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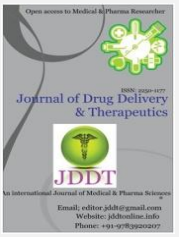

Open Access Review Article

A NOVEL APPROACHES ON OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of this review is giving a current update of the knowledge in this field of ocular drug delivery. The ocular drug delivery has been a major challenge to drug delivery scientists mainly due to its unique anatomy and physiology. One of the major problems encountered by the conventional ocular dosage forms include the rapid precorneal drug loss due to its nasolacrimal drainage, tear turnover and drug dilution resulting in poor bioavailability. These efforts lead to development of novel drug delivery dosage forms such as nanoparticles, liposome, ocuserts, and mucoadhesive formulations. Controlled drug delivery systems offer many advantages over conventional dosage forms in terms of improving drug bioavailability, reducing toxicity and decreasing dosage frequency. Designing noninvasive 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.

Keywords: Ocular drug delivery, Eye, Conventional drug delivery, novel dosage forms, approaches.

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INTRODUCTION

The human eye is an organ which reacts to light and pressure. As a sense organ, the mammalian eye allows vision. Human eyes help provide a three dimensional, moving image, normally colored in daylight[1]. Rod and cone cells in the retina allow conscious light perception and vision including color differentiation and the perception of depth. The human eye can differentiate between about 10 million colors and is possibly capable of detecting a single photon[2]. The eye is a complex organ with a unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment, anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment[3]. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor [4]. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age related macular degeneration and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye [5].

STRUCTURE OF THE EYE

The eye is made up of 3 main parts:

i. Eyeball

ii. Orbit (eye socket)

iii. Accessory (adnexal) structures

The eyeball: The main part of the eye is the eyeball (also called the globe). Each eye is sphere-shaped and is about 2.5 cm (1 inch) in diameter [6]. The eyeball is rich in blood vessels. The inside of the eyeball is filled mostly with a clear, jelly like fluid called vitreous humor. Vitreous humor fills the back (posterior) part of the eye. It helps support the internal structures and maintain the shape of the eye. The outer part of the eyeball is called the wall of the eye, structure of eye as shown in figure 01. It can be divided into 3 layers (or tunics): an outer, middle and inner layer (from the outside to the inside of the eye).

Outer layer: The outermost layer or covering of the wall of the eye is made up of the sclera and cornea and is called the fibrous tunic.

Sclera: The sclera is the tough, white connective tissue that covers most of the outside of the eyeball. The sclera is seen as the white portion of the eye and serves as the protective covering. The optic nerve and blood vessels pass through the sclera in the back of the eye. Muscles that control the movement of the eye attach to the sclera[7].

Cornea: The cornea is the clear, dome-shaped covering at the front of the eye that lets in light. The cornea covers the pupil and the iris [8]. It does not contain any blood vessels.

Middle Layer: The middle layer of the wall of the eye is called the vascular tunic. The uvea has 3 main parts:

Iris: The iris is the thin, muscular, colored part of the eye. It is located at the front (anterior) of the eye, between the cornea and the lens [9]. The iris opens and closes the pupil (the small central opening) to change the amount of light entering the eye.

Choroid: The choroid is a thin layer of tissue that contains many tiny blood vessels that supply oxygen and nutrients to the retina. The choroid contains many pigment producing cells called melanocytes [10]. These cells help absorb any excess light and minimize reflections within the eye.

Ciliary body: The ciliary body lies just behind the iris and extends forward from the choroid. It is the muscular ring of tissue that helps the eye focus. It changes the shape of the lens so it can focus on near or far objects [11]. The ciliary body contains cells that make aqueous humor, which is the clear fluid in the front of the eye between the cornea and lens.

Inner Layer: The innermost layer of the wall of the eye is made up of the retina or neural tunic. The retina is the thin layer of cells at the back of the eyeball and works like the film of a camera. It is made up of nerve cells that are sensitive to light [12]. These cells are connected to the brain by the optic nerve, which sends information from the eye to the brain and allows us to see.

Lens: The lens is a transparent structure in the inner part of the eye, which lies directly behind the cornea and iris. The lens changes shape to allow the eye to focus on objects. The lens focuses light rays on the retina [13].

Orbit: The orbit (eye socket) is a bowl-shaped cavity made up of bone formed from the skull that contains the eyeball and the connective tissues surrounding the eyeball. The bone and connective tissues cushion and protect the eye. Muscles attached to the eyeball make it move in different directions[14]. These small muscles attach to the sclera near the front of the eye and to the bones of the orbit at the back. The orbit also contains nerves, fat, blood vessels and a variety of connective tissues.

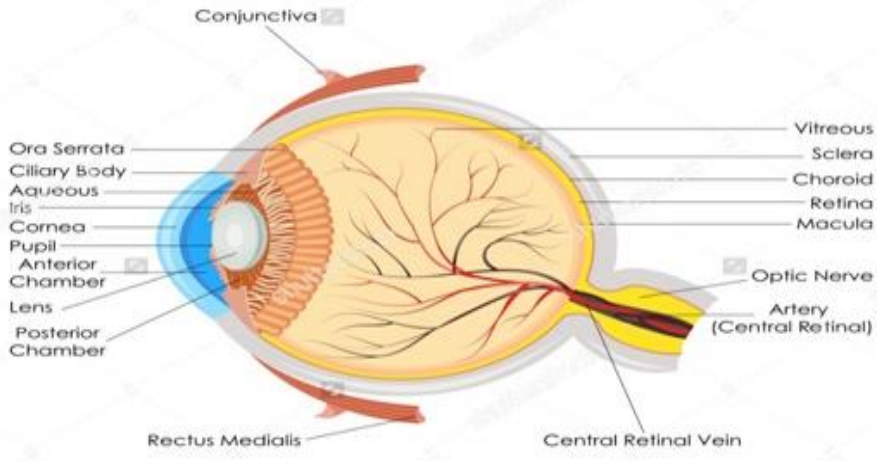

Figure 1: Structure of Eye [5]

Accessory structures: The accessory (adnexal) structures of the eye include the eyelids, conjunctiva, caruncle and lachrymal (tear) glands, accessory structures of the eye as shown in figure 02.

Eyelids: The eyelids (palpebrae) are folds of skin that cover and protect the eye. Muscles raise and close the eyelids [15]. The eyelids contain glands, which produce an oily secretion that covers the tear layer and prevents

tears from evaporating and the eyelids from sticking together.

1. The eyelid is described as having an anterior (front) and a posterior (back) lamella.
2. The anterior lamella consists of skin, a layer of fatty connective tissue and a layer of muscle fibers. It helps protect the eye and regulate the amount of light that reaches the eye.
3. The posterior lamella consists of a layer of muscle, the palpebral conjunctiva and the tarsal plates. The tarsal plates are 2 thick plates of dense connective tissue found inside each eyelid (upper and lower) that help form and support the eyelid.
4. Eyelashes grow from the edges of the eyelids. They help protect the eye from dust and debris.

Conjunctiva: The conjunctiva is a clear membrane mucous membrane. The thin, moist layer of tissue that lines some organs and body cavities, including the nose, mouth, lungs, airways, vagina and gastrointestinal (GI) tract. That lines the inner surface of the eyelids and the outer surface of the eye. The conjunctiva secretes mucus to lubricate the eyeball and keep it moist [16]. Bulbar conjunctiva is the part of the conjunctiva that covers the front, outer surface of the eyeball. Forniceal conjunctiva is the loose fold that connects the conjunctiva membrane that lines the inside of the eyelid with the conjunctiva membrane that covers the eyeball. Palpebral (or tarsal) conjunctiva is part of the conjunctiva that covers the inner surface of the eyelids [17]. The plica is a small fold of conjunctiva tissue next to the caruncle in the inside corner of the eye.

Caruncle: The caruncle is the small, pinkish portion of the innermost corner of the eye (or inner canthus) that contains oil and sweat (sebaceous) glands and conjunctival tissue.

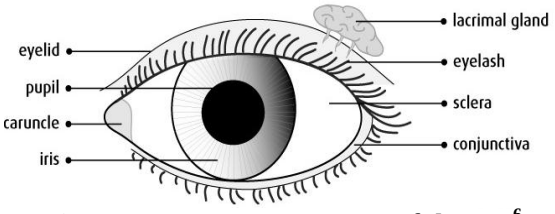

Figure 2: Accessory structures of the eye [6]

Lacrimal gland: The lacrimal gland (tear gland) is the almond-shaped gland located at the upper, outer corner of each eye. The lacrimal gland secretes tears to help keep the surface of the eye and lining of the eyelids moist and lubricated [18]. Tears help reduce friction, remove dust and debris from the eye and prevent infection. Small lacrimal ducts (lacrimal canaliculi) drain tears from the lacrimal gland through very tiny, openings (lacrimal punctum) inside the inner corner of each eyelid.

Function:

1. The eye is the organ that works with the brain to provide us with the sense of sight. It works much like a camera.
2. The main function of the eye is to collect light and turn it into electric signals, which are sent to the brain [19].
3. If we lose the vision in one eye, we continue to see most of what we could see before. When light enters the eye, it first passes through the cornea.
4. The light then passes through the pupil, where the iris adjusts the amount of light entering the eye.
5. The light then passes through the lens of the eye. The lens focuses light rays onto the retina, where it is changed into a signal that is transmitted to the brain by the optic nerve.

ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEMS [20]

1. Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.

2. To provide sustained and controlled drug delivery.

3. To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.

4. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.

5. To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.

6. To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.

7. To provide better housing of delivery system.

8. They can easily administered by the patient himself.

9. They have the quick absorption and less visual and systemic side effects.

10. Ocular drug delivery system has better patient compliance.

DISADVANTAGES OF OCULAR DRUG DELIVERY SYSTEM [21]

1. The drug solution stays very short time in the eye surface.

2. It shows poor bioavailability.

3. Shows instability of the dissolved drug.

4. There is a need to use preservatives.

LIMITATIONS OF OCULAR DRUG DELIVERY [21]

1. Dosage form cannot be terminated during emergency.

2. Interference with vision.

3. Difficulty in placement and removal.

4. Occasional loss during sleep or while rubbing eyes.

Physiology of vision: Light waves travel at a speed of 3into10^8m/s. Light is reflected into the eyes by the object within the field of vision white light is the combination of all the colors of the visible spectrum [22].

A specific color is seen by eye when only one wavelength is reflected by the object and all the others are absorbed. In order to achieve the clear vision, light reflected from objects within the visual field is focused on to the retina of each eye.

The processes involved in producing a clear image are

i. Refraction of the light rays
ii. Accommodation of the lens
iii. Constriction of the pupil
iv. Convergence of eyes
v. Activation of photoreceptors

Refraction of the light rays: The light rays from the object pass through the conjunctiva, cornea, aqueous humor, lens and vitreous humor in that order. All these structures refract the light such that it falls on the retina. This is called focusing. Maximum focusing is done by the cornea and the lens [23]. The light then falls on the retina. This light is received by the photoreceptors rods and cones, on the retina. The absorbed light activates the pigments present in the rods and cones. The pigments are present on the membranes of the vesicles. Thus, the light is then converted into action potentials in the membranes of the vesicles. These travel as nervous impulses through the rod or the cone cell and reach the synaptic knobs. From here the impulses are transmitted to the bipolar nerve cells, then to the ganglions and then to the optic nerves. Thus the nervous impulses generated in the retina are carried to the brain by about a million neurons of the optic nerve [24]. The vision is controlled by the occipital lobe at the back of the brain. The information received is processed and we are able to see the image. The image formed on the retina is inverted, as shown in figure 03 an over view of refraction of the light rays. However, the brain makes us see the image erect. So, though the eyes are essential for vision, any damage to the optic nerves also results in impairment of vision.

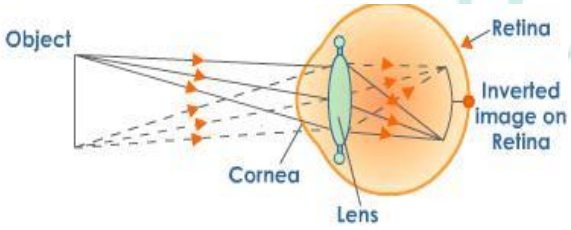

Figure 3: Over View of refraction of the light rays [11]

Accommodation of lenses: Accommodation is a reflex action of the eye to focus the light from an object on the retina [25]. The adjustment to the distance of the object is done by the ciliary muscles. The ciliary muscles contract and expand to make the lens thin and thick, respectively. This changes the focal length of the lens. If the object is far, then the focal length is increased and if the object is near, then the focal length is decreased. The optimal focal length is 6 meters or 20 ft.

Constriction of pupil: Pupils size influences accommodation by controlling the amount of light the pupils are constricted in a dim light they are dilated, as shown in figure 04 constriction of pupil. If the pupils are dilated if the bright light, to much light enters and damages the sensitive retina. If the pupil is constricted in dim light insufficient light would enter the eye to activate the light sensitive pigments. The iris consists of one layer of circular and one radiating smooth muscle fibers [26]. Contraction of the circular fibers constricts the pupil and contraction of the radiating fibers dilates it.

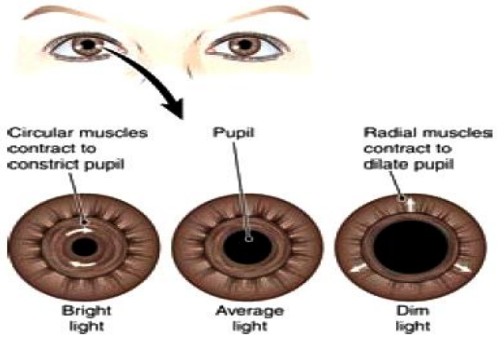

Figure 4: Constriction of pupil [15]

Convergence of eyes: Light rays from nearby objects enter the two eyes at different angles and for clear vision they must stimulate corresponding areas of two retinas [27]. An extrinsic muscle moves the eyes and obtains a clear image they rotate the eyes so that they convert on the object view and there is voluntary movement of the eyes both eyes moves and convergence is maintained. The eyes are focus on different objects is on different points of the same object.

Activation of photo receptors: It is the process by which the eye detects the energy of light via the Photoreceptors (rods and cones). It starts when the photoreceptors protein absorb the photon and cause changes in the cell membrane`s potential, leading to photo transduction [28].

To understand that lets have an idea about the structure of Photoreceptor is composed of the following parts:

1. The axon terminal of the photoreceptor that release neurotransmitter is the closest part to the visual field i.e. Cell body which contains nucleolus and the cell organelles.

2. The inner segment: full of mitochondria to provide the photoreceptor by ATP

3. The outer segment: modified cilia with large surface area. It contains a light absorbing protein, called opsin and sodium channels. The photon hits rhodopsin. And the process of phototransduction occurs as follows:

1. When Rhodopsin absorbs the photon, a conformational change in the retinal occurs (from cis to Trans).

2. This change of retinal activates a G protein that will from its side activate an intracellular protein that is called Transduction. This activation occurs in (amplification manner) because each G protein activates 100 transduction.

3. Transducin will activate an enzyme that is called cGMP Phosphodiesterase.

4. Glutamate release in the synapses will stop.

Glutamate release stops because no more calcium ions will be able to enter the photoreceptor. Calcium ions are necessary for exocytose of glutamate into the synapse.

Muscular control of the eyes: There are three types of movements associated with the eye that are due to the action of muscles [29]. They are the movement of the eye, the change in size of the pupil and the change in thickness of the lens as shown in figure 05 Binocular and stereoscopic vision. The movement of the eye is controlled by six eye muscles that attach the sclera to the bones lining the optic cavity. These six muscles are superior and inferior rectus, internal and external rectus and superior and inferior oblique muscles.

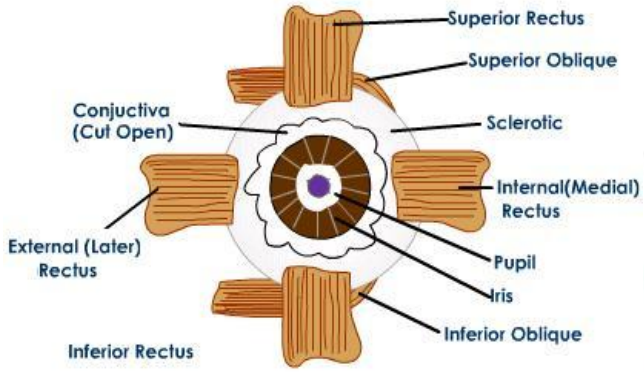

Figure 5: Binocular and stereoscopic vision [16]

Associated structures: There are certain structures associated with the eyes and carry out, mainly, the function of protection [30]. These structures are-

Eye brows: Along the arched upper ridges of the eye sockets are hairs that form the eye brows. They prevent the dust, rain, sweat, etc from entering the eyes.

Eye lids: Each eye in man is protected by two eyelids upper and lower. The upper lid moves and covers the eye at regular intervals. This is called blinking. This action protects the eye from foreign particles. In certain animals, like the fishes and frogs, there is a third eyelid called the nictitating membrane. In man, it is very small and vestigial.

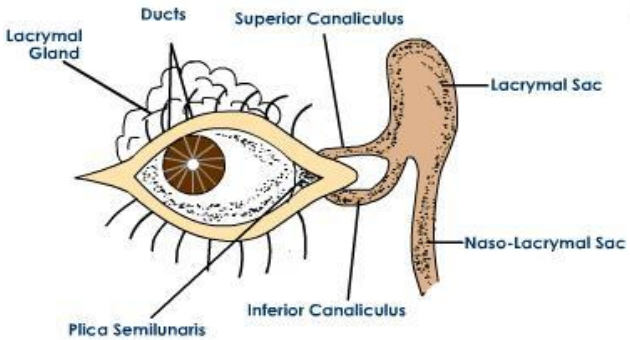

Figure 6: Secretions of lachrymal glands [27]

Lachrymal glands: They are also called the tear glands as they produce secretion called tears.

The lachrymal glands are present one on the outer upper border of each eye, Secretions of lachrymal glands as shown in figure 06. The lachrymal secretion is watery, alkaline and carries out the following functions

I) cleans the eyes

II) keeps the eyes moist

III) keeps the eyes free of bacteria as it contains bacteriolytic lysozyme

IV) Provides nutrition to the cornea.

Tears physiology: Tears are product of many glands in the eye that form the (tear film) that coats the eye [31]. Tear film is composed of many layers and has many physiological functions.

Layers of tear film:

Aqueous layer: It composed of layers, electrolytes, and proteins. It is produced by the lachrymal gland, and assists in distribution of tears, and osmo regulation [32]. While the proteins of the aqueous layer has a protective functions and other roles as follows:
Lipocalin: a protein found in tears and has a role in immune response and interaction with the cancer cells.
Lactoferrin: Has an antiviral, antifungal, and antibacterial activity. It also has enzymatic activity that possesses anticancer properties.
Lysozymes: enzymes that have antibacterial activity.
Lacritin: A glycoprotein that promotes tear secretion, and proliferation and survival of the epithelial cells.
Lipid layer: This layer coats the aqueous layer and prevents the evaporation of tears and spilling them onto the face .It is composed of an oily liquid that is called sebum. Sebum is produced by the tarsal glands.
Ocular drug delivery routes [33]:

Intra vitreal: It is a route of administration of a drug or other substance injected with in the vitreous humor of the eye in which the substance is delivered in to the eye. Intra vitreal administration of drugs is used to treat various conditions of the eye, Routes of administration Ocular drug delivery as shown in figure 7.

Intra cameral: The route of administration of drug with in a chamber, such as the anterior or posterior chamber of the eye. Example: anesthesia injection of an anesthetic agent in to the anterior chamber of the eye, usually during surgery.

Peril ocular: It is the route of administration of drug around the eye is called peril ocular. Example: peril ocular steroid injection involves placement of steroid around the eye to treat intraocular inflammation or swelling of the eye.

Suprachoroidal: The administration of the drug in the supra choroid region of the eye. The suprachoroidal space is a space lying between the sclera and the choroid.

Sub conjunctiva: The route of administration of the drug to the mucus membrane that lines the exposed portion of the eyeball and inner surface of the eyelids.

Topical: Topical administration is employed mostly in the form of eye drops, ointments, gels or emulsions to treat anterior segment diseases. It is the most preferred method due to the case of administration and low cost.

Systemic: The blood aqueous barrier and blood retinal barrier are the major barriers for the anterior segment and posterior segment ocular drug delivery respectively.

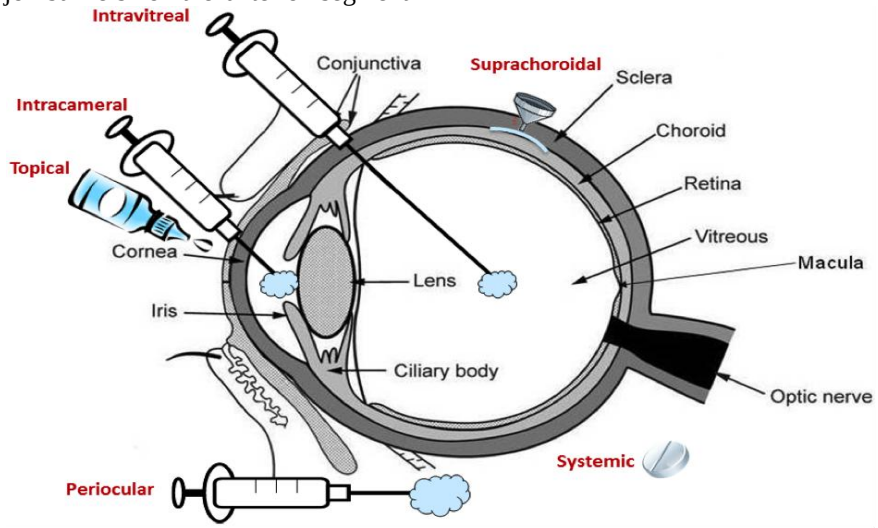

Figure 7: Routes of administration Ocular drug delivery [29]

OCULAR SUSTAINED DRUG DELIVERY SYSTEMS

In the novel drug delivery system various approaches like In situ gelling, use of mucoadhesive polymers, polymer coated Nanoparticles and Liposomal formulations are used. These delivery systems delay the elimination of active ingredient from eye and also improve corneal penetration of drug molecule [34].

Novel ocular drug delivery systems

1. Liposome:

Liposome is biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25-10,000 nm in diameter. They are having an intimate contact with the corneal and conjunctiva surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weights and thus increases the probability of ocular drug absorption[35]. The corneal epithelium is thinly coated with negatively charged mucin to which the positive charged surface of the liposome may bind. Formulated and evaluated soft contact lenses coated with ciprofloxacin entrapped in liposome.

2. Implants:

For chronic ocular diseases like cytomegalovirus retinitis, implants are effective drug delivery system. Earlier non biodegradable polymers were used but they needed surgical procedures for insertion and removal. Presently biodegradable polymers such as Poly Lactic Acid are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs [36].

3. Dendrimers:

The majorities of topically applied ocular drug-delivery systems are formulated either as solutions, ointments, or suspensions and suffer from various disadvantages such as quick elimination from the precorneal region, poor bioavailability, or failure to deliver the drug in a sustained fashion. Several research advances have been made in ocular drug delivery systems by using specialized delivery systems such as polymers, liposomes, or dendrimers to overcome some of these disadvantages. Ideal ocular drug-delivery systems should be nonirritating, sterile, isotonic, biocompatible, and biodegradable. The viscosity of the final product should be optimized so that the dosage form does not run out of the eye. Dendrimers provide solutions to some complex delivery problems for ocular drug delivery[37].

Some recent research efforts in dendrimers for ocular drug delivery include PAMAM dendrimers that were studied by Vandamme and Brobeck as ophthalmic vehicles for controlled delivery of pilocarpine and tropicamide to the eye. PAMAM dendrimers with carboxylic or hydroxyl surface groups, have been reported in improving residence time and enhancing bioavailability of pilocarpine in the eye. In the New Zealand albino rabbit model, the residence time of pilocarpine in the eye was increased by using dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability.

4. Nanotechnology based ocular drug delivery:

In a last few decades, many approaches have been utilized for the treatment of ocular diseases [38]. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposome's, nanomicelles and dendrites have been developed for ocular drug delivery [39]. Some of them have shown promising results for improving ocular bioavailability.

***4.1 Nanosuspensions*:**

Nan suspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect [40]. For commercial preparation of nanosuspensions, techniques like media milling and high pressure homogenization have been used. The higher drug level in the aqueous humor was reported using Eudragit RS 100 nanosuspensions for the ophthalmic controlled delivery of ibuprofen.

4.2 Nanoparticles:

Nanoparticles are colloidal carriers with a size range of 10 to 1000 nm. For ophthalmic delivery, nanoparticles are generally composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Drug loaded nanoparticles can be nanocapsules or nanospheres. In nanocapsules, drug is enclosed inside the polymeric shell while in nanospheres; drug is uniformly distributed throughout polymeric matrix [41]. From past few decades, nanoparticles have gained attention for ocular drug delivery and several researchers have made attempts to develop drug loaded nanoparticles for delivery to both anterior and posterior ocular tissues.

4.3 Niosomes:

These are bilayered, lamellar structures primarily composed of non ionic surfactants and a rigidizing agent which are hydrated by different methods in order to form a vesicle. They are either unilamellar or multilamellar enclosing an aqueous compartment. Being amphiphilic in nature, the non ionic surfactants are known to possess the ability to self assemble. Critical parameters in niosome preparation govern the formation of vesicular structures instead of micelles[42, 43]. The surfactants being non-ionic in nature do not cause any irritation to the ocular tissue and their ability to act as penetration enhancers can also be exploited.

Conventional ocular drug delivery systems

Topical drop instillation into the lower precorneal pocket is a patient compliant and widely recommended route of drug administration. However, most of the topically administered dose is lost due to reflux blinking and only 20% of instilled dose is retained in the precorneal pocket [44]. Concentration of drug available in the precorneal area acts as a driving force for its passive diffusion across cornea. However, for efficient ocular drug delivery with eye drops, high corneal permeation with longer drug cornea contact time is required. Several efforts have been made toward improving precorneal residence time and corneal penetration [45]. To improve corneal permeation iontophoresis, prodrugs, ion-pair forming agents and cyclodextrins are employed.

1. Topical liquid/solution eye drops:

Topical drops are the most convenient, safe, immediately active, patient compliant and non-invasive mode of ocular drug administration. An eye drop solution provides a pulse drug permeation post topical drop instillation, after which its concentration rapidly declines. The kinetics of drug concentration decline may follow an approximate first order. Therefore to improve drug contact time, permeation and ocular bioavailability; various additives may be added to topical eye drops such as viscosity enhancers, permeation enhancers and cyclodextrins [46].

2. Emulsions:

An emulsion based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. There are two types of emulsions which are commercially exploited as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems. For ophthalmic drug delivery, o/w emulsion is common and widely preferred over w/o system. The reasons include less irritation and better ocular tolerance of o/w emulsion [47].

3. Suspensions:

Suspensions are another class of non-invasive ocular topical drop drug carrier systems. Suspension may be defined as dispersion of finely divided insoluble API in an aqueous solvent consisting of a suitable suspending and dispersing agent. In other words, the carrier solvent system is a saturated solution of API. Suspension particles retain in precorneal pocket and thereby improve drug contact time and duration of action relative to drug solution. Duration of drug action for suspension is particle size dependent. Smaller size particle replenishes the drug absorbed into ocular tissues from precorneal pocket [48]. While on the other hand, larger particle size helps retain particles for longer time and slow drug dissolution. Thus, an optimal particle size is expected to result in optimum drug activity. Several suspension formulations are marketed worldwide to treat ocular bacterial infections. TobraDex suspension is one of the widely recommended commercial products for subjects responding to steroid therapy.

CONCLUSION

Finally I concluded that a novel approaches on ocular drug delivery system was developing the ophthalmic solutions are easy because we can easily target the eye to treat ocular diseases with wide variety of novel approaches. Progress in the field of ocular drug delivery has been established recently with controlled loading and sustained release. Hence, effective drug delivery and targeting is faced by challenges to overcome these barriers as a conventional drug delivery system.

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