INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

A Review Article on Ocular Drug Delivery Advances

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ARTICLE INFO

Published: 22 Nov. 2024
Keywords:
Eye , structure of eye, ocular drug delivery, novel ocular drug delivery.
DOI:
10.5281/zenodo.14204297

ABSTRACT

The human eye is a sophisticated organ with distinctive anatomy and physiology that hinders the passage of drugs into targeted ophthalmic sites. Effective topical administration is an interest of scientists for many decades. Their difficult mission Is to prolong drug residence time and guarantee an appropriate ocular permeation. Several ocular obstacles oppose effective Drug delivery such as precorneal, corneal, and blood-corneal barriers. Routes for ocular delivery include topical, interatrial, intraocular, juxtascleral, subconjunctival, intracameral, and retrobulbar. More than 95% of marketed products exists in Liquid state. However, other products could be in semi-solid (ointments and gels), solid state (powder, insert and lens), or Mixed (in situ gel). Nowadays, attractiveness to nanotechnology-based carries is resulted from their capabilities to entrap Both hydrophilic and lipophilic drugs, enhance ocular permeability, sustain residence time, improve drug stability, and argument bioavailability. Different in vitro, ex vivo, and in vivo characterization approaches help to predict the outcomes of the Constructed nanocarriers. This review aims to clarify anatomy of the eye, various ocular diseases, and obstacles to ocular Delivery. Moreover, it studies the advantages and drawbacks of different ocular routes of administration and dosage forms.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. The ocular drug delivery deviates through a number of anatomical and physiological barriers,

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

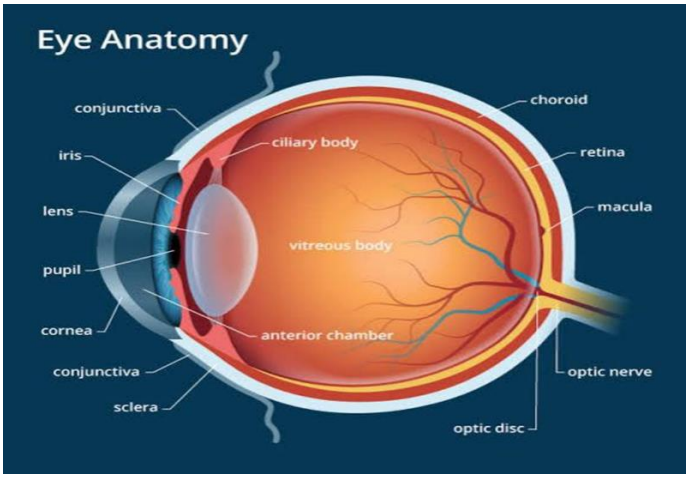
which have been a bottleneck for the Ophthalmologists. The ocular barriers, static and dynamic, decrease the absorption of the therapeutic agents and the entry of the xenobiotics. Thus, A conventional ocular dosage form has various disadvantages of its use in ocular diseases. Hence, an ideal ocular delivery system has always been Aimed, where the bioavailability of a drug is maintained for a longer period of time. The present review aims to focus on the drawbacks of the Conventional ocular therapy and the advantages of designing novel delivery systems, with their certain specific advantages in ocular Pharmacokinetics and the enhancement of bioavailability.

INTRODUCTION

Eye is a very sensitive organ with a sophisticated physiology. It is composed of anterior and posterior segments. Generally, Quality of life is significantly influenced by visual impairment Resulted from various diseases. Cataract is the main cause Of blindness worldwide. About 40–60% of blindness in the World is caused as a complication of cataract [1]. Early cataract development results from mutations in α, β, and γ crystallin and its associated genes [2]. Glaucoma is a well-known Optic neuropathy disease that is connected with elevation in Intraocular pressure (IOP). It leads to permanent blindness In the late stage [3]. Furthermore, vision impairment is also Related to aging, diabetes, and fungal infection. Examples Of ocular diseases include age-related macular degeneration (AMD), diabetic retinopathy (DR), retinoblastoma, and fungal keratitis. A new study valued that approximately 76 Million people suffered from glaucoma, 196 million people With AMD, and 92.6 million have DR [1].

Although many potent drugs are available to treat most Of ocular complaints, there are many ocular barriers such As tear film, corneal, conjunctival, and blood-ocular barriers that hinder their therapeutic efficacy. Conventional eye Drops are wasted by blinking and tear flow. Therefore, their Bioavailability is minimized to less than 5% [4]. Cornea is Composed of epithelium, stroma, and endothelium. Epithelium allows only the passage of small and lipophilic drug. However, stroma allows the passage of hydrophilic drugs [5]. Endothelium conserves the transparency of the cornea and affords selective entry for hydrophilic drugs and Macromolecules into the aqueous humor. The conjunctiva Provides a minor impact to drug absorption compared to The cornea, though certain macromolecular nanomedicines, Peptides, and oligonucleotides penetrate to the deep layers of The eye absolutely through these tissues. Blood-ocular barriers prevent the passage of xenobiotic compounds into the Blood stream. They are classified into blood-aqueous barrier (BAB) in the anterior segment and blood-retinal barrier (BRB) in the posterior segment of the eye [6].Ocular formulations are intended to be applied on the Anterior surface (topical route) of the eye, delivered intraocular (inside the eye), periocularly (subtenon or juxtascleral), Or in combination with ocular devices. Ocular dosage forms Could be liquid, semi-solid, solid, or mixed. Liquid dosage Include drops, suspension, and emulsion. Eye drops represent More than 95% of the marketed ocular products [7].

Structure of 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 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 .

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) 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 directions14. 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.

Accessory structures:

The accessory (adnexal) Structures of the eye include the eyelids, conjunctiva, Caruncle and lachrymal (tear) glands, accessory Structures of the eye .

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 eyelid.

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.

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

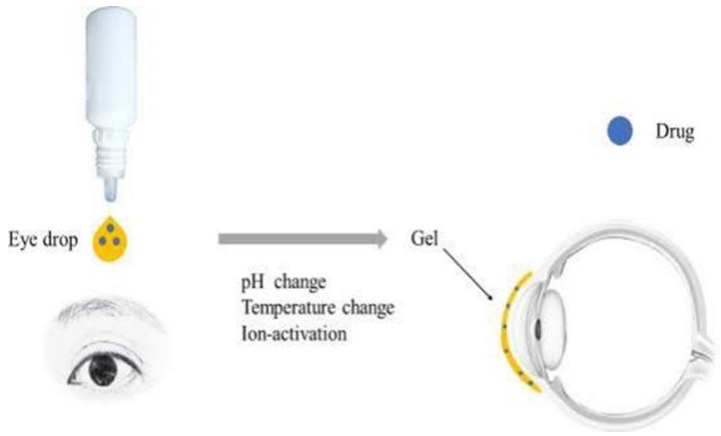
1. Dosage form cannot be terminated during emergency.
2. Interference with vision.
3. Difficulty in placement and removal.
4. Occasional loss during sleep or while rubbing eyes.

Approaches to improve ocular bioavailability

Use of viscosity enhancers

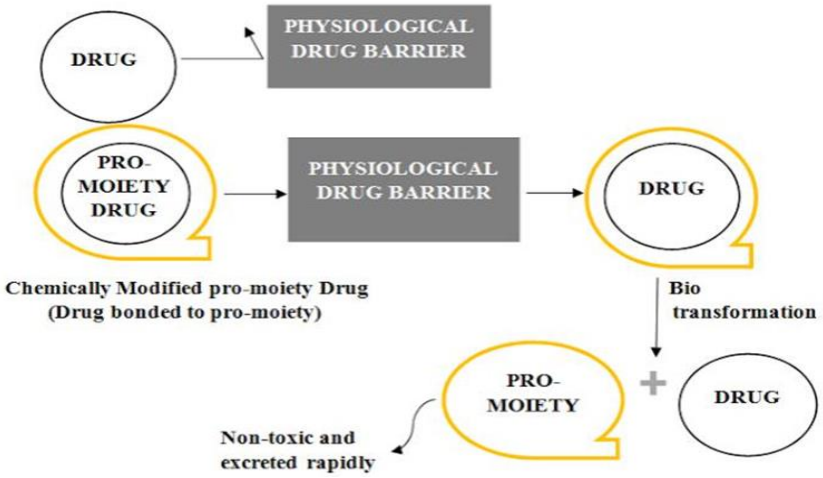
Viscosity-increasing polymers are highly preferred additive in the Ophthalmic formulations due to their properties of enhancing viscosity And thereby imparting benefit to the penetration of the drug into the Anterior chamber of the eye by lowering the elimination rate from the Preocular area, resulting in increase in precorneal residence time and Transcorneal penetration, but having very fewer effects for enhancing Bioavailability in human beings. Examples of polymers are polyvinyl Alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, Hydroxylethylcellulose, hydroxylpropyl methylcellulose (HPMC) and Hydroxypropyl cellulose [21]. As per Saettone et al. (1984), in their Study of tropicamide solution, by using PVA, HPMC, and PVP solution, At concentrations yielding the same viscosity of 20 cst, PVA has been Reported to be the most effective among all, probably due to the Adhesive property of PVA and its capability to enhance the thickness of The precorneal tear film [21]. Saettone et al. (1982) have stated in their Study that the retention of drug in the precorneal tear film does not Strictly belong to vehicle viscosity, but also with surface spreading Properties of the vehicle and to the capability of a polymer to use Water as the vehicle spreads over the ocular surface with each eye Blinking [22].

Gel formulation



Gels are known to be significantly dilute cross-linked systems, which Show rigidity in the steady-state. Gels are generally liquid, but behave Like solids due to their three-dimensional cross-linked structure within The liquid [23-25]. On the other side, if the gels have extremely high Viscosity, they cannot improve bioavailability; instead, they will Control the release, which leads to reduced frequency of dosing to once A day. The highly viscous solution even leads to blurred vision and Matted eyelids, which substantially decrease patient's compliance. In Aqueous gel, viscosity building agents, such as PVA, polyacrylamide, Poloxamer, HPMC, Carbomer, polymethylvinylether, Maleic anhydride, And hydroxylpropylethylcellulose are incorporated, whereas hydrogel Or swellable water-insoluble polymers give rise to controlled drug Delivery systems [26].

Prodrug formulation



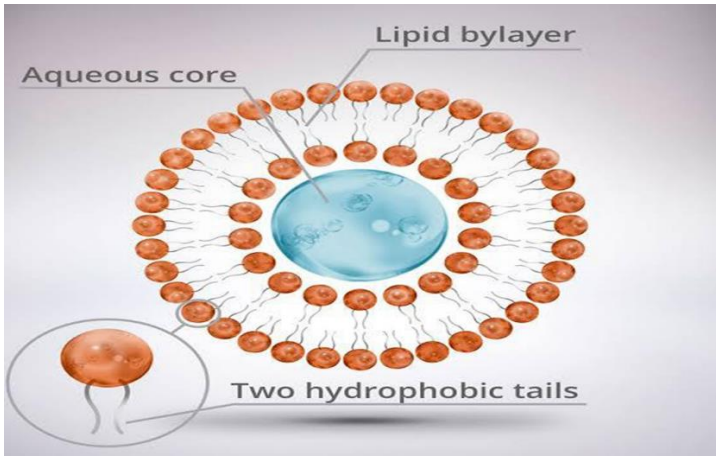
By the development of prodrugs, many properties of the formulation Can be improved, which make it suitable for increasing drug Permeability through the cornea. It includes modification of the Chemical structure that imparts new characteristics to the active Moiety i.e. site-specificity and selectivity [27]. This can be explained Through examples; the formulations which have been developed as Prodrugs, are epinephrine, phenylephrine, timolol, and Pilocarpine. Other prodrugs are dipiverine, diester of pivalic acid and Epinephrine showing seventeen fold more permeability via cornea As compared to that of epinephrine, which is caused by its six Hundred folds more lipophilicity at pH 7.2. So a minor dose of the Drug solution (dipiverine), spreads over the entire eyeball and has a Therapeutic effect exactly the same as of epinephrine. When Compared with conventional eye drops consist of 2% epinephrine, Eye drops of

dipiverine 0.1% show only mild activity by lowering the Intraocular pressure with a significant reduction of side effects [28].

Penetration enhancers

Corneal epithelial membrane plays an important role in terms of Permeability. So, by increasing its permeability, the transport Property around cornea can be enhanced [29, 30]. Agents showing Such properties are chelating agents, preservatives (like Benzalkonium chloride), surfactants and bile acid salts, but due to Local toxicity, they cannot be used in development ophthalmic Formulation [31, 32].

Liposomes

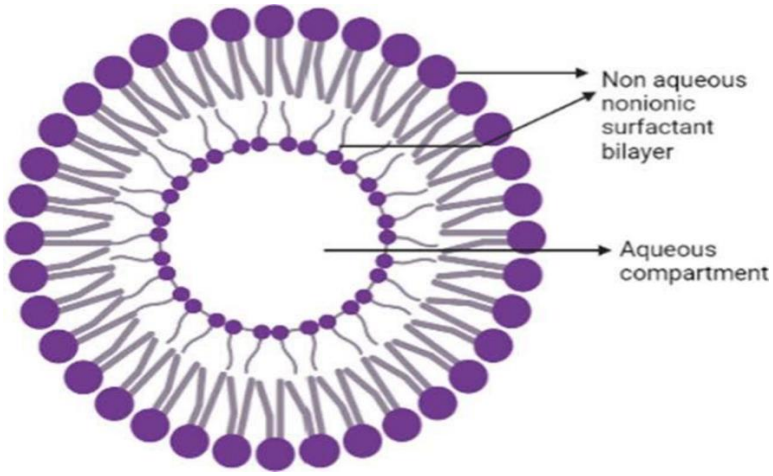


Liposomes are defined as microscopic vesicles which consist of one or More concentric lipid bilayers, divided via water or aqueous buffer Compartments. Liposomes are widely used in ocular formulations due to Their property of having intimate contact with eye surfaces, mainly Corneal and conjunctival area, thus drug absorption through ocular route Can be increased [33]. Formulation of liposomes can be developed by Using phosphatidylcholine, stearylamine and various amounts of Cholesterol or lecithin and L-dipalmitoyl-phosphatidylcholine [34-37].Major advantages of this type of delivery system are due to their Properties, i.e., biocompatibility, biodegradability, amphiphilic property, Relative toxicity [34, 35, 38]. Delivery of drug on targeted site or site-Specificity and release of drug in a sustained manner, are also its Advantages. Liposomes are generally prepared for the drugs which have Poor absorption, lower partition coefficient, poor solubility and having Molecular weights in the range of medium to high [39]. Surface charge of Liposomes is to be considered during the formulation of ocular delivery System; if liposomes are positively charged, they are observed to be Preferably captured by negatively charged corneal surface, while the Neutral or negatively charged liposomes are not captured by corneal Surface. According to the number of researches reported, the active Pharmaceutical ingredients being used in liposomal ophthalmic Formulations are acyclovir, pilocarpine, acetazolamide, chloramphenicol And ciprofloxacin [36, 37

Niosomes

Niosomes are chemically stable, bi-layered nanocarriers made up of Nonionic surfactants and used as carriers for both hydrophilic and Hydrophobic drugs. They do not have drawbacks like liposomes that Are chemical instable, susceptible to oxidative degradation and made Up of phospholipids that are very much unstable as well as Expensive [34, 35, 40, 41]. Thus, niosomes have lots of advantages Including that they are biodegradable, biocompatible and Nonimmunogenic, which make them increase the contact time Between drug and cornea, thereby increasing the bioavailability of Drugs. A

modified form of niosomes is desmosomes that also acts as Carrier for ophthalmic drugs. The size of desmosomes lies between 12 To 16 .This gives it a benefit of not allowing it to enter in the General circulation and its disc shape provides better fit into the Conjunctival sac [35]. The size of desmosomes makes it different from Niosomes, as the former consists of nonionic surfactants and SolulanC[24], a derivative of lanolin and a mixture of ethoxylated



Cholesterol (ether of cholesterol and polyethylene glycol) and Ethoxylated fatty alcohols (ether of cetyl alcohol and polyethylene Glycol). Use of niosomal carrier as a drug delivery system has been Reported for genciclovir [42], cyclo-pentolate, or timolol [35].

Nanoparticles/nanospheres

These are polymeric colloidal particles, size varying from 10 nm to 1 nm, Where the drug is being dissolved, entrapped, encapsulated, or adsorbed [43]. It consists of a number of biodegradable substances, like natural or Synthetic polymers, lipids, phospholipids and metals. To obtain Nanoparticles, the drugs can be formulated in many ways as by Integrating with the matrix or by attaching to the surface of Biodegradable polymers used for the preparation. Nanoparticles used in Delivering drug to ocular tissues are polylactics (PLAs), Polycyanoacrylate, poly (D, L-lactides) and natural polymers such as Chitosan, gelatine, sodium alginate and albumin. Approximately, since last 10 y, nanoparticles have been used as carriers in delivering drug for Ocular disorders and given promising results. A specific type of Nanoparticles can be classified as small capsules having a central cavity Surrounded by a polymeric membrane and solid matrix spheres, known As nanocapsules and nanospheres, respectively. Marchal et al. (1993) Have reported that the nanocapsules

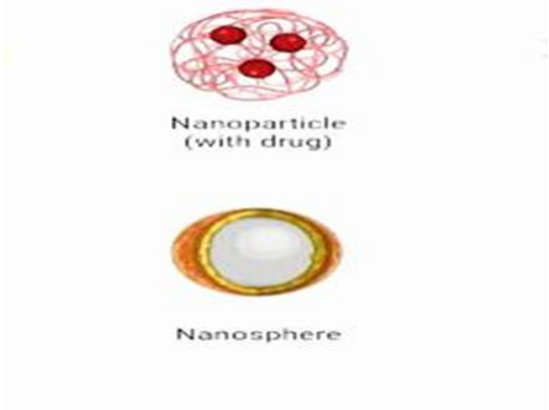


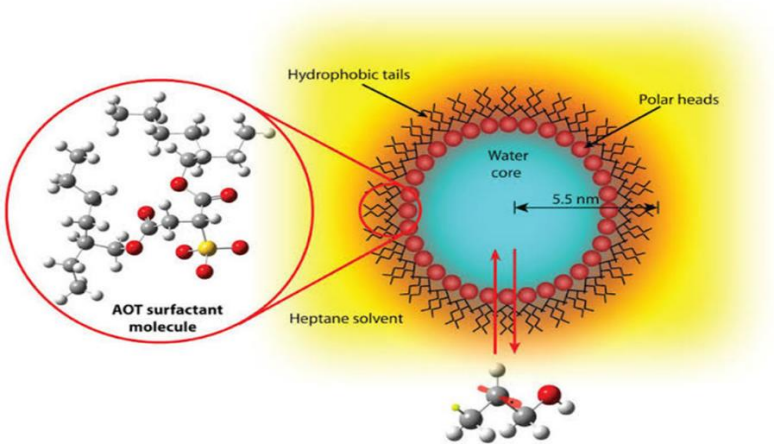
exhibit better effect as compared to That of the nanospheres, because drug (betaxolol, carteolol) present in Unionized form in the oily core, diffuses at a higher rate into the cornea [44]. A number of authors have reported that the nanocapsules are more Efficient due to the presence of mucoadhesive property in it that shows a Rise in the residence time and biological responses [45]. So, these can Enhance the bioavailability of drugs at ocular site and also decrease the Frequency of dosing. Alonso et al. (1995) have reported in their study That the nanoparticles made from poly-e-

caprolactone having Cyclosporine exhibit better corneal absorption with respect to the drug's Oily solution [46].

Nanosuspension and nanodispersions

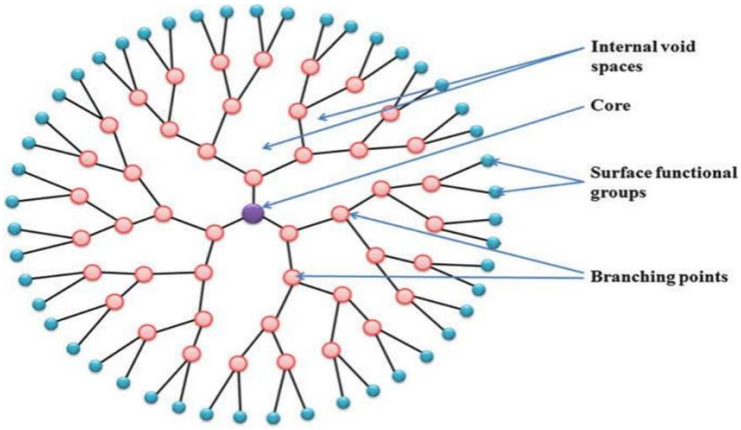
Nanosuspensions are generated for poorly water-soluble drugs Suspended at nano size range in a suitable dispersion medium. This Technology can be utilized in a good way for drug moiety that forms Crystals with high energy content, due to which they are insoluble in Organic (lipophilic) or hydrophilic media. Polymeric nanoparticle Suspensions are being formulated using inert polymeric resins, Which can be used as vital drug delivery vehicles, having the capacity To increase drug release as well as improve its bioavailability. The Carriers having such type of properties can be used as inert carriers For ophthalmic drugs, because they do not cause any irritation to the Cornea, iris or conjunctiva. An example of such carrier is polymeric Nanoparticle suspension having flurbiprofen (FLU) as an active Ingredient and eudragit RS 1001 and RL 1001 are polymers used. Nanodispersions of alginate chitosan produced for sustained drug Delivery and improved transcorneal permeation have been reported By Morsi et al. (2015) [47, 48].

Microemulsion



A stable dispersion of water in oil, facilitated by adding surfactant and Co-surfactant in combination in a way to decrease interfacial tension, is Termed as a microemulsions. Microemulsion leads to decrease in Administration frequency and enhancing ocular drug bioavailability. Major advantages of this dosage form are its high thermodynamic Stability, smaller droplet size, i.e., 100 nm (approx.) and clear Appearance. Ansari et al. (2008) have reported a microemulsions Formulation, which is an oil in water system consisting of pilocarpine as a Drug, lecithin, propylene glycol, PEG 200 as surfactant/co-surfactants And isopropyl myristate forming the oil phase [49].

Dendrimers



Dendrimers are symmetric structures made from repetitive Branched molecules surrounding a central core, proposed recently As topical ocular drug delivery systems [50]. Frequently used Dendrimers for delivery in ocular system are poly-(amidoamine) (PAMAM), PLL, polypropylenimines (PPI) and phosphorus Dendrimers. These are used as carriers to deliver nucleic acid-based Drugs, mostly in ocular delivery system [51], but sometimes used for Drugs with low molecular weight that can be hydrophilic (antibiotics) or lipophilic (anti-glaucoma) drugs as well [52–58]. According to the reported methods, it has been found that the carrier's performance can be increased by making a change on their Surface using methods like PEGylation or acetylation, which also Help in reducing their toxicity factors [53, 54, 59]. So, the advantages Of using dendimers as carrier of drugs for topical applications are Enhancement of the drug residence time in the pre-corneal area, Increase in bioavailability of drugs and prolonged therapeutic effect [52, 55, 57, 58].

In situ forming gel

Researchers have found the new concept of in situ gel in the Early1980s. Delivery of drug to ocular system through in situ gel is Mainly for enhancing viscosity to decrease drug drainage from the Cornea. The pourable gels are in liquid form when applied, after Which they undergo a phase transition, when reaches to cul-de-sac Of eye and converted into a visco-elastic gel giving rise to a response To changes environmentally, thereby increasing the bioavailability of The drug automatically. The major disadvantages of the in situ gels Are that they get affected by temperature, pH or ions. Bazzaz et al.(2018) reported that in situ gelling system provides better and Prolonged effect of a drug rather than conventional eye drops [60].

Approaches for controlled and continuous ocular drug delivery

The following ocular drug delivery systems have been reported for Controlled as well as continuous release of drugs:

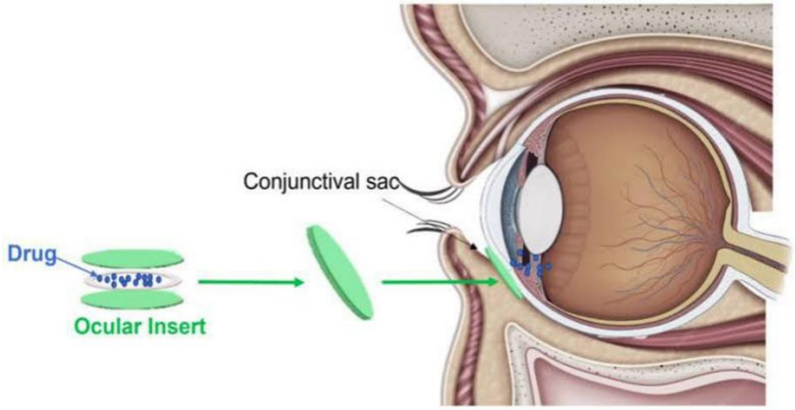
Microparticles

Microparticles are isotropic, transparent, translucent, Thermodynamically stable system of oil, surfactant and water Droplets the size of which ranges between 20 to 200 nm [61].Microparticles are defined as micron-sized polymeric particles in Which drugs in the polymeric matrices are suspended in liquid Medium. Drugs are uniformly dispersed in the polymeric matrix or Covalently bound to the backbone of the polymer [62]. During Topical application in the eye these particles go into the ocular cul-De-sac and the drug releases from it through a number of processes Like diffusion, chemical reaction or polymer degradation. Microparticles increase precorneal residence time, which allow Continuous and sustained release of the drug. Ultimately this leads To increased ocular bioavailability of the drug and minimizes Frequency of dosing, but

microparticulate preparations are generally Not administered to the eye as they cause irritation due to their large Particle size. Microparticles have properties like biodegradation, Bio-adhesion, and biocompatibility, which make it suitable for Fabrication with polymers.

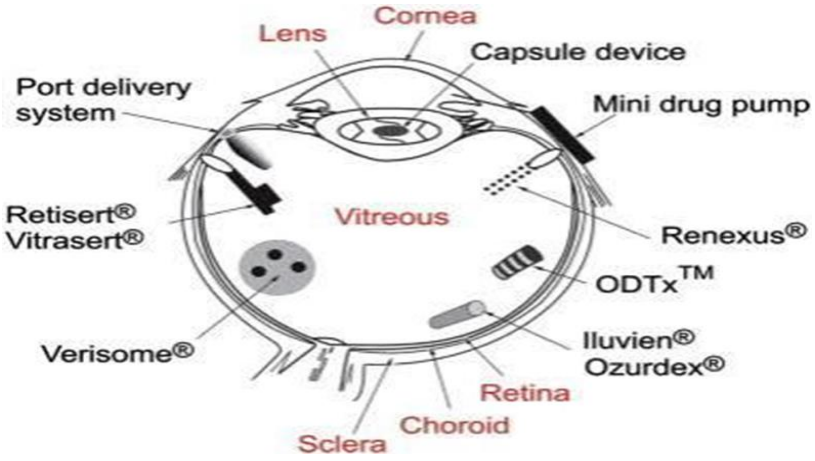
Ocular inserts

Ophthalmic inserts are solid patches, which, when placed in the Conjunctival sac of the eye, slow down the rate of drug release. Ocular inserts also overcome the problem of frequent dosing by Maintaining drug concentration in an effective manner and give rise To controlled, sustained and continuous drug delivery. Ocular Inserts Also have various advantages like enhanced drug absorption due to Increased contact time and minimized



dose and application Frequency. The major disadvantages of these inserts are patient Noncompliance with frequent feeling like the entry of foreign body In the eye, difficulty in self-insertion feels and feeling of loss of the Insert from eye. Ocular inserts are made by various techniques that Make them soluble, erodible and in hydrogel form.

Implants



The aim of designing an intraocular implant is to prolong the activity Of the drug, along with its controlled release by using a polymer or Polymer system. An injectable delivery system of drug, like Liposomes and nanoparticles, is easy to administer, but having Limitation that after insertion, it becomes difficult to retract those Particles during any complication, like toxic responses. So it is Beneficial to use implants for balancing the rate and duration of drug Release. Removal of ocular implants is easy and can be removed by Surgical intervention. Implants can be categorized into two types Based on the characteristics of the polymer(s) used:

Nonbiodegradable implants

They do not dissolve to any significant extent and are not even Eroded in vivo [66].

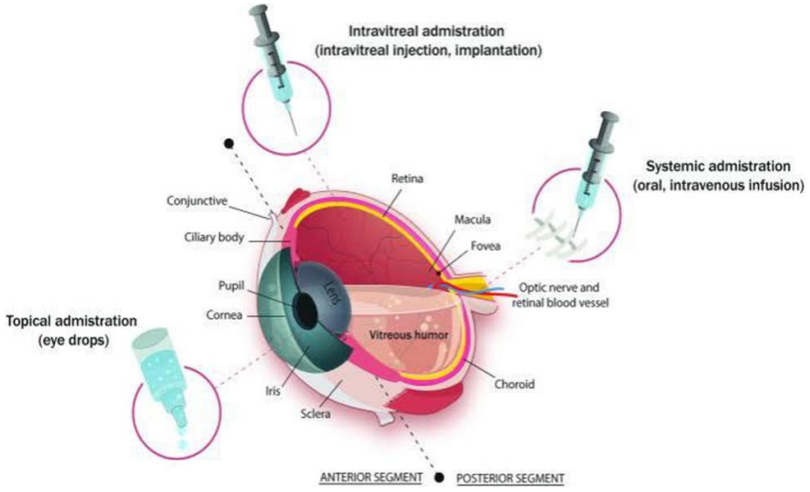
Biodegradable implants

They mostly dissolve in vivo with soluble components by processes Such as enzymatic or nonenzymatic degradations [67, 68]. Examples Of marketed implants used worldwide.

Approaches for posterior segment drug delivery

Intravitreal injections

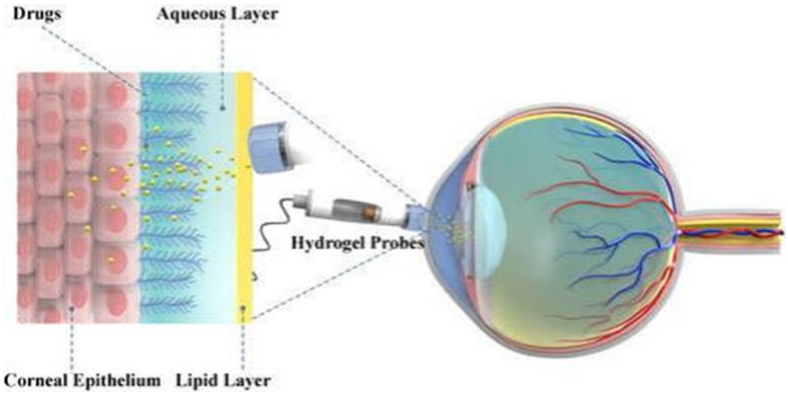
Research reports reveal that intravitreal injections for the posterior Segment are gaining worldwide popularity as a drug delivery System, over the past few years. Injections are directly given into the Posterior segment via pars plana for delivering drugs to overcome All barriers. A number of studies have been conducted to find out the Pharmacokinetic parameters of antiviral agents, like ganciclovir [71], foscarnet [71] and cidofovir [72], antibiotics: Cefazolin [73], Amikacin, moxifloxacin [74], ceftizoxime, ceftriaxone ceftazidime [75], clindamycin [76] and gentamicin [77], steroids: Dexamethasone [78], triamcinolone acetonide [79] and monoclonal Antibodies, such as rituximab [80], bevacizumab [80] following Intravitreal injections. If the molecular weight of the drug is very High, vitreal retention times seem to be higher as well. Molecules That are larger, i.e., linear>40 kDa and globular molecules>70 kDa Seem to have long retention time due to the presence of tight Barriers around the vitreous humor [81, 82]. So, this route is Preferable for higher molecular weight drugs (>500 Da) and also Having longer half-lives. First-order rate kinetics is mainly Responsible for the elimination of residues out of the vitreous Humour [83]. Even the drug delivery through intravitreal injections Can be gained by increasing concentrations of drugs in neural retina; Side effects like retinal detachment due to repeated injections, Retinal hemorrhage, endophthalmitis and other toxicities in the Retina occurs because of more concentrations upon bolus dose Administration that can cause



patient's non-compliance [84-87].Ausayakhun et al. (2005), have found in their study, that the Cytomegalovirus (CMV) retinitis can be controlled by using Intravitreal ganciclovir (2 mg in 0.1 ml per) and the reported data Has shown that 60% of the treated eyes have remained stable, 13% Have shown improvement and 26% have shown a reduction in Visual acuity [88]. However, a retinal detachment has been noticed In 6%, intravitreal hemorrhages observed in 1% and Endophthalmitis observed in 1% of treated eyes. So we can observe From the study that the problems associated with intravitreal Injections should be taken into consideration [88]. A number of Other studies have also been carried out for similar findings, which Have stated that the intravitreal injections

are useful, but not good For posterior segment diseases [89-91]. Development in designing of Drug delivery system and surgical procedures has led to the Development of intravitreal implants that can be instilled inside the Vitreous chamber for a longer duration. The difference between Intravitreal injections and intravitreal implants is their Administration time. Injections can be taken 2 or 3 times a week and Preferably can be changed every month, respectively.

Iontophoresis



Ocular iontophoresis is one of the growing fields in research due to Its noninvasive nature of delivering drugs to both the anterior and Posterior segments of eye. Iontophoresis is defined as a noninvasive Procedure for the transfer of ionized drugs via membranes with low Electrical current [92, 93]. The drugs can move across the Membranes by two ways, migration and electro-osmosis. Ocular Iontophoresis, categorized as transcorneal, corneoscleral, or transscleral [92], is considered as one of the most attractive options. OcuPhor™ system has been designed with the help of an applicator, Dispersive electrode and a dose controller for trans scleral Iontophoresis [94]. The device works, as it releases the active drug Moiety into retina-choroid. Another similar device being made Known by name called Visulex™, which allows specific transport of Ionized molecules through the sclera. Antibiotics, which are Successfully used, are gentamycin, tobramycin, and ciprofloxacin, But not vancomycin, due to its high molecular weight [95]. Fruitful Results of delivery have been observed with drugs such as Dexamethasone and antisense ODNs [96].

CONCLUSION

Treatment of ocular diseases in an effective manner is a major Challenge for scientists working in the field of ocular drug delivery Because of nature of the ocular diseases, unique structure of the eye And barriers present in the system; particularly the posterior ocular Segments make the system unapproachable. Many attempts have Been made to enhance ocular bioavailability by manipulating Product formulation using factors, such as viscosity and use of Mucoadhesive polymers. These approaches have been found to be Capable of increasing the corneal contact time and improving ocular Bioavailability also. Therefore, it could be concluded that modern Technology seems to be logically explored in various ways over the Conventional approaches, examples of non-conventional approaches Being the use of nanotechnology, microspheres, liposomes, Appropriate prodrug in situ forming gel and iontophoresis as Effective means of ocular drug delivery enhancing ocular absorption Along with reduction in side effects.

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HOW TO CITE: Prajakta Bichkule*, Ulka Mote A Review Article on Ocular Drug Delivery Advances, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 11, 930-947. https://doi.org/10.5281/zenodo.14204297