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REVIEW ARTICLE

Ocular drug delivery system: A review

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ABSTRACT

The eye's complicated anatomy makes it difficult for pharmaceutical researchers to transport drugs to the patient desired areas via various methods of administration. The nano-based system's creation aided in the delivery of the medicine in the required concentration. Low drug contact time and poor ocular bioavailability are problems with older approaches, which are caused by Lacrimation, tear turnover and drainage of solution. Also as a result of its uniqueness architecture and physiology, Barriers of several kinds, such as distinct layers of cornea, sclera, and retina, containing conjunctival blood flow, choroidal blood flow blood retinal and blood aqueous barriers and so on, ocular medication the delivery has been successfully a big issue for scientists. Furthermore, anatomical obstacles and eye physiological circumstances are crucial factors that influence medication delivery system design. Nanosized carriers have been created to improve penetration, bioavailability, and residence duration, including micro/nanosuspensions, liposomes, niosomes, dendrimers, nanoparticles, hydrogels, and prodrug methods. This review examines different elements of ocular medication administration, with a focus on nanocarrier-based techniques, such as the anatomy of the eye, its obstacles, distribution pathways, and the problems and constraints involved with the creation of innovative nanocarriers. Drug distribution via the ocular route has shown to be a key advancement in the future.

INTRODUCTION

Pharmaceutical scientists find ocular medication delivery to be one among the most popular fascinating and challenging. Eye is the complex organ challenging to analyse from a drug perspective since it is an isolated organ; Drugs are generally administered to the ocular system to get a local effect on the surface or interior eye's surface [1]. The eye's distinctive anatomy prevents medication molecules from reaching the needed region of action. Drugs can be sent to the anterior or posterior parts of the eye sight. The most frequent disorders affecting the anterior chamber include glaucoma, uveitis, cataracts, allergic conjunctivitis, and infections. According to the World Health Organization, about 1 billion people are affected by uncorrected refractive error (88.4 million), diabetic retinopathy (3.9 million), cataract (94 million), corneal opacities (4.2 million), glaucoma (7.7 million), and trachoma (2 million), and also close visual impairments induced by uncorrected presbyopia. Traditional formulations like eye drops, solutions, most of suspensions, creams and ointments are utilized to treat anterior segment eye disorders. Even though eye drops represent for greater than 90% of all commercial ocular formulations, they cannot be considered appropriate for the treatment of ocular conditions. Due to a various types of mechanisms (tear dilution, lachrymal drainage and tear turnover), the majority of transdermally administered drugs are rinsed out of the eye, and as a result, ocular bioavailability is minimal [1]. Poor bioavailability for ocular drug is generated Structural and physiological limitations, such as the nasolacrimal drainage, corneal epithelial membrane's relative impermeability and tear dynamics poor corneal permeability, systemic absorption and blurred vision [2]. The main reasons why the conventional drug delivery systems no more suitable to

gratify criteria for providing at a steady rate over an extended period of time is poor bioavailability due to a lack of residence time at the activity site [1].

Many techniques have been created to solve the problem in recent decades [3]. Thenovel drug delivery systems (NDDS), including liposomes, nanoparticles, nanoemulsions, nanosuspensions, micelles, nanofibers, etc. have been developed to optimize the ocular drug delivery to overcome the limitations of conventional dosage forms. These systems are claimed to provide a prolonged residence time at the ocular surface, minimizing the effect of natural eye clearance systems. It should be possible with controlled and sustained drug delivery to provide drug therapeutic levels for a prolonged time at the activity site.[3]It also helps in terms of increasing corneal medication absorption while reducing precorneal drug loss [4]. This review provides the study of new upcoming approaches in the administration of ocular drugs systems to enhance contact time and controlled release, increase the therapeutic efficacy of the drug, to improve the bioavailability and to reduce the frequency of administration [1].

The Anatomical and Physiological Structure of the Eye

The eye is a one-of-a-kind essential sense organ of a human body, both physically and physiologically, because it contains a variety of structures with distinct physiological roles [3]. The human eye is circular in form, having a diameter of nearly around about 23mm. Behind its visible components are a complex array of sensitive systems that work together to transfer an image of the observed item to the brain. Vitreous humour, ciliary body, lens, cornea, conjunctiva, aqueous humour, iris, choroid, retina, and sclera comprise up the human eye from anterior to posterior section [2].

Conjunctiva:

The human eye conjunctival membrane is a thin mucous epithelial barrier that borders the first third of the eyeball and the interior of the eyelids. The conjunctiva assists to the tear film's production by secreting significant amounts of electrolytes, fluid, and mucins [4].

Cornea:

The cornea is a strong clear Transparent epithelial membrane located at the front of the eye. It performs a key optical function by refracting light reaching the eye, passing through the pupil and into the lens, which usually focuses the light across the retina [4].

Sclera:

The sclera is a strong white coating that surrounds the eyeball on all sides. It is composed up of a membrane that keeps the form of the eye and offers a connection to the eye's extrinsic muscle [5].

Pupil:

The pupil is the opening through which light enters the eye, hence the images we see and receive. The iris is important for this. The pupil's size drops or increases in proportion to the iris's diameter [5]. The pupillary reflex regulates the diameter of the pupil (and consequently the quantity of light absorbed into the eye) (also called as "light reflex") [4].

Iris:

Another membrane iris is a spherical contractile covering that lies behind the cornea and in front of eye lens. The iris functions as a diaphragm with a changeable size that adjusts the size of the pupil to control the quantity of light that enters the eye. It refers to the visible coloured portion of the eye [4].

Lens:

The lens is a narrow clear capsule encasing a transparent structure. The ciliary muscles encircle it and it is placed behind the pupil of the eye. It aids in the refraction of the passage of light through eye [4].

Aqueous Humor:

It's a jelly-like substance that is found in the eye's anterior chamber. The "anterior chamber of the eye," which is placed directly beneath the cornea and in front of the lens, is full of a watery fluid substance. The aqueous humour is a mildly alkaline salt solution containing trace amounts of sodium and chloride ions [4].

Ciliary Muscles:

The ciliary muscle, which is connected to the iris, is a ring-shaped muscle. The ciliary muscle controls the shape of the lens by contracting and relaxing it [5].

Vitreous Humour: The vitreous humour (also called as the vitreous body) is a huge area in each eye that takes up around 80% of the space in the human body. The vitreous humour, which fills

the chamber behind the lens of the eye, is a totally clear thin jelly-like fluid. The hyaloid membrane is a fragile translucent membrane that contains an albuminous fluid [4].

Retina:
The retina can be thought of as a "screen" on which light that has travelled via means of aqueous humour, cornea, pupil, lens, and ultimately the vitreous humour previously they approaching the retina forms a picture. The retina's job isn't merely to be a screen on which an image can be produced; it also collects the information contained in that image and sends it to the brain in a format that the body can understand. Photosensitive components in the retina convert light into nerve impulses which pass via the optic nerve on their way to the brain [5].

Choroid:
The choroid layer, which is located behind the retina, absorbs unwanted radiation and feeds the retina's outer layers. The choroid has one of the greatest blood flow rates in the body. The lamina fusa is a thin layer of tissue that connects the choroid to the sclera's inner surface.

Optic Nerve:
The second cranial nerve is the optic nerve which transmits nerve signals from the eye to the brain. These nerve transmissions carry picture information for the brain to process. The visible front surface of a optic nerve on the retina is referred to as the optic disc [4].

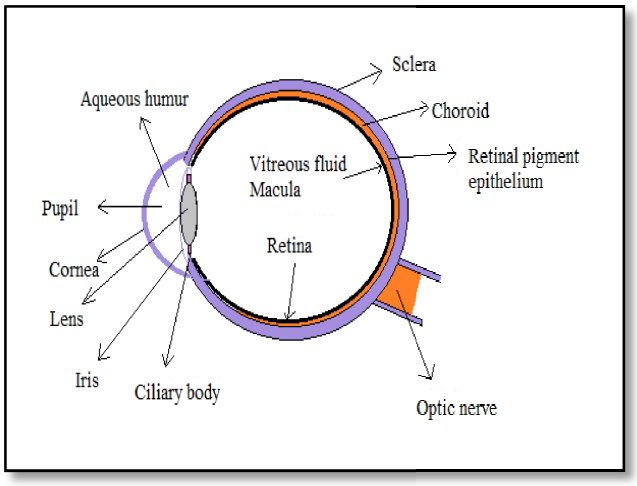

Figure 1: Stucture of human eye

Routes of Ocular Delivery
Drug administration into the ocular tissues can take a variety of routes. The route of administration is mostly determined by the target tissue. Topical, subconjunctival, intra-vitreal, retrobulbur, and intra-cameral are all prominent routes for ocular drug delivery [2, 4].

1. Topical Route:
To treat anterior segment illnesses, topical medication, generally in most cases, eye drops are used. Drugs are lost in the precorneal region and anterior segment, and the Schlemn canal removes them from the anterior chamber, or medication absorption through the iris-ciliary body are all problems with administration of a topical medication to the posterior section. Enzyme degradation in the anterior chamber limits the capacity of intact medicines to penetrate to posterior section tissues. In the domain of posterior segment drug delivery, topical administration has had limited effectiveness [3].

2. Subconjunctival Administration:
Drugs that don't go through the anterior section are introduced via the subconjunctival pathway. Because the sclera is having greater permeability than cornea, the medication is injected below the conjunctiva and travels through the sclera into the eye. Antibiotics, cycloplegics, and mydriatics are all widely used. Subconjunctival injections have traditionally been used to transfer medications to the uvea at higher concentrations. For a variety of reasons, this procedure of drug delivery is currently gaining traction. Progress in materials research and pharmaceutical formulation has opened up new doors for manufacturing controlled release formulations to deliver medications in the posterior section and direct the healing process following surgery [2, 4].

3. Intra-vitreal Route:
The medications are supplied to the vitreous immediately and retina via the intravitreal route. Small molecules, usually less than 500 Da, diffuse faster than large molecules. After intravitreal injection, there are two major methods for the drug to be removed: anterior and posterior channels [2].

Direct medication administration into the vitreous has the specific benefit of allowing for easier access to the vitreous and retina. It should be emphasised, however, that due to the Retinal Pigment Epithelium barrier, transport also it is more difficult to move from the vitreous to the choroid.. Small molecules can move quickly through the vitreous, whereas big molecules,

especially those that are positively charged, have limited mobility [4].

4. Retrobulbur Route:

Also because orbit isn't well-vascularized, adequately vascularized, medication administered via the retrobulbur route may penetrate the globe, resulting in minimal effect. In a retrobulbar injection, a needle is inserted between the orbital fascia and eyelid, and a medication is injected into the retrobulbar region behind the globe. This method is utilised to provide medicine to the posterior section in order to affect the nerve structure in that area. Retrobulbar injections are typically used for orbital or facial regional anaesthesia, but they may be used to deposit therapeutic drugs such as antibiotics, corticosteroids, and vasodilators locally. The other orbital structures and optic nerve can be damaged by retrobulbar injection [2].

5. Intracameral Route:

Medication is delivered directly towards the anterior region (e.g. acetylcholine) and the vitreous chamber is accomplished using intracameral injections (e.g. amphotericin B). In order to provide intracameral injections, general anaesthesia is required. Intraocular structures, such as the cornea endothelium, iris, and more, can be damaged by intracameral injections due to physical or chemical damage. Finally, the drug's method and mechanism of action, as well as sick circumstances, are critical factors that limit the formulator's route selection [2].

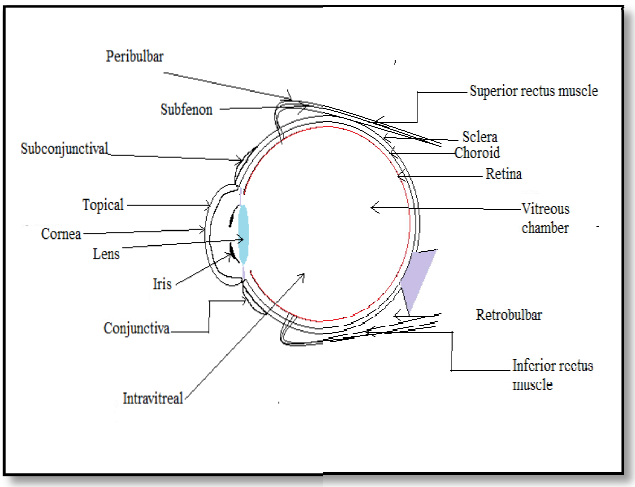

Figure 2: Route of drug administration

Table 1: Route of drug administration [3, 6]

Route of Administration	Benefits	Limitations	Approches in Disease Treatment
Topical Route	Shows high Patient compliance because to the self-administration and noninvasive nature of the treatment.	Tear dilution and turnover rates are higher, the cornea acts as a barrier, and efflux pumps are present.	uveitis, scleritis, conjunctivitis, Keratitis, blepharitis, episcleritis
Subconjunctival administration	Delivery toward the posterior and anterior segments, also the location of the depot formulations	Due to the existence of retinal pigment epithelium, it is difficult to transport medications to the retina.	retinitis ,Glaucoma, PU, CMV, AMD
Intra-vitreal route	Injections and implants are utilized to directly distribute drugs towards the vitreous and retina.	As a side effect, conjunctivitis, keratitis, retinal detachment, and haemorrhage might develop.	Retinal detachment, hemorrhage, cataract, endophthalmitis, patient incompliance
Retrobulbur Route	IOP involvement is minimal, making it excellent for administering a large amount of local anesthetic.	Because the medicine may penetrate the globe of the eye, the effect provided through this route is minimal.	Anesthesia
Intracameral Route	Deliver medications to the anterior and vitreous chambers directly.	Delivery of drug is difficult to the posterior segment.	Pupil dilation Anesthesia, inflammation, prevention of endophthalmitis, TASS, TECDS
Scleral administration	A promising vector for medication delivery in the posterior section.	Anterior segment has minimal drug delivery	glaucoma, diabetic retinopathy (DR) and age-related macular degeneration (AMD)
Systemic administration	When compared to eye drops, it's easier to distribute a greater volume.	Drug bioavailability and systemic absorption are poor in the retina.	posterior uveitis Scleritis, retinitis, episcleritis, CMV

PU - posterior uveitis, AMD - age-related macular degeneration, TASS - toxic anterior segment syndrome, TECDS - toxic endothelial cell destruction syndrome, CMV – cytomegalovirus.

6. Scleral Administration:
The sclera has lately emerged as a potential channel for medication delivery in the posterior region due to its huge surface area, easy accessibility, and permeability to macromolecules is rather high various methods of scleral drug delivery have been tried, including scleral plugs and implants, sun conjunctival injection, and subtenon injection. For the treatment of numerous posterior segment illnesses, trans-scleral medication delivery is a viable therapeutic option [3].

7. Systemic Administration:
Systemic administration has had limited effectiveness in delivering medications to the vitreo-retinal tissues because of the existence of the blood retinal barrier. The vitreous humour achieves just 1-2 percent of the plasma drug concentration, necessitating repeated injection to maintain therapeutic drug levels. This mode of delivery may produce systemic cytotoxicity due to non-specific drug binding to adjacent organs [3].

Advantages of Ocular Drug Delivery Systems:

- Self-medication, with ease of use and no need for trained personnel support, improves patient compliance when compared to parenteral methods.
- The eye can be utilized for achievement of good penetration of hydrophilic, low molecular weight medicines. Because of the huge absorption surface area and strong vascularization, the drug absorbs quickly and acts quickly.
- As an alternative to traditional routes of administration, ocular delivery of a suitable medicine could be beneficial in emergency therapy.
- Hepatic first-pass metabolism is avoided. and, as a result, the possibility of a dose reduction when compared to oral administration.

Disadvantages of Ocular Drug Delivery:

- The physiological limitation is the cornea's limited permeability, which results in low ophthalmic drug absorption.
- Because a large amount of the injected dose clears out through lacrimal duct, undesirable systemic adverse effects may occur.
- Because the drug is rapidly eliminated through tear flow and eye blinking, the therapeutic effect lasts only a short time, necessitating a frequent dosing regimen [5].

Barriers for Ocular Drug Delivery:
The human eye is 23 mm in diameter and has a cylindrical structure. The eyeball's structural components are categorised into 3 parts:

On the outside, there is a transparent cornea and a white, clear, opaque sclera. On the inside, there is a ciliary body, an extended form of the central nervous system, and the iris is located anteriorly, the choroid posteriorly[3]. Static and dynamic ocular barriers exist in human ocular anatomy to prevent hazardous chemical compounds, particularly therapeutic molecules, from reaching various tissues of the eye. The passive absorption of many medicinal medicines is slowed by ocular barriers in the posterior and anterior regions, lowering ocular bioavailability. Drug absorption is hampered by both static (corneal stroma, blood-aqueous barrier, corneal endothelium, corneal epithelium), dynamic (conjunctival barrier, tear dilution, and retinal-blood barrier) barriers, affecting topical formulation drug bioavailability [6].

1. Ocular Surface Barrier :
The ocular surface in touch with the tear film is formed from the conjunctival and corneal superficial layers. The ocular surface's purpose is to form a defence barrier against unwanted molecule penetration. The corneal surface accounts for only 5% of the overall ocular surface, with the conjunctiva6 occupying the remaining 95%. The cornea has five layers: epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium, however only the outermost layers of corneal squamous epithelial cells act as a barrier to intercellular drug penetration [3].

2. The Ocular Wall Barrier :
The stiff scleral collagenous shell, which is bordered internally by the uveal tract, is the structure of human eye globe. The optic nerve head occupies a little posterior aperture, the sclera contains 80% of the eye globe's posterior, while the cornea contains the globe's rest anteriorly. Scleral stroma is made up of collagen bundles, fibroblasts, and a little quantity of ground substance. The vascular episclera lines the surface of this tissue, which is essentially a vascular. The sclera is punctured by a vast number eye channels that allow arteries and nerves to pass across to the side of the choroid.

Scleral thickness varies between 0.3 and 1.0 mm in people, with the posterior pole being the thickest. The choroid is among the most well-known vascularized tissues in the body, with one of the greatest blood flow rates. The fenestrated innermost layer of chorio-capillaris, middle medium, and outer most huge vessels make up this layer, which has an average thickness of 0.25 mm [3].

3. Retinal Barrier :

The retina is divided into ten several layers: 1. the Retinal Pigment Epithelium, 2. the external limiting membrane, 3. photoreceptor outer segments, 4. the outer nuclear layer, 5. the outer plexiform layer, 6. the inner nuclear layer, 7. the inner plexiform layer, 8. the ganglion cell layer, I the nerve fibre layer, and 9. the internal limiting membrane [3].

This barrier, which is situated in the posterior chamber, prevents medications from the systemic circulation from reaching the retina. It is made up of the retinal capillaries tight walls and retinal pigment epithelium. Although medications can easily reach the choroid's extra vascular space thanks to the choroid's leaky and vast vasculature, retinal endothelia and retinal pigment epithelium prevent them from reaching the retina. The blood–retinal barrier, like the blood–aqueous barrier, keeps xenobiotics and hazardous chemicals out of the eyes. Drug transport to the retina and vitreous humour via the choroid via the systemic circulation is limited by this natural defence mechanism. Intravitreal injections, local injections, lipophilic prodrugs, and ocular implants have all been employed in the delivery of retinal drugs, in addition to systemic and topical administration. These approaches have their own drawbacks and limits, thus new drug carriers that are safe, convenient, and effective in traversing potential ocular barriers are needed [7].

4. The Loss of Drugs Through the Ocular Surface:

The removal of lacrimal fluid is accomplished by the flow of lacrimal fluid which implanted substances from the eye's surface after instillation. Although the reality that lacrimal turnover is only around 1 litre per minute, the surplus volume of the injected fluid is quickly transported towards the nasolacrimal duct. Systemic absorption rather than ocular absorption is other non-productive source medication elimination. Bioavailability can happen after the fluid has gone through the nasal cavity or straight from the conjunctival sac via local bloodstream [4].

5. Lacrimal Fluid – Eye Barriers:

The corneal epithelium inhibits drugs from being absorbed into the eye from the lacrimal fluid. Tight connections occur between ocular epithelial cells, limiting paracellular drug permeation. As a result, lipophilic medications often have a corneal permeability that is at least a factor of greater than hydrophilic pharmaceuticals. The conjunctival membrane is a leakier epithelium than the cornea in general, and conjunctiva surface area is almost 20 times that of the cornea [4].

6. Blood- Ocular Barriers:

Blood-ocular barriers protect the eye from xenobiotics in the bloodstream. The blood-aqueous barrier and the blood-retina barrier are the two elements of these barriers. In the uvea, endothelial cells ((beneath the sclera, the middle layer of the eye)) make up the anterior blood-eye barrier. The iris, ciliary body, and choroid make up the iris.

This barrier inhibits plasma albumin from reaching the aqueous humour, as well as hydrophilic medicines from plasma reaching the body fluid (aqueous humour). The posterior barrier between the circulation and the eye is formed by the retinal pigment epithelium (RPE) and the tight walls of retinal capillaries. The choroid's vasculature, unlike retinal capillaries, has a lot of blood flow and permeable walls. Drugs can easily penetrate the choroidal extra vascular space, but their distribution into the retina is limited by the RPE and retinal endothelia [4].

7. Blood-Aqueous Barrier:

This barrier is made up of uveas endothelial cells and is situated in the anterior portion of the eye. It prevents hydrophilic medicines from entering the aqueous humour from the systemic circulation. This barrier is occasionally compromised by inflammation, resulting in increased transient drug absorption. They make up the blood–ocular barrier, together with the blood–retinal barrier. The iris epithelium and cilliary bodies are responsible for pumping anionic medicines from the aqueous humour into the systemic circulation [7].

Mechanism of Ocular Drug Absorption:
Drugs injected into the eye must pass through the cornea first, then through the non-corneal pathways. Drug diffusion over the conjunctiva and sclera is included in these non-corneal pathways, which appear to be especially relevant for medicines which are poorly absorbed via the cornea [4, 8].

1. Corneal Permeation:
From the precorneal region, medicines permeate across the corneal membrane.

a) **Drug Absorption Barriers:** The efficiency of medication absorption into the inner eye is directly influenced by tears. The diffusional mechanism through the corneal membrane is responsible for the effective absorption of most ophthalmic medications. The rate and magnitude of which the eye's transporting mechanisms occur determine the efficiency of the absorption process. The physicochemical features of the permeating molecule and its interaction with the membrane determine the flow of any medicinal molecule over the biological membrane. The amount of transport or absorption that occurs is also determined by the precorneal fluid leakage or turnover physiological process. For Transcorneal drug permeation, cornea is categorized into three different layers: endothelium, epithelium and stroma.

The resistance supplied by the different layers varies substantially depending on the physicochemical features of a diffusing medication. Because epithelium is lipodal, it acts as a diffusional barrier against ionic or other water soluble or polar substances. Compounds having a low polarity, on the contrary, face greater diffusional barrier in the hydrophilic stroma layer. The "differential solubility notion" is a widely used concept for medication absorption over the corneal membrane [4].

2. Non Corneal Permeation:
In the specific case of structurally comparable corneal stroma, the most common path of drug absorption is likely diffusion through the intercellular aqueous media. As a result, it is impossible to rule out the existence of a partitioning mechanism. The conjunctiva, like the cornea, is made up of an epithelial layer that covers an underlying stroma. However, the conjunctival epithelium provides far less resistance than the corneal epithelium.

Different factors responsible for diposition of ocular drugs:

- The bioavailability of drugs given to the eyes is crucial. Protein binding, drug metabolism, and lachrymal drainage are only few of the physiological aspects that might alter a medication's bioavailability.

- The scale of the protein drug complex prevents medicines attached to proteins from entering the corneal epithelium. Protein binding of a pharmacological ingredient might quickly nullify its therapeutic efficacy by leaving it inaccessible for absorption due to the short period an ophthalmic drop may stay present in the eye (due to lachrymal drainage).

- The ocular residence period of traditional solutions is only a few minutes, and a topically administered drug's total absorption is only 1–10 percent. Tears, like other biological fluids, include enzymes (such as lysozymes) that can break down the drug ingredient metabolically.

- The drug substance's physicochemical characteristics, and also product formulation, are essential. Because the cornea is a membrane-barrier with bothhydrophilic and lipophilic layers, pharmacological compounds with those of lipophilic and hydrophilic properties permeate it most efficiently.

- Adjusting solution pH to increase the fraction of unionised medication in the administered dosage is beneficial for corneal penetration. Drugs that are extremely insoluble in water do not easily pass through the cornea [8].

a) Formulations for Ophthalmic Drugs

Ophthalmic medications are designed to bring active ingredients into touch with the eye's surface so that they may be absorbed. Increased medication penetration and intraocular drug delivery may arise from extending the corneal contact duration. Other components, Moreover active medicine, should be included in ophthalmic formulations to manage different

formulation properties, such as buffering and pH, osmolality and tonicity, viscosity, and antimicrobial preservatives. Regardless of the fact that many components are labelled as inactive, they can change medication permeability across ocular surface barriers and alter the medicine's therapeutic efficacy.

b) Nasolacrymal Drainage System

Three components make up the nasolachrymal drainage system: the distributive system, the secretory system and the excretory system.

The eyelids and tear meniscus surrounding the open eye's lid margins forms the distributive system, which disseminate tears around the ocular surface by blinking, preventing dry regions from forming.

Basic secretors, which are triggered both blinking as well as temperature changes caused by tear evaporation, and reflex secretors, which have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimuli, make up the secretory system.

The nasolachrymal drainage system consists of the excretory components: the lachrymal sac; the nasolachrymal duct, and the nasolachrymal duct, the lachrymal puncta, superior, inferior.

The two puncta of the lachrymal canaliculi in humans are referred to as the apertures, and they are located on the lachrymal papilla, which is a raised region. The mucous layer that lines the ducts as well as the lachrymal sac is thought to absorb the majority of tears, with just a little amount reaching the nasal tube [9].

c) Interests of Novel Ophthalmic Drug Delivery:

The ocular medication delivery environment is extremely competitive and continuously changing. The desire for innovative medication delivery is being fueled by new kinds of medicines and biologics. Pharmacotherapeutics' principal objective is to create an efficient system. medication concentration at the action's site for a long enough time to elicit a reaction. The objective is to create a system that has increased ocular medication absorption and activity duration while posing a low risk of ocular problems. The achievement of their appropriate concentration at the action's site, rather than the absence of efficient medications, is a key difficulty in ocular drug delivery [8, 9].

The introduction of new and novel methods for boosting treatment efficacy predicts that physicians and patients will have a broader selection of dose forms to choose from in the coming decade. The bulk of formulation efforts are aimed at improving ocular medicine absorption by lengthening drug retention time in the cornea as well as conjunctival sac, and also delaying drug release from the delivery system by reducing precorneal drug loss [10, 11].

Novel Drug Delivery Systems:

Treatment strategies based on nanotechnology are now commonly used to treat ocular problems affecting the human eye's anterior and posterior portions. The influence of nanotechnology on this issue is that it can effectively overcome the limits of traditional delivery techniques in ocular medication administration as well as various obstacles found inside the eye. Transferring medication through the ocular channel is challenging owing to underlying variables such as rapid removal of eye-drops at the corneal surface due to quick nasolacrimal drainage, transportation of pharmaceuticals beyond the cornea blood, and the ocular barrier. Drug absorption to the posterior surface of the eye is also limited due to the sclera, conjunctiva, cornea, and vitreous barriers. Nanocarriers, whose are currently routinely used for regulated and targeted medication delivery, appear to be the next best chance. Nanocarriers allow for precise targeting and long-term release of chemicals at the desired location. There have been established liquid dosage forms such as nanosuspension and microemulsions; particulate carriers such as polymeric micelles and lipid - nanoparticles, microparticles, SLN, NLC; vesicular carriers such as niosomes, liposomes; and many others such as prodrug approaches, dendrimers and hydrogel systems. These nanocarriers and their potential in ocular drug delivery will be discussed in detail in the subsequent areas [2].

1. Microemulsion:

Microemulsion has been utilised as a medication carrier for percutaneous, ophthalmic, oral, and parenteral delivery. It is a thermodynamically stable colloidal dispersion of water and oil stabilised by surfactant and cosurfactant [12-14]. Because of their greater solubilization capacity, thermodynamic stability, transparency, ease of preparation, and high diffusion as well as absorption rates, microemulsions offer an intriguing and potentially quite powerful

alternative carrier system for drug delivery when compared to a solvent without a surfactant system [15-17]. Because of their inherent qualities, which are unique to the natural protection of the eye. They can be readily sterilised and are made using low-cost technologies such as auto-emulsification or energy supply. *In vivo* findings and early tests using microemulsion on healthy volunteers revealed a delayed impact and an increase in drug bioavailability. The postulated process is based on the adsorption of the nanodroplets that make up the internal phase of the microemulsion on the cornea, which acts as a reservoir for the medication and so prevents it from draining [2]. Vandamme et al., study on utilization of microemulsions in ocular medication administration takes a thorough look at the different advancements and limitations in the area. The aqueous phase, organic phase, and surfactant/cosurfactant systems chosen are all essential characteristics that might impact the system's stability. The solubility of the therapeutic molecule, such as indomethacin or chloramphenicol, is significantly improved by optimising these components. Microemulsion systems have utilized to increase permeability through the cornea, in addition to solubility. propylene glycol, Pilocarpine, PEG 200, lecithin, as a surfactant/co surfactant, & isopropyl myristate even as oil phase have been created as a nonirritating oil-in-water system for the rabbit animal model [18-19].

2. Nanosuspension:

Another nano-controlled release technology is nanosuspension, which help in the treatment of a variety of eye ailments. Surfactant stabilises the colloidal discrete system, which is heterogeneous in character. Their size spans from 10 to 1000nm, which aids in overcoming the challenges of ocular medication delivery. Nanosuspension can be thought of as a safe haven for solutions that have a hard time dissolving in lachrymal fluids. They can act as carriers for hydrophobic solutions, increasing medication dissolvability [20, 21].

Silva and colleagues created silicone-based imprinted and non-imprinted hydrogels in which they contained the antibiotic MXF (moxifloxacin hydrochloride) and tested its therapeutic efficiency as Soft Contact Lenses (SCLs). There were no significant differences in the release of silicone (3-tris (trimethylsilyloxy) silylpropyl 2-methylprop-2-enoate) hydrogels between TRIS/AA and TRIS + D hydrogels. TRIS/AA + D hydrogels and TRIS had faster and longer release times, respectively. As a result, this comparison was beneficial for imprinted materials used in daily therapy SCLs [22].

Using the nanoprecipitation process, Ahuja and his colleagues created a Eudragit S100-based nanosuspension encapsulated with diclofenac *In-vivo* experiments on a rabbit model of PGE2-induced ocular infection demonstrated that the proposed formulation inhibited PGE2-induced polymorphonuclear leukocyte score for lid closure and migration better than diclofenac's aqueous solution. As a result, The Eudragit S100 nanosuspension were discovered to be effective a more powerful and effective anti-allergic drug for ophthalmic administration [23].

3. Micro and Nano- Particles:

Nanoparticles carriers for ocular applications include microspheres, microparticles, nanospheres, and nanoparticles. Because of the substantially slower ocular clearance rate of particles, absorption of medication of eye is significantly increased as compared to eye drop solutions. Large microparticles may not be well tolerated by ocular tissues, resulting in patient noncompliance. Nanoparticles, on the contrary, have been extensively researched as possible ophthalmic extended action delivery methods. In 1986, Li et al. Nanoparticles were explored as a possible delivery of progesterone to the eye. Following topical application of either the nanoparticle suspension or the control solutions, concentrations of [3H] progesterone in several ocular tissues of the albino rabbit were measured at various periods. According to a study of concentration-time profiles, the tissue concentration of progesterone after dermal application of nanoparticles about four to five times lower than that attained with control solutions [24].

In comparison to a commercial formulation, Calvo et al. 1996 found that PECL nanoparticles, PECL nanocapsules, and submicron emulsion containing indomethacin increase indomethacin ocular penetration [25].

De Campos et al. 2001 studied the use of chitosan (CS) nanoparticles to increase the transport of cyclosporine A to the ocular surface. They discovered that rabbits were given CyA-loaded CS nanoparticles by topical instillation, they were able to achieve significantly exterior ocular tissues with greater therapeutic doses (i.e.,

cornea and conjunctiva) for at least 48 hours while maintaining negligible or undetectable CyA levels in inner ocular structures (i.e., iris/ciliary body and aqueous humour), blood, and plasma, as compared to plain CS solution [26].

4. Solid Lipid Nanoparticles (SLN):

Colloidal nanoparticles with an array of sizes 10 nm to 01 m are referred to as SLN. The nanoparticle is made from synthetic or natural lipids and is useful for improving medication delivery and lowering toxicity [27-29]. These are distributed colloidal systems with steroid, triglycerides, and fatty acids as components. The solid lipid in SLN aids in the regulated release of the medicine by impeding the substance's mobility in the solid state compared to the liquid state [30-32]. These nanoparticles have a number of benefits over conventional carriers, including the ability to incorporate compounds that are equally hydrophilic and lipophilic. Toxicity is less of a worry since the medications are entrapped in the carrier owing to biocompatibility [33].

Because of their nano size, SLN can pass through eye barriers such as the epithelial barrier, the blood–aqueous barrier, and the blood–retinal barrier, and have been discovered to be effective for opthalmic drug delivery system because they help to increase corneal absorption, thus increasing bioavailability and retention time at the ocular site, allowing for sustained drug release [34]. SLN have a number of advantages, including the capacity to detect the drug, high drug loading capacity for either hydrophilic or hydrophobic medicines, long-term stability, and ease of production at large scale [35]. Because of their lipophilic nature, drugs can easily pass through the corneal site, increasing their absorption by ocular tissue [36-38].

By incoropting Natamycin in SLN, Khames and coworkers created a therapy for fungal keratitis using the emulsification-ultrasonication approach (FK). The proposed formulation assisted in overcoming NAT's limited corneal penetration and extending its duration within the eye. The antifungal activity of the medication was discovered to be greater without creating any ocular harm [39].

Using meltemulsification and ultrasonication, Ahmad and colleagues produced a formulation that loaded etoposide into solid lipid nanoparticles. A Box-Behnken design was used to optimise the prepared formulation. To characterise the size of a formulation, penetration ability, and entrapment effectiveness, many measures were employed. Albino rats were used in the scintigraphic study to assess the amount of a substance in the ocular region. According to the findings of the study, SLN loaded with etoposide assisted in keeping dosage at the correct concentration without causing any major side effects [40].

5. Liposomes:

Phospholipids, lipid conjugated polymers, and cholesterol are all components of liposomes. Liposomes are classified primarily by the presence of multiple phospholipid layers and their size, which includes small unilamellar vesicles with sizes ranging from 10 to 100 nm, large unilamellar vesicles with sizes varying from 100 to 300 nm, and multilamellar vesicles with more than a single phospholipid bilayer [41, 42].

Liposomes' unusual shape allows them to transport both hydrophobic and hydrophilic drugs to their target sites. The presence of a lipid coating on the outer core of liposomes makes them biodegradable in nature. The presence of charged particles on the surface of liposomes is determined by the kind of lipid utilised in their creation [43]. Because of their specificity, structure framework, which entraps both hydrophilic and lipophilic drugs exerts targeted delivery at the location of action, the liposomal formulation helps in minimising various effects such as endophthalmitis, vitreous haemorrhage, and retinal detachment that are associated with intravitreal instillation of drugs. The drug's reduced bioavailability after topical instillation is attributed to a shortened precorneal residence period caused by quick nasolacrimal drainage and tear turnover, which results in less absorption via the conjunctiva [44, 45].

Macular edoema (ME) is a condition caused by a decrease in the permeability of the retinal capillaries. Li et al. used the calcium acetate gradient technique to manufacture a liposome formulation loaded with Triamcinolone Acetonide (TA) medication, which was then coated with chitosan (TA-CHL) to boost the efficacy of TA. The TA formulation was discovered to be safe for ocular administration. The study indicated that TH-CHL was a more successful new delivery method because of its physical stability, high Entrapment Efficiency (EE), long-term drug release, and low toxicity when used as an eye drop [46-48].

De Sá et al. developed a topical liposomal formulation containing voriconazole (VOR) to treat fungal keratitis with the assistance of a coworker. The formulation's characterisation properties included average diameter, drug entrapment efficiency, the Poly-Dispersity Index (PDI) and drug recovery. *Ex vivo* permeation investigations, irritancy levels, *in vitro* mucosal interaction and *in vitro* mucosal interaction were all evaluated. On completing the hen's egg-chorioallantoic membrane test (HET-CAM test), the EE was determined to be 80%, also the preparation labelled as "non-irritant." According to the findings, VOR liposomes have a lot of capability to cure fungal keratitis [49].

Huang et al. developed a glaucoma medication. In need to succeed low ocular bioavailability, a liposomal formulation of Betaxolol Hydrochloride and Montmorillonite (Mt) was created. The designed and refined Mt-BH-LP was discovered to be beneficial in lowering IOP and retaining greater ocular bioavailability in this investigation [50].

6. Niosomes:

Niosomes are bilayered primary vesicles made up of non-ionic surfactants with the unusual capacity to capture both of lipophilic and hydrophilic molecules (in vesicular bilayer membranes) (in aqueous compartments). The size of niosomes is typically between 10 nm and 1 m. Because of the functional group present on their hydrophilic heads, niosomes are simple to manufacture and modify. Niosomes are non-immunogenic and biodegradable. They are chosen over liposomes for a variety of reasons, including cost and lengthy storage period (shelf life), also the fact that they do not require particular handling or storage conditions. As niosomes can lessen the drug's negative effects by lowering its systemic absorption, they can also improve the drug's therapeutic efficacy [51].

Niosomes are adept in transporting medication to the ocular cavity in a targeted manner. The niosomes' vesicles serve as a storage facility for the medication, allowing it to transporting to the particular site of action over time. Niosomes can be injected into the eyes as drops, which increases preocular retention on the eye's surface owing due to cholesterol, which improves the hardness of the niosome membrane's bilayer, minimising systemic drainage and improving precorneal retention on the eye's surface. The *in vitro* stability profile of niosomes is preferable greater as compared to that of traditional dosage forms. Niosomes are lipid vesicles that increased the pace and extent of drug absorption by loading and passing the drug across an eye barrier, changing the permeability of the conjunctival and scleral membranes in the ophthalmic area, and thereby increasing drug absorption. Niosomes provide a longer duration of effect by inhibiting opthalmic biotransformation into lachrymal fluid. Ocular blood pressure, dried eyes, eye infection and glaucoma can all be treated using niosomes [52].

Topically applied natamycin filled niosomes in Ketorolac Tromethamine gels enhanced penetration rate, boosting natamycin efficiency by lowering infection associated with Fungal Keratitis (FK). During the *in vitro* testing, it was discovered that when created formulation was compared to commercial preparation, hindrance increased by up to 57.32 percent. When compared to other formulations as well as combination commercial formulations, the formulation exhibited encouraging outcomes into the therapy of candida keratitis (Natacyn and Ketoroline). All *in vitro*, *in vivo* experimental, and histological examinations revealed that the niosomal formulation provided superior outcomes [53].

7. Nanostructured Lipid Carrier (NLC):

The second generation of nano lipid carriers is known as NLC. They're composed of a mix of biocompatible lipids, surfactants, and pharmaceuticals. In compared to SLN, NLC is a preferable alternative because to its biocompatibility and stability. NLC was created to address drug escape via the matrix during storage as well as poor drug loading efficiency. NLC is prepared using a variety of processes, including cold homogenization, heat emulsification, ultrasonication, and hot homogenization.

Because of its greater biocompatibility, NLC shows the most promise for ocular delivery. They have altered drug release kinetics as well. Its biocompatibility makes it a possible medication delivery method. NLCs are also nonimmunogenic, physiologically non-toxic, and compatible, in addition to all of these qualities. Because the majority of medicines are lipophilic, biocompatibility with lipids and solubility are important aspects of NLC formulation [54].

Almedia and colleagues created an eye drop containing ibuprofen in type of dispersion that

included a mixture of lipid nanoparticles and a thermo responsive polymer with mucomimetic capabilities (Pluronic F-127). The toxicity to the cell of the formed dispersion was then tested in Y-70 human retinoblastoma cells, and considerable cytotoxicity was found. The reduction test Alamar Blue was used to screen for NLC-related cytotoxicity, which revealed that it was harmless. The results later revealed improved bioavailability and therapeutic effectiveness of ibuprofen, as well as sustained-release drug profiles [55].

8. Polymeric Micelles:

Polymeric micelles have a nanoscopic core surrounded by an amphiphilic copolymer shell. They vary in size from 10 nm to 100 nm and offer good solubilizing properties for poorly soluble medicines. Surface modification is also feasible. Polymeric micelles confirmed excellent carriers of hydrophobic medicines and have aided in protein distribution across biological membranes as a drug delivery mechanism. They're also in charge of improving the stability of unstable medications and regulating drug release patterns [56].

Nifedipine loaded in PLA-PEG micelles was created by Xu and his colleagues. This was used as a cataract preventative eye drop. The appearance of a negative calcium ion influx aided in the refinement of anticataract action. It also shown satisfactory results by effectively inhibiting anticataract action by limiting extracellular calcium ion influx, as well as high biocompatibility and bioavailability [57].

Li and his colleagues created Diclofenac-loaded Rb1 micelles (Rb1-Diclofenac micelles) and tested them for ocular penetration and anti-inflammatory properties. The rabbit's eyes were tested for irritability with Rb1-Dic micelles, which were determined to be non-irritant. Rb1 improved *in vivo* corneal permeability and anti-inflammatory efficacy when compared to commercial diclofenac eye drop [58].

9. Hydrogels:

Hydrogels are cross-linked polymeric assemblies made up entirely of water. Because of their hydrophilic functional group, hydrogels have a unique capacity to absorb water. It is possible to employ a natural or synthetic polymer to make hydrogels. Hydrogels are frequently employed within the domain of ocular tissue engineering. Hydrogels are often modified for ocular medication delivery in the therapy of ophthalmological problems. It is claimed that a high hydrophilicity in the drug in the hydrogel result to rapid drug liberation [59, 60].

Silva and colleagues created silicone-based imprinted and non-imprinted hydrogels in which they contained the antibiotic moxifloxacin hydrochloride along with tested its therapeutic efficiency as Soft Contact Lenses (SCLs). There were no significant differences in the release of silicone (3-tris (trimethylsilyloxy) silylpropyl 2-methylprop-2-enoate) hydrogels with TRIS/AA hydrogels and TRIS + D. TRIS and TRIS/AA + D hydrogels had quicker and longer release times, respectively. As a result, this comparison was beneficial for imprinted materials used in daily therapy SCLs [61].

Liu and colleagues developed a degradable microsphere formulation that delivered aflibercept in a precise manner. They suspended the medication in a thermo responsive poly (ethylene glycol)-co-(lactic acid) diacrylate/N-isopropyl acrylamide (PEG-PLLA-DA/NIPAA) hydrogel. They investigated EE and *in vitro* drug release patterns using radiolabelled aflibercept Iodine-125 (125I), which also demonstrated changes in dry weight that produced a degradation profile of hydrogel. Finally, the degraded toxicity of drug delivery system byproducts was assessed using the LIVE/DEAD® test method to determine cell viability. In comparison to bolus injection loaded hydrogel, the use of a microparticles hydrogel system to treat ocular neovascularization was shown to be both safe and effective [62].

10. Prodrugs:

Prodrugs are simple drug derivatives that are transformed to the active parent medication chemically and/or enzymatically. Most opthalamic medications, such as dipivalyl epinephrine, timolol, cyclosporine A, and tilisolol [63], have functional groups like carboxylic acid, alcohol, phenol also amines which providing for themselves to derivatization by improved corneal permeability.

Prodrugs can extend the duration a dosage spends in the conjunctival sac. Drugs with a low absorption rate and unable to pass the blood-brain barrier are transformed to prodrugs, which easily cross the barrier and are bioconverted to generate drug and pro-moiety. The addition of polymer and cyclodextrin to eye solutions

changed pilocarpine prodrug ocular absorption and irritation [2].

Ganciclovir with its monoesters prodrugs-acetate, propionate, butyrate, and valerate-were examined in the eyes by Mitra and colleagues. They discovered that when the ascending ester chain length rises, the prodrug's vitreal clearance increase and hydrolysis rate, and the prodrug's mean residence period climbs 3-4 times that of ganciclovir [64].

11. Dendrimer:

Dendrimers have successfully investigated new drug delivery routes and can deliver drugs with greater water solubility, bioavailability, and biocompatibility [65]. Vandamme et al. 2005 designed and analysed poly (amidoamine) dendrimers including fluorescein as regulated ocular medication delivery. In various series of dendrimers, they investigated the effects of a molecular weight, gradual but controlled growth in size, and the quantity of amine, hydroxyl surface groups and carboxylat. Dendrimers having carboxylic and hydroxyl surface groups were utilized in the solutions have a longer residence duration. As the concentration of dendrimers (0.25-2 percent) rose, the remanence time increased.

CONCLUSION

In the fields of pharmaceutical technology and ophthalmology, ocular drug transporters are extremely important. Because tear fluids wash away the topically administered medication solution, ocular bioavailability is hampered by the eye's specific features and ocular barriers. As a result, formulation of innovative and adequate drug delivery methods for the therapy of ocular illnesses is required. Niosomes, Liposomes, Microemulsions, nanosuspensions, hydrogel, NLC (nanostructured lipid carrier), SLN (solid lipid nanoparticles), Prodrugs and polymeric micelles are just a few of the nanoformulations that have been studied and found to deliver drugs at therapeutic doses in a sustained manner while also assisting in the cumulative improvement of drug bioavailability at the target site. Drugs encapsulated in various nanocarriers have discovered the effective in treating a variety of ocular ailments. The area of ocular medication administration has shifted from traditional drops to sustained release and targeted ocular delivery devices as an outcome of recent technical advancements. Combinatorial approaches appear to be a focus of study in the creation of safe and efficient ocular medication delivery systems in the current technological era.

REFERENCES

[1] Patil S, Kadam A, Bandgar S, Patil S. Formulation and evaluation of an *in situ* gel for ocular drug delivery of anticonjunctival drug. Cellulose Chem Technol. 2015 Jan 1; 49(1):35-40.

[2] Wadhwa S, Paliwal R, Paliwal SR, Vyas SP. Nanocarriers in ocular drug delivery: an update review. Current pharmaceutical design. 2009 Aug 1; 15(23):2724-50.

[3] Palani S, Joseph NM, Goda CC, Zachariah A, Ayenew Z. Ocular drug delivery: A Review. Int J Pharm Sci Res. 2010; 1(3):1-1.

[4] Dhanapal R, Ratna JV. Ocular drug delivery system–a review. International Journal of Innovative drug discovery. 2012; 2(1):4-15.

[5] Kumar A, Malviya R, Sharma PK. Recent trends in ocular drug delivery: a short review. Eur J Appl Sci. 2011; 3(3):86-92.

[6] Gote V, Sikder S, Sicotte J, Pal D. Ocular drug delivery: Present innovations and future challenges. Journal of Pharmacology and Experimental Therapeutics. 2019 Sep 1; 370(3):602-24.

[7] Seyfoddin A, Shaw J, Al-Kassas R. Solid lipid nanoparticles for ocular drug delivery. Drug delivery. 2010 Oct 1; 17(7):467-89.

[8] Meqi SA, Deshpande SG. Ocular drug delivery: Controlled and novel drug delivery. New delhi: CBS Publishers; 2002, p 82-84.

[9] Eva M, Amo D, Urtti A. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. *Drug Discov Today*, 2004; 13, 2004, 135-143.

[10] Blondeau JM. Fluoroquinolones: Mechanism of Action, Classification, and Development of Resistance. *Surv Ophthalmol*., 49, 2004, S73-S78.

[11] Hiremath SS, Dasankoppa FS, Nadaf A, Jamakandi VG, Mulla JS, Sholapur HN. Formulation and evaluation of a novel *in situ* gum based ophthalmic drug delivery system of linezolid. Scientia Pharmaceutica. 2008 Sep; 76(3):515-32.

[12] Santos P, Watkinson AC, Hadgraft J, Lane ME. Application of microemulsions in dermal and transdermal drug delivery. Skin Pharmacol Physiol 2008; 21: 246-59.

[13] Mulla JA, Mabrouk M, Choonara YE, Kumar P, Chejara DR, du Toit LC, Pillay V. Development of respirable rifampicin-

loaded nano-lipomer composites by microemulsion-spray drying for pulmonary delivery. Journal of Drug Delivery Science and Technology. 2017 Oct 1; 41:13-9.

[14] Mulla JA, Khazi MI, Khan AY, Gong YD, Khazi IA. Design, Characterization and *In vitro* Evaluation of Imidazo [2, 1-b][1, 3, 4] thiadiazole Derivative Loaded Solid Lipid Nanoparticles. Drug Invention Today. 2012 Aug 1; 4(8).

[15] Jadhav KR, Shaikh IM, Ambade KW, Kadam VJ. Applications of microemulsion based drug delivery system. Curr Drug Deliv 2006; 3: 267-73.

[16] Mulla JAS, Shetty NS, Panchamukhi SI, Khazi IAM. Formulation, Characterization and *in vitro* Evaluation of Novel Thienopyrimidines and Triazolothienopyrimidines Loaded Solid Lipid Nanoparticles. International Journal of Research in Ayurveda & Pharmacy. 2010; 1(1): 192-200.

[17] Mulla JA, Suresh S, Khazi IA. Formulation, characterization and *in vitro* evaluation of methotrexate solid lipid nanoparticles. Research J. Pharm. and Tech. 2009 Oct; 2(4):685-9.

[18] Gaudana R, Jwala J, Boddu SH, Mitra AK. Recent perspectives in ocular drug delivery. Pharmaceutical research. 2009 May; 26(5):1197-216.

[19] Mulla JS, Khazi IM. Influence of Process Variables on Particle Size of Solid Lipid Nanoparticles. Indian Journal of Novel Drug Delivery2009; 1(1): 47-49

[20] Qamar Z, Qizilbash FF, Iqubal MK, Ali A, Narang JK, Ali J, Baboota S. Nano-based drug delivery system: recent strategies for the treatment of ocular disease and future perspective. Recent Patents on Drug Delivery & Formulation. 2019 Dec 1; 13(4):246-54.

[21] Patel MH, Patel BU, Shah C, Akbari B. Formulation and development of nanosuspension as an alternative approach for solubility and dissolution enhancement of aceclofenac. IJAP 2018; 7(5): 33- 47.

[22] Silva D, de Sousa HC, Helena Gil M, *et al.* Moxifloxacin imprinted silicon based hydrogels for sustained ocular release. Ann Med 2019; 51: 103-4.

[23] Ahuja M, Dhake AS, Sharma SK, Majumdar DK. Diclofenac loaded Eudragit S100 nanosuspension for ophthalmic delivery. J, Microencapsul 2011; 28(1): 37-45.

[24] Li VH, Wood RW, Kreuter J, Harmia T, Robinson JR. Ocular drug delivery of progesterone using nanoparticles. J Microencapsul 1986; 3: 213-8.

[25] Calvo P, Vila-Jato JL, Alonso MJ. Evaluation of cationic polymer coated nanocapsules as ocular drug carriers. Int J Pharm 1997; 153:41-50.

[26] De Campos AM, Sánchez A, Alonso MJ. Chitosan nanoparticles: a new vehicle for the improvement of the delivery of drugs to the ocular surface. Application to cyclosporin A. Int J Pharm 2001; 224: 159-68.

[27] Mukherjee S, Ray S, Thakur RS. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. Indian J Pharm Sci 2009; 71(4): 349-58.

[28] Jameel Ahmed S. Mulla, Shivanandswamy P. Hiremath, Naveen Kumar Sharma. Repaglinide Loaded Solid Lipid Nanoparticles: Design and Characterization. Rajiv Gandhi University of Health Sciences Journal of Pharmaceutical Sciences. 2012; 2(4):41-49.

[29] Mulla JS, Khan AY, Panchamukhi SI, Khazi MA, Kalashetti MB, Khazi IM. Synthesis and Antitubercular Activity of Mannich bases of imidazo[2,1-*b*][1,3,4]thiadiazoles. Indian Journal of Novel Drug delivery. 2011; 3(4): 289-295.

[30] Salata O. Applications of nanoparticles in biology and medicine. J Nanobiotechnology 2004; 2(1): 3.

[31] Zur Mühlen A, Schwarz C, Mehnert W. Solid Lipid Nanoparticles (SLN) for controlled drug delivery--drug release and release mechanism. Eur J Pharm Biopharm 1998; 45(2): 149-55.

[32] Panchamukhi SI, Mulla JA, Shetty NS, Khazi MI, Khan AY, Kalashetti MB, Khazi IA. Benzothieno [3, 2-e][1, 2, 4] triazolo [4, 3-c] pyrimidines: Synthesis, Characterization, Antimicrobial Activity, and Incorporation into Solid Lipid Nanoparticles. Archiv der Pharmazie. 2011 Jun; 344(6):358-65.

[33] Rostami E, Kashanian S, Azandaryani AH, Faramarzi H, Dolatabadi JE, Omidfar K. Drug targeting using solid lipid nanoparticles. Chem Phys Lipids 2014; 181: 56-61.

[34] Seyfoddin A, Al-Kassas R. Development of solid lipid nanoparticles and nanostructured lipid carriers for improving

ocular delivery of acyclovir. Drug Dev Ind Pharm 2013; 39(4): 508-19.
[35] Kaur IP, Kanwar M. Ocular preparations: The formulation approach. Drug Dev Ind Pharm 2002; 28(5): 473-93.
[36] Kaur IP, Rana C, Singh H. Development of effective ocular preparations of antifungal agents. J Ocul Pharmacol Ther 2008; 24(5): 481-93.
[37] Cavalli R, Gasco MR, Chetoni P, Burgalassi S, Saettone MF. Solid Lipid Nanoparticles (SLN) as ocular delivery system for tobramycin. Int J Pharm 2002; 238(1-2): 241-5.
[38] Mandal S, Ratan GN, Mulla JS, Thimmasetty J, Kaneriya A. Design and *In Vitro* Evaluation of Gastro Retentive Sustained Release Tablets of Tizanidine Hydrochloride. Indian Journal of Novel Drug delivery. 2010; 2(4): 144-152.
[39] Khames A, Khaleel MA, El-Badawy MF, El-Nezhawy AOH. Natamycin solid lipid nanoparticles - sustained ocular delivery system of higher corneal penetration against deep fungal keratitis: preparation and optimization. Int J Nanomedicine 2019; 14: 2515-31.
[40] Ahmad I, Pandit J, Sultana Y, Mishra AK, Hazari PP, Aqil M. Optimization by design of etoposide loaded solid lipid nanoparticles for ocular delivery: Characterization, pharmacokinetic and deposition study. Mater Sci Eng C 2019; 100: 959-70.
[41] Bhattacharjee A, Das PJ, Adhikari P, et al. Novel drug delivery systems for ocular therapy: With special reference to liposomal ocular delivery. Eur J Ophthalmol 2019; 29(1): 113-26.
[42] Mulla JS, Khazi IM, Sharma NK. Solid Lipid Nanoparticles: Measures of Characterization. Indian Journal of Novel Drug delivery. 2011; 3(4): 259-264.
[43] Yadav KS, Rajpurohit R, Sharma S. Glaucoma: Current treatment and impact of advanced drug delivery systems. Life Sci 2019; 221: 362-76.
[44] Geroski DH, Edelhauser HF. Drug delivery for posterior segment eye disease. Invest Ophthalmol Vis Sci 2000; 41(5): 961-4. PMID: 10752928.
[45] Mulla JS, Khazi IM, Sharma NK, Hiremath SP, Jamakandi VG. Solid Lipid Nanoparticles: Methods of Preparation. Indian Journal of Novel Drug delivery. 2011; 3(3): 170-175.
[46] Li J, Cheng T, Tian Q, et al. A more efficient ocular delivery system of triamcinolone acetonide as eye drop to the posterior segment of the eye. Drug Deliv 2019; 26(1): 188-98.
[47] Sahoo SK, Dilnawaz F, Krishnakumar S. Nanotechnology in ocular drug delivery. Drug Discov Today 2008; 13(3-4): 144-51.
[48] Mulla JAS, Shetty NS, Panchamukhi SI, Khazi IAM. Formulation, Characterization and *in vitro* Evaluation of Novel Thienopyrimidines and Triazolothienopyrimidines Loaded Solid Lipid Nanoparticles. International Journal of Research in Ayurveda & Pharmacy. 2010; 1(1): 192-200.
[49] De Sá FAP, Taveira SF, Gelfuso GM, Lima EM, Gratieri T. Liposomal voriconazole (VOR) formulation for improved ocular delivery. Colloids Surf B Biointerfaces 2015; 133: 331-8.
[50] Huang Y, Tao Q, Hou D, et al. A novel ion-exchange carrier based upon liposome-encapsulated montmorillonite for ophthalmic delivery of betaxolol hydrochloride. Int J Nanomedicine 2017; 12: 1731- 45.
[51] Sharma R, Dua JS, Prasad DN, Hira S. Advancement in novel drug delivery system: Niosomes. J Drug Deliv Ther 2019; 9(3-s): 995- 1001.
[52] Biswas GR, Majee SB. Niosomes in ocular drug delivery. Eur J Pharm Med Res 2017; 4(7): 813-9.
[53] El-Nabarawi MA, Abd El Rehem RT, Teaima M, et al. Natamycin niosomes as a promising ocular nanosized delivery system with ketorolac tromethamine for dual effects for treatment of candida rabbit keratitis; *in vitro / in vivo* and histopathological studies. Drug Dev Ind Pharm 2019; 45(6): 922-36.
[54] Salvi VR, Pawar P. Nanostructured Lipid Carriers (NLC) system: A novel drug targeting carrier. J Drug Deliv Sci Technol 2019; 51: 255-67.
[55] Almeida H, Lobão P, Frigerio C, et al. Preparation, characterization and biocompatibility studies of thermo responsive eye drops based on the combination of Nanostructured Lipid Carriers (NLC) and the polymer Pluronic F-127 for controlled delivery of ibuprofen. Pharm Dev Technol 2017; 22(3): 336-49.
[56] Özsoy Y, Güngör S, Kahraman E, Durgun ME. Polymeric micelles as a novel carrier

for ocular drug delivery. In: Mihai A, (editor). Nanoarchitectonics in biomedicine. Oxford: William Andrew Publishing. 2019; 1: pp. 85-117.

[57] Xu L, Qiu WX, Liu WL, et al. PLA–PEG micelles loaded with a classic vasodilator for oxidative cataract prevention. ACS Biomater Sci Eng 2019; 5(2): 407-12.

[58] Li M, Lan J, Li X, et al. Novel ultra-small micelles based on ginsenoside Rb1: A potential nanoplatform for ocular drug delivery. Drug Deliv 2019; 26(1): 481-9.

[59] Barar J, Aghanejad A, Fathi M, Omidi Y. Advanced drug delivery and targeting technologies for the ocular diseases. Bioimpacts 2016; 6(1): 49-67.

[60] Mulla JAS and Karande BS. Microemulsion Based Hydrogel Formulation for Topical Drug Delivery - A Concise Review. Indian Journal of Novel Drug Delivery. 2021Apr-Jun; 13(2): 63-69.

[61] Silva D, de Sousa HC, Helena Gil M, et al. Moxifloxacin imprinted silicon based hydrogels for sustained ocular release. Ann Med 2019; 51: 103-4.

[62] Liu W, Lee BS, Mieler WF, Kang-Mieler JJ. Biodegradable microsphere-hydrogel ocular drug delivery system for controlled and extended release of bioactive aflibercept *in vitro*. Curr Eye Res 2019; 44(3): 264-74.

[63] Kawakami S, Nishida K, Mukai T, Yamamura K, Kobayashi K, Sakaeda T, et al. Ocular absorption behavior of palmitoyl tilisolol, an amphiphilic prodrug of tilisolol, for ocular drug delivery. J Pharm Sci 2001; 90: 2113-20.

[64] Macha S, Mitra AK. Ocular disposition of ganciclovir and its monoester prodrugs following intravitreal administration using microdialysis. Drug Metab Dispos 2002; 30: 670-5.

[65] Mulla JAS.Drug Delivery and Therapeutic Approaches to Prostate Cancer. Indian Journal of Novel Drug Delivery. 2018; 10(3): 98-109.