulations primarily address eye disorders of the anterior segment. The majority of the medications given topically are removed from the eye by a variety of mechanisms, including lacrimation, tear dilution, and tear turnover which reduces the drug's ocular bioavailability. Furthermore, the human cornea which is made up of endothelium, substantia, propria, and epithelium limits the entry of drug molecules into the eye. Less than 5 % of medicine injected reaches the eye due to this consideration. Alternative strategies like adding cyclodextrin or permeation enhancers and making the solution more viscous did not result in a discernible improvement. A notable improvement in ocular drug absorption was attained after the identification of numerous drug efflux pumps in recent times [3]. Treatment for ocular disorders that pose a threat to vision cannot be deemed best when using conventional methods such as eye drops, suspensions, and ointments. Nonetheless, eye drops make for more than 90% of the commercially available ophthalmic formulations. The anterior segment eye disorders are the primary target of these formulations [4]. With a focus on the anatomy of the eye, this article offers a thorough summary of the state of research, advancements, and difficulties in the field of ocular drug delivery systems today. It provides information on the most recent formulations, technologies, and techniques such as nanoparticles, bioadhesive systems, and drug carriers that have been developed to improve ocular drug delivery.

Ocular drug delivery system:

An ocular drug delivery system (ODDS) is a sterile dosage form, vehicle, or system intended for instilling, administering, or delivering drug/medicine to the eye against any ailment or disorder involving or affecting vision. The intricate structure and barrier makeup of the eye make ocular drug delivery a highly demanding field for drug delivery experts and ophthalmologists. Drug distribution to the anterior region of the eye is limited by barriers such as the distinct layers of the cornea, sclera, conjunctival blood flow, and tear dilution as well as additional barriers that are located in the back of the eye. Consequently, scientists have conceived and investigated a range of delivery methods to improve medication delivery and treatment effectiveness to the retina [5].

Anatomy of Eye:

The eyes are sensory organs that allow us to see.

- Outer fibrous layers; sclera and cornea.
- Middle vascular layer or uveal tract; consisting of the choroid, ciliary body, and iris.
- Inner nervous tissue layer; retina [6].

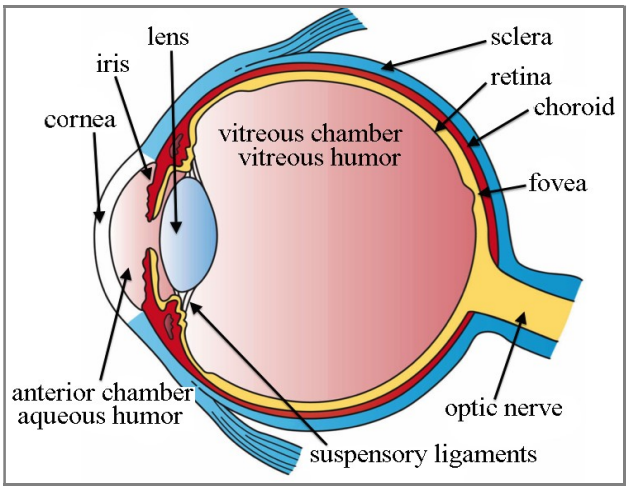

Fig 1. Anatomy of eye

Lens:

The lens of the eyeball is crystalline in nature. It is situated behind the pupil. It is biconvex, transparent, and helps focus the image of the object on the retina. The lens is supported by suspensory ligaments which are attached to ciliary bodies.

The lens consists of the lens capsules, epithelium, and fibers. The lens capsule is a smooth, transparent outermost layer of the lens, the lens fibers are long, thin, transparent cells from the bulk of the lens [7].

Iris:

Iris is the pigmented membrane that surrounds the pupil; it arises from the margin of the ciliary body and forms a dark-centered opening called the pupil. The space between the cornea and the lens is another segment.

It is divided into two parts by iris;

The space between the iris and cornea is the anterior chamber. The space between the iris and lens is the posterior chamber. They are filled with a clear fluid, the aqueous humor [8].

Cornea:

The clear lens in front of the eye. The transparent covering of the front of the eye allows for the passage of light into the eye and functions as a fixed lens.

Transparent vascular tissue with five distinct layers functions to allow light rays to enter the eye surrounded by a vascular limbus which nourishes the cornea should be smooth and clear [9].

Anterior Chamber and Aqueous Humor:

The anterior chamber is the aqueous humor-filled space inside the eye between the iris and the cornea's innermost surface.

Blood cells fill the anterior chamber as a result of hemorrhage, most commonly after a blunt eye injury. Anterior uveitis is an inflammatory process affecting the iris and ciliary body with resulting inflationary signs in the anterior chamber.

Aqueous humor is a clear fluid that fills sand and helps the eye. The aqueous humor serves as ocular blood to provide nutrition, remove excretory products from metabolism and contribute to homeostatic regulation of these vascular structures [10].

Sclera:

The sclera is the skeleton of the eye; it defends the size of the eye, provides a stable support for its optical elements and is essential to the achievement of a focused retinal image. The overall elastic properties sclera naturalizes short-term fluctuation of the intraocular pressure [11].

Sclera or the white part of the eye forms the outermost layer of the eyeball. The sclera consists of densely packed collagen bundles, interspersed with fibroblasts and embedded in ground substance.

The bundles are Composed of parallel collagen fibrils, branch, and intermingle in various planes. The water content of the sclera is approximately 70 % [12].

Retina:

The retina is a filmy piece of tissue barely half a millimeter thick, that lines inside the eye. The retina is therefore considered part of the brain; the retina includes both the sensory neurons that respond to light and intricate neural circuits that perform the first stage of image processing [13].

The retina is a thin, delicate, transparent sheet of tissue derived from the neuroectoderm; it comprises the sensory neurons that begin the visual pathway the neural retina is divided into nine layers [14].

The retina converts light that enters your eye into electrical signals from your optic nerve ends to your brain. Which creates the image to see it's a key part of the vision the retina is the very back of your eyeball [15].

Choroid:

The choroid represents the main structure of the eye which ensures the blood supply of the external layer of the retina consisting of most of it from blood vessels. Except vascularization which is the main function [16].

The choroid is the middle layer of the eye and is located in the posterior uveal. The inner layer will form the choroid and the external layer the sclera. Meanwhile, with the development of the choroid, the monocyte precursors migrate from the neural crest toward the choroid. The precursors will differentiate into pigmented melanocytes starting with 7 to 8 months of gestation [17].

Fovea:

The fovea is responsible for sharp central vision which is necessary in humans for activities for which visual detail is of primary importance, such as reading and driving. The fovea is surrounded by the parafovea belt and the perifovea outer region.

Approximately half the nerve fibers in the optic nerve carry information from the fovea, while the remaining half carry information from the rest of the retina. The parafovea extends to a radius of 1.25 mm from the central fovea and the perifovea is found at a 2.75 mm radius from the fovea centralis [18].

Optic nerve:

The optical nerve is the second cranial nerve but is not a true nerve instead it is an extension of the brain parenchyma. The optic nerve transmits electrical impulses from the retina to the brain which will be processed in visual information.

The optic nerve is not clear and magnetic resonance imaging plays a crucial role in addition the optic nerve can be affected by several diseases. The optic nerve is a white matter without surrounding Schwann cells. The optic nerve's intraocular segment is formed by the axons of the retinal ganglion cells. Several primary and secondary diseases can affect it [19].

Suspensory Ligament:

The suspensory ligament forms a hammock-like-sling underneath the eyeball between the check ligaments of the medial and lateral rectus muscle. This ligament encloses the inferior rectus and inferior oblique muscles. The suspensory of the eyeball functions to support the eyeball and prevent downward displacement.

The suspensory ligament of the lens is a series of fibers that connect the ciliary body of the eye with the lens holding it in place. The suspensory ligament along with

the superficial digital flexor tendon acts to stabilize the fetlock joint [20].

Vitreous Chamber and Vitreous Humor:

The vitreous chamber is the largest of the three chambers and is located behind the lens in front of the optic nerve. This chamber is filled with a thick and clear gel-like substance called vitreous humor also the vitreous body.

The aqueous humor is a transparent water-like fluid similar to blood plasma but containing low protein concentrations it is secreted from the ciliary body a structure supporting the eyeball it is filled with both the anterior and posterior chambers of the eye.

Vitreous humor is located in the space between the lens and the retina as a posterior cavity or various chamber blood cannot normally enter the body [21].

Advantages of ODDS:

Enhanced precision in dosage administration to get around the negative effects of conventional systems pulsed dosing.

- To offer consistent and regulated medication administration.
- To prolong corneal contact duration to enhance the drug's ocular bioavailability.
- To offer targeting inside the ocular globe to stop other ocular tissues from being lost.
- To get beyond defense mechanisms include conjunctival absorption, lacrimation, and drainage.
- To offer a superior delivery system housing.
- To improve patient comfort, drug performance, and compliance [22-24].

Disadvantages of ODDS:

- The residence time of the drug at the eye surface is less.
- Poor bioavailability.
- The instability of the dissolved drug.
- The low concentration of preservatives reduces shelf life after opening the bottle.
- Frequent dosing.
- Rapid precorneal elimination and short acting.
- Blurred vision.
- Poor patient compliance, sticking of eyelids [25-26].

Formulations for Ocular Drug Delivery:

Eye drops:

Among all topical eye preparations, topical eye drops are the most non-invasive and patient-compliant. However, according to Pahuja and Arora, eyes decrease a few obstacles in therapies. According to the report, a significant number of patients had trouble injecting the drop. Moreover, the tear flow that rises in proportion to the amount of eye drops may cause the solution to be lost or diluted. Apart from that, the quantity of medication absorbed into the tissue of the eyes cannot be calculated because of the eye pocket's restricted capacity. The popular preservative benzalkonium chloride can also lead to several issues, including the shedding of the cells that make up the corneal epithelium at their edges, which reduces cell proliferation and widens the intracellular space gaps in the corneas surface cells. Benzalkonium chloride may enhance the permeability of various drugs. Viscosity enhancers can extend the contact duration and use a permeation enhancer to the active ingredients absorption and the carrier cyclodextrin seeking hydrophobic compounds to boost the topical eye drop's bioavailability [27].

Emulsion:

Submicron emulsion, which has a particle size range of 0.1 to 0.3 µm has revived interest in employing emulsion in the past. Use a nonionic surfactant to improve its stability. The emulsion-based composition could improve both the bioavailability and solubility of medication for the eyes. There are typically two kinds of emulsions that are already accessible on the market as a means of active medical components, such as o/w (oil in water) and emulsion of water and oil (w/o). On the other hand, ophthalmic emulsions have certain restrictions. They have limited stability and are vulnerable to a range of instability occurrences, including creaming, coalescence, and flocculation [28]. The dispersed phase gives way to flocculation emerging from suspension to form flakes. Another instability process is coalescence which is how the suspension of scattered droplets is continually collectively to create bigger droplets. Aside from that, one phase in the mixture may move to the top or the bottom based on how dense they are in comparison, creating a layer that was divided into two phases and was called creaming [29].

Suspension:

A suspension is the result of finely insoluble active pharmacological compounds being dispersed in a solvent. This kind of drug delivery system offers several advantages over eye drops. The primary advantage is that it can get better the length of the drug's activity and contact time because of the retention of an insoluble

suspension in the pre-corneal pocket rather than being removed and neutralized by tear. Furthermore, a suspension with a higher concentration was found to be more effective than one with a lower concentration. The fact that the suspension formulations must be shaken to achieve the necessary dosage level is one of the disadvantages. This will alter the dosage of the medication given to the eye and lower patient compliance [30].

Ointment:

An ointment is made up of a combination of solid and semi-solid hydrocarbons, including paraffin, that melts at room temperature and does not irritate the eyes. Usually, there are 2 several ointments, including basic ointment, which consists of a single, continuous ointment phase, and compound-based cream that is divided into two phases such as an emulsion system. The ointment when administered to the eye will fragment into tiny drops that stay in the prolonged duration of the conjunctival sac. This results in the ointment's primary benefit, which is that it acts as a medication depot in the conjunctival sac, enhancing and extending its absorbance [31].

Ocuserts:

The term “ocular inserts” (OIS) refers to sterile, thin multi-layered, solid, or semisolid drug-embedded synthetic devices that are used to provide medication to the surface of the eye. With the primary goal of prolonging the drug's contact time with the conjunctival tissue, they are primarily designed to provide a suitable alternative to the problematic issue of short precorneal pharmaceutical residence times [32]. Consequently, OIs can be placed right into the conjunctival sac, which is situated in the space between the lower eyelid and the eye. Here they can use one of 3 primary mechanisms-diffusion, osmosis, or bioerosion to guarantee the medications release under controlled and prolonged conditions [33]. The medicine is continuously and carefully released through the tear fluid during the diffusion process. Osmosis is a characteristic of OIs that is typified by the existence of an elastic membrane. In actuality, the water in the eye enlarges this elastic membrane when the device is placed in the conjunctival sac, which causes the medicine to be released. Finally, when the device comes into contact with the aqueous milieu of the eye, the matrix directly erodes, causing bioerosion to occur in the bio-erodible OIs. Increasing the duration of contact between pharmacological conjunctival tissue is the primary goal of using OIs as a drug delivery system these enhance the release and therapeutic efficacy of medications that are typically provided through topical or systemic routes and compared to conventional delivery methods, drug-loaded OIs offer several benefits, such as increased drug bioavailability and activity [34]. Additionally, because OIs are loaded with a precise amount of the active ingredient, which is then completely retained at the injection site after release, they enable exact medication dosing. Thus, this final factor improves patient compliance by lowering the number of injection cycles and any systemic or ocular side effects. However, OIs have certain drawbacks as well. These include challenges encountered during their placements and administration. Furthermore, the sensation of an extraneous body in the eye caused by their solid or semi-solid might irritate patients and cause discomfort. Furthermore, vision impairment may result from the potential migration of OIs surrounding the eye [35].

CONCLUSION:

Various types of ocular drug delivery systems are found in the literature and market. Topical eye drops remain the most preferred approach for eye treatment, especially for the anterior application due to ease of administration. The ocusert system is the only medicated insert marketed in Western countries and the acceptance of these devices has been, to the present date, far from enthusiastic. Ocular drug delivery systems have been developed as options to improve treatment efficiency examples are ocular emulsion, suspension, ointment, and polymeric gels. Scientists are developing nano micelles, nanoparticles, liposomes, and ocular inserts. It is hoped that future novel systems would overcome all the drawbacks while retaining its efficacy, safety, and improving patient compliance.

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