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Review Article

A review on nanotechnology based ophthalmic drug delivery system

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Abstract

The field of ophthalmic drug delivery has witnessed significant advancements through the integration of nanotechnology. Despite having numerous conventional dosage forms employed in the ocular drug delivery system the problem of less bioavailability and less retention time is a significant concern. Along with it there are various barriers also involved that affects the drug permeability, solubility due to the lower residence time of the drug on ocular surface. To overcome these problems the nanotechnology approach can be most suitable. All nanocarriers have emerged as a promising career for precise drug targeting to ocular tissues. Their small size, biocompatibility and surface modification enable improved drug solubility, sustained release and enhanced bioavailability. Moreover nanotechnology facilitates the incorporation of therapeutic agents for various ocular conditions, including glaucoma, macular degeneration and infections. These advancements aim to overcome the challenges and barriers in ocular drug delivery system. This review underscores the immense potential of nanotechnology to revolutionize ophthalmic drug delivery, offering the prospect of more efficient and patient-friendly treatments for ophthalmic disorders.

Keywords: Ocular drug delivery, Nanotechnology, Nanocarriers, Intraocular pressure, Ophthalmic barriers

1. Introduction:

The eye is a delicate organ with a complex physiology. Anterior and posterior portions make up its structure.[1] Three levels can be identified by the human eye. The cornea and sclera make up the outer region. The cornea shields the eye from infection and structural damage to the deeper regions of the eye while refracting and transmitting light to the lens and retina. The eye is shielded from internal and external forces by the sclera, a connective tissue layer that also helps the eye keep its shape. At the limbus, the cornea and sclera are joined. The conjunctiva, a transparent mucous membrane, covers the portion of the sclera that is visible to the eye. The iris, ciliary body, and choroid make up the central layer of the eye. The iris regulates the pupil's size, which affects how much light reaches the retina; the choroid is a vascular layer that provides oxygen and nutrients to the outer retinal layers, the ciliary body regulates the power and shape of the lens and it is the site of aqueous production. The retina, a complex, layered arrangement of neurons that stores and processes light, makes up the inner layer of the eye. The aqueous, the vitreous, and the lens are the three transparent structures that make up the ocular layers.[2]

1.1 Barriers of ocular drug delivery system:

The physiochemical characteristics of the drugs, its elimination from lacrimal fluid, corneal barriers, and non-corneal absorption are the key barriers and determining variables in ocular drug delivery. The drug is mostly transported across the corneal epithelium via a paracellular or transcellular pathway. Hydrophilic drugs prefer the paracellular route, which involves passive or altered diffusion via intercellular gaps, whereas lipophilic drugs prefer the transcellular route.[3] The diffusion and productive absorption of the topically administered drugs are the most common ODDS physiological barriers. They can be found in both the precorneal and corneal regions. Tear dilution, solution drainage, lacrimation, tear turnover, and conjunctival absorption are all precorneal constraints that cause the poor ocular bioavailability of conventional ophthalmic dosage forms.[4] After using the indefinite quantity type of the drug within the ocular system, the flow of lacrimal fluid removes out some of the drug from its surface, with a turnout rate of approximately one l/min, whereas a large amount of the drug is drained through the channel quickly at intervals of minutes.[5] Tear film is one of the precorneal barriers that decreases the effective concentration of drugs administered due to dilution by tear turnover (about 1 L/min), much more rapidly clearance, and drug molecule binding to tear proteins. Additionally, the instillation dose volume usually ranges from 20-50 L, whereas the size of a cul-de-sac is just 7-10 L. Excess volume may escape through the nasolacrimal duct or spill out on the cheek. The bloodstream comprises blood-ocular barriers, which protect the eye from xenobiotics. It is divided into two parts: the blood aqueous barrier and the blood-retina barrier. This barrier prevents hydrophilic drugs in plasma from entering the aqueous humor and also inhibits the passage of plasma albumin into the aqueous humor. The posterior barrier which resides in between the eye and stream of plasma consists of retinal pigment epithelium (RPE) and retinal capillaries, resulting in tight wall junction.[6] In ocular wall barriers generally, the ocular wall barriers are the skeleton of the eye globe consists of the rigid scleral collagenous shell. That is generally lined internally by the uveal tract.[4]

1.2 Diseases of Eyes:

1. Glaucoma
2. Diabetic Retinopathy
3. Keratitis
4. Conjunctivitis
5. Cataract

1.2.1 Glaucoma:

Glaucoma is a common eye illness that, if left misdiagnosed and untreated, can result in irreversible blindness. Glaucoma is caused by high intraocular pressure (IOP), which damages the optic nerve and causes vision field loss. Although increased IOP is not usually a sign of glaucoma, it is a key risk factor and a cause of glaucomatous optic neuropathy.[7] Primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) are the two most common types of glaucoma.[8]

1.2.1.1 Primary open-angle glaucoma:

The angle of the eye is the point where the trabecular meshwork drains aqueous fluid from the anterior chamber of the eye. The angle remains open in POAG because the trabecular meshwork is not obstructed by iris tissue. Intraocular pressure is conveyed as mechanical stress to the axons of retinal ganglion cells at the optic nerve, resulting in cell death. However, around 50% of glaucoma patients have intraocular pressure within the so-called "normal" range of 10 to 21 mm Hg at the time of diagnosis. Perimetric testing detects visual field impairments only when 30% of retinal ganglion cells have been destroyed.[8] POAG pathogenesis is unknown. IOP, ocular perfusion pressure, ocular blood flow, myopia, central corneal thickness, and optic disc hemorrhages have all been proposed as ocular risk factors. Age, smoking, African ancestry, family history, genetic factors, systemic hypertension (HTN), low blood pressure (BP) (especially nocturnal BP), atherosclerosis, lipid dysregulation, type 2 diabetes mellitus (DM), glucose intolerance, obesity, vasospasm, migraine, Raynaud syndrome, stress, and primary vascular dysregulation are all systemic risk factors.[9]

1.2.1.2 Primary angle-closure glaucoma:

In 90% of instances, pupillary obstruction causes primary angle-closure glaucoma (PACG). Pupillary block is generated by the iris apposition against the lens, which restricts aqueous efflux from the posterior chamber to the anterior chamber and subsequent drainage through the trabecular meshwork. The accumulation of aqueous in the posterior side causes the iris to bow anteriorly and eventually close the angle. This might happen suddenly, intermittently, or over time. PACG is associated with a number of risk factors. PACG is associated with a number of risk factors. Patients with hyperopia, or a short axial length of the eyeball, and an anterior chamber length of less than 2.5 mm are more likely to develop cataracts. Symptoms include impaired vision, discomfort, colored halo rings surrounding lights, nausea, and vomiting emesis and frontal headache.[10]

In the early stages of angle closure, the angle may only be appositionally convex. The iris's convex shape puts it in appositional contact with the trabecular meshwork, impeding drainage and perhaps allowing PAS to form and advance down the path to PACG. Due to the apposition of the pupil and anterior lens capsule, shallow anterior chambers are prone to pupillary obstruction.[11]

1.2.2 Diabetic Retinopathy:

Diabetic Retinopathy (DR) is a leading cause of blindness. Diabetes patients' retinal blood vessels are damaged by DR. Non proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR) are the two main kinds of DR. The DR in its early stages is known as NPDR, and it is further classified as Mild, Moderate, and Severe. There is one micro-aneurysm (MA) in the mild stage, which is a little circular red dot at the end of blood vessels. In the Moderate stage, the MAs rupture into deeper layers of the retina, causing a flame-shaped hemorrhage.[12]

1.2.3 Keratitis:

Infected keratitis is a corneal infection also known as an infected corneal ulcer or corneal opacity. Infectious keratitis is characterized as either microbial keratitis (caused by bacteria, fungus, or parasites) or viral keratitis (caused by herpes viruses).[13]

1.2.3.1 Bacterial Keratitis:

Bacterial Keratitis is most commonly connected with contact lens use. Severe cases can advance quickly and result in permanent vision loss, necessitating corneal transplantation. The first-line treatment for bacterial keratitis is still topical antibiotics. The use of adjuvant corticosteroids in the treatment of bacterial keratitis has long been questioned. Corticosteroids, according to proponents, improve results by decreasing inflammation, which reduces scarring, neovascularization, and stromal melt.[14]

1.2.3.2 Viral Keratitis:

One of the most common types of infectious keratitis is viral keratitis (VK). The alpha-herpes virus herpes simplex virus (HSV) is the most common cause of keratitis among the many viruses that have been identified. The beta-herpes virus cytomegalovirus (CMV), the alpha-herpes virus varicella-zoster virus (VZV), and the gamma-herpes virus Epstein-Barr virus (EBV) are all common causes of viral keratitis. The alpha-subfamily has the broadest host range and establishes latency predominantly in sensory neurons, the beta-subfamily has an intermediate host range and establishes latency largely in lymphoid tissues, and the gamma-subfamily has a limited host range and establishes latency only in lymphoid tissues.[15]

1.2.3.3 Fungal Keratitis:

Fungal keratitis, also known as keratomycoses, are corneal infections that must be evaluated in cases of corneal trauma, prior corneal surgery, chronic ocular surface illness, topical corticosteroids, or contact lens wear. Filamentous fungi or yeasts may be involved. Clinical symptoms such as corneal infiltrates with feathery edges and/or elevated surface, intact epithelium with deep stromal involvement, satellite lesions, endothelial plaques, lack of response with antibiotics, and worsening with steroids are suggestive of fungal keratitis. Corneal scraping for laboratory evaluation is required. Medical treatment with antifungal eye drops and systemic medications should begin as soon as possible. In many situations, surgical treatments are required to control the infection. The prognosis of fungal keratitis is poorer than that of bacterial keratitis.[16]

1.2.4 Conjunctivitis:

The conjunctiva is a thin, transparent membrane that lines the anterior sclera and the interior of the eyelids. It is divided into two sections: bulbar and palpebral. The bulbar section starts at the edge of the cornea and extends to encompass the visible sclera; the palpebral portion lines the inner of the eyelids. Conjunctivitis is an inflammation or infection of the conjunctiva that is characterized by dilatation of the conjunctival capillaries, resulting in hyperemia and edema of the conjunctiva, generally with accompanying discharge.[17]

Bacterial conjunctivitis is typically classified as hyper acute, acute, or chronic based on its duration and severity. Neisseria gonorrhea is the most common cause of hyper acute bacterial conjunctivitis, which is then classified as an oculogenital disease that affects both newborns and sexually active adults. Acute bacterial conjunctivitis is distinguished by its sudden onset, profuse, thick, yellow-green purulent discharge, mixed ocular injection and chemosis, and the creation of an inflammatory membrane.[18]

1.2.5 Cataract:

Cataract is characterized as opacity within the clear lens inside the eye, which limits the amount of incoming light and causes eyesight to deteriorate. A natural lens is a crystalline substance with a precise structure of water and protein that allows light to flow through. Cataract is frequently compared to peering through a waterfall or waxed paper.[19]

The majority of cataracts are caused by crystalline lens aging. As new lens fibers are laid down in the crystalline lens and existing ones are not replaced, the lens is one of the few structures in the body that continues to grow throughout life. The lens's transparency is maintained by a number of interdependent elements, including its microscopic structure and chemical contents, which are responsible for its optical homogeneity. With aging, there is a progressive buildup of yellow-brown pigment within the lens, reducing light transmission.[20]

2. Marketed conventional formulations:

In response to the introduction of effective and flexible therapeutic agents during the last few decades, the diversity of traditional ophthalmic formulations has gradually expanded, reaching well beyond basic solutions and currently including a variety of drug administration methods. Recent articles have expanded the concept of typical ophthalmic delivery methods to include more than basic solutions and suspensions.[21] There are various problems related to various conventional ocular products such as in case of eye drops although they are easily administrable but the main disadvantage is low residential time on ocular surface which ultimately decreases the bioavailability. Ointments and in situ gels are also available in the market but main constraint is the blurred vision and also low patient compliant.[22] Due to these disadvantages there is a need to formulation nanotechnology based ophthalmic drug delivery system.

Table 1: Marketed conventional ophthalmic formulations

Brand	Drug	Dosage Form	Drawbacks	Refs
Ciplox	Ciprofloxacin	Eye drops	Drug loss due to blinking of the eyes	
Betinisol N	Betamethasone	Eye drops	Drug loss due to blinking of the eyes	23
Dexcin	Dexamethasone	Eye drops	Drug loss due to blinking of the eyes	
Refresh Tear	Hydroxypropyl methylcellulose	Eye drops	Drug loss due to blinking of the eyes	
Acivir eye	Acyclovir	Ointment	Poor patient compliance due to blurring of vision	
Chloromycetin	Chloramphenicol palmitate	Ointment	Poor patient compliance due to blurring of vision	
Pred Forte	Prednisolone acetate	Suspension	It does not shows any dose uniformity after storage	
Restasis	Cyclosporine	Emulsion	Emulsion can lose their stability at storage condition	
Timolol Xe	Timolol maleate	In-situ gel	It require high level of fluid and more susceptible to stability problem due to chemical degradation and also causes blurred vision.	24
Pilocarpine HS	Pilocarpine hydrochloride	In situ gel	More fluid is needed and unstable due to chemical degradation and also causes blurred vision.	

3. Nanotechnology based ophthalmic drug delivery system:

Nanotechnology, derived from the Greek word nano, which means dwarf, applies engineering, electronics, physical and material science, and manufacturing processes at the molecular or submicron level. Nanomaterials can be devices or systems, or they can be supramolecular structures, complexes, or composites. Albert Franks, a founder of nanotechnology, characterized it as a branch of science and technology with dimensions and tolerances ranging from 0.1 to 100 nm.[25] The eye is a one-of-a-kind organ, both physically and physiologically, with numerous components with independent physiological activities that make the organ highly resistant to external chemicals. Apart from cartilage, the cornea and crystalline lens are the only tissues in the body that do not have a blood supply. Because of the eye's intricacy, pharmaceutical scientists face particular problems when developing medication delivery systems.[26] The eye is a unique organ, both physically and physiologically, including multiple vastly disparate components with autonomous physiological activities that render the organ highly impenetrable to outside chemicals. Aside from cartilage, the cornea and crystalline lens are the only tissues in the body that do not have a blood supply. Because of the eye's intricacy, pharmaceutical scientists have particular problems in developing medication delivery systems.[27] The various nanotechnology based opthalmic formulation are given below.

3.1 Liposomes:

Liposomes are microparticulate or colloidal carriers with a diameter of 0.05-5.0 micrometres that develop spontaneously when specific lipids are hydrated in aqueous conditions. Liposomes are made up of natural or synthetic lipids (phospho and sphingo-lipids), and they may also contain cholesterol and hydrophilic polymer linked lipids. Liposomes are categorized into five categories based on their composition and intracellular mechanism: ordinary liposomes, cationic liposomes, immunoliposomes, and long circulating liposomes.[28] Liposomes for drug delivery are typically unilamellar and range in diameter from 50 to 150 nm. The packing of the hydrocarbon chains of the lipid molecules determines the mechanical strength and function of the liposomal membrane as a permeability barrier.[29] Liposomes demonstrate their method of action by attaching to cellular membranes and fusing with them, releasing their material into the cell. They are sometimes taken up by the cell, and their phospholipids are incorporated into the cell membrane, allowing the medication stored inside to be released.[30] Liposome development for ocular medication delivery has gotten less attention than other routes of administration, and as a result, there is no liposomal ophthalmic medicinal product on the market. The most convenient and common method of administration for ocular therapy is topical instillation, and most studies have used this route to give liposomes.[31] Liposome binding affinity to the cornea suggests that liposome uptake by the cornea is greatest for positively charged liposomes, least for negatively charged liposomes, and least for neutral liposomes, implying that the initial interaction between the corneal surface and liposomes is electrostatic. Positively charged unilamellar liposomes increase penicillin G transcorneal flux across isolated rabbit cornea by more than fourfold.[32] Acyclovir liposome formulated by using phosphatidylcholine, steryl amine, cholesterol, diacetyl phosphate and the method employed for the preparation of the liposome is lipid film hydration which ultimately resulted in increased residential time on the ocular surface.[33]

3.2 Nanostructured Lipid Carriers:

Nanoparticulate carriers, with their nanoscale dimensions and specific features, have showed considerable promise as a delivery system in recent years. Their benefits include active component protection from moisture, physiologic pH enzymes, increased bioavailability, dose reduction, controlled drug release, and targeted medication delivery to specific sites. Lipid carriers are classified into several categories based on how they are prepared.[34] Lipid, water, and emulsifiers are necessary elements for nanostructured lipid carriers. Glyceryl behenate, glyceryl palmitosterate, fatty acids, steroids, and waxes are examples of solid lipids often utilized in NLCs. At normal temperature, these lipids are solid.[35] NLCs are divided into imperfect, amorphous, and numerous oil-in-solid fat-in-water (O/F/W) types based on the composition of lipid and oil mixes as well as the manner of manufacturing.[34] Preservatives such as phenols and their derivatives, aromatic alcohols, organic mercury compounds, and others can be used to preserve nanostructured lipid carriers.[36] Xiang Li has formulated ibuprofen loaded nanostructured lipid carriers for ocular drug delivery to enhance the drug loading and corneal permeation of the lipophilic molecules by using triglycerides as a lipid with the help of melted ultrasonic method.[37] Similarly the NLC of triamcinolone acetonide has formulated which improved the corneal permeability, drug loading which ultimately results in increased bioavailability of triamcinolone acetonide. The method used was high pressure homogenization.[38]

3.3 Nanosponges:

The "Nanosponges" strategy uses a nanoparticle-sized system to distribute both hydrophilic and hydrophobic compounds. Because nanosponges particles are soluble in water, encapsulation can be accomplished within the Nanosponges by the addition of a chemical known as an adjuvant reagent to eliminate undesirable flavors and to convert liquids to solids with fewer adverse effects.[39] The nanosponges are encapsulating nanoparticles that contain the therapeutic molecule within their core. The nanoparticle can be characterized as encapsulating, complexing, or conjugating based on its mode of drug attachment. Polymers and crosslinking agents are vital in the manufacture of nanosponges. Cyclodextrin and its derivatives such as Methyl B-cyclodextrin, alkyloxy carbonyl cyclodextrins, and crosslinking agents such as diphenyl carbonate, diarylcarbonates epicholridine, glutarldehyde are polymers used in the manufacturing of nanosponges.[40] The most often utilized approach in the manufacture of nanosponges is emulsion solvent diffusion. In the case of nanosponges formulation, there should be some dose dumping.[41] Besifloxacin HCL was loaded by Mousumi Pillai utilizing ethyl cellulose as a polymer in the presence of polyvinyl alcohol as a surfactant, which increased ocular retention and permeability.[42]

3.4 Nanospheres:

Nanoparticles are particles with a diameter of less than one micrometer that are made up of biodegradable or nonbiodegradable polymers, phospholipids, lipids, or metals. Depending on whether the medicine has been equally dispersed or coated with the polymeric material, they are classed as nanospheres or nanocapsules.[43] Polymeric colloidal particles with sizes ranging from 10 nm to 1 nm are used to dissolve, entrap, encapsulate, or adsorb drugs. It is composed of biodegradable substances such as natural or artificial polymers, lipids, phospholipids, and metals. In order to produce nanoparticles, drugs can be manufactured in a variety of ways, including integrating with the matrix or adhering to the surface of the biodegradable polymers employed in the preparation. Polylactides (PLAs), polycyanoacrylate, poly (D, L-lactides), and natural polymers such as chitosan, gelatine, sodium alginate, and albumin are examples of nanoparticles utilized in medication delivery to ocular tissues. Nanoparticles have been employed as drug carriers for eye illnesses for around the last ten years, with positive results.[6] The distribution of nanoparticles for posterior segment delivery is determined by their size and surface quality. After periocular injection to Sprague-Dawley rats, 20 nm particles were rapidly removed from periocular tissues. Removal by conjunctival, episcleral, or other periocular circulatory systems may account for the fast clearance. Particles in the 200-2000 nm range, on the other hand, remained at the administrative site for at least two months. Furthermore, due to the quick clearance and drug release, small size nanoparticles were unable to maintain retinal drug levels. As a result, it can be inferred that nanoparticles with slow drug release and low clearance by blood and lymphatic circulations are appropriate drug delivery candidates for sustained transscleral drug administration to the back of the eye.[44] Poly(lactide-co-glycolide) acid (PLGA) nanospheres incorporating flurbiprofen (FB) were produced by J. Araújo by using the solvent displacement technique, for ocular applications aiming to avoid/minimize inflammation induced by surgical trauma.[45] Similarly Rahul Garhwal has also formulated conventional contact lenses that incorporate nanosphere-encapsulated the drug ciprofloxacin and demonstrated that the lenses provide sustained antibacterial activity.[46]

3.5 Niosomes:

Niosomes are vesicles made up of non-ionic surface active agent bilayers that function as novel drug delivery methods. Their size is on the nanometric scale and is formulated by combining non-ionic surfactants of the alkyl or dialkylpolyglycerol ether class with cholesterol and then hydrating in aqueous media. Depending on the method of preparation, niosomes can be unilamellar or multilamellar.[47] They can be delivered to the site of action via parenteral or topical routes. Niosomes are osmotically active and stable, and they improve the stability of drug entrapment.[48] Cholesterol and nonionic surfactant are the two key components utilized in the formation of niosomes; cholesterol gives the formulation rigidity and appropriate shape. Nonionic surfactants such as span, tween, and brij are commonly utilized in the manufacture of niosomes.[49] There are three types of niosomes that are proniosomes, aspasomes and defarmable niosomes.[50] Aza A. Hasan has formulated the niosomes of Dorzolamide Hydrochloride by using cholesterol with sorbitan monoesters. Niosomes are prepared by mechanical shaking technique. Dorzo-loaded niosomal preparations as a promising ophthalmic carrier to prolong the drug effect on the intraocular pressure.[51] Zubairu et al. developed niosomal system of gatifloxacin composed of span 60 cholestrol and chitosan which shows enhanced antimicrobial activity with good ocular permeability.[52]

3.6 Solid Lipid Nanoparticles:

The introduction of solid lipid nanoparticles (SLN) in 1991 represents an alternate carrier system compared to conventional colloidal carriers. The system is made up of nanometer-sized spherical solid lipid particles that are dispersed in water or an aqueous surfactant solution. It is identical to an oil-in-water emulsion for parentral nutrition, except that the emulsion's liquid lipid (oil) has been replaced by a solid lipid, resulting in Solid Lipid Nanoparticles.[53] Because of their nonirritant and nontoxic properties, SLNs were considered one of the best carriers for ocular drugs. The sustained and controlled drug release features of SLN may be advantageous in ocular formulations. Furthermore, a good biocompatibility of SLN may aid in resolving the issue of standard ophthalmic solutions' limited bioavailability.[54] Solid lipid nanoparticles (SLNs) entrapped gatifloxacin drug were produced and characterized utilizing stearic acid (SLN-A) and a mixture of stearic acid and Compritol (SLN-B) as lipid matrix and poloxamer-188 as surfactant, with sodium taurocholate and ethanol as co-surfactant mixtures. Positive -potential of the formulations suggested that the SLNs were dispersive and would promote corneal retention of the lipid nanoparticles, hence increasing ocular bioavailability of the drug.[55] The formulation study was carried out to produce and analyze methazolamide (MTZ)-loaded solid lipid nanoparticles (SLN) with and without low molecular weight chitosan (CS) modification, and to compare their potential for ocular drug delivery. A modified chemical oxidative degradation process was used to produce low molecular weight CS. Enhancement of transcorneal permeation and absence of cytotoxicity in vivo was occurred.[56]

3.7 Leciplex:

Leciplex is a self-assembled, lecithin-based cationic nanoparticles; the leciplex system's essential constituents include phospholipid, a cationic surfactant, and a biocompatible surfactant such as Transcutol HP.[57] There are various advantages to using Leciplex over alternative nanovesicular carrier systems. It is simply manufactured without the need of an organic solvent in a single step manufacturing approach.[58] It also promotes corneal penetration, which is related to the presence of positive charges, which allows the nanovesicles to engage intimately with the negatively charged corneal mucus membrane. This results in increased corneal penetration and residence, which is also supported by its small particle size, as well as reduced drug deposition via lachrymal flow and increased ocular bioavailability.[59] Sertaconazole-Nitrate-Loaded Leciplex has formulated by using soy phosphatidylcholine (SPC), cetyltrimethylammonium bromide (CTAB), and dimethyldidodecylammonium bromide (DDAB) which has ultimately improved corneal permeability and retention time of the lipophilic drug.[57]

3.8 Nanomicelles:

Micelles are made up of amphiphilic molecules that self-assemble to form structured supramolecular structures in aqueous conditions. Micelles come in a variety of sizes (10-1000 nm) and forms (spherical, cylindrical, star-shaped, and so on). So far, nanomicelles studied for ODD can be categorized into three basic categories: polymeric, surfactant, and polyionic complex (PIC) micelles.[60] Amphiphilic di-block (hydrophilic-hydrophobic) polymers, tri-block (hydrophilic-hydrophobic-hydrophilic) polymers, graft (hydrophilichydrophobic) and ionic (hydrophilic-ionic) copolymers make up the majority of polymeric micelles utilized in drug delivery. The principal hydrophilic element in the majority of these systems is poly(ethylene glycol) (PEG).[61] A drug is expected to reach posterior segment tissues via the corneal or conjunctival-scleral pathway after topical application of an eye drop.[62] This work was done in situ gelling system and a loaded drug self-assembling nanomicellar carrier as a new possible Ocular Drug Delivery System (ODDS) for Cyclosporine-A (CyA), a weakly water-soluble medication. The nanomicelles were created using two non-ionic surfactants (d--tocopherol polyethylene glycol succinate, VitE-TPGS, and polyoxyl 40 hydrogenated castor oil, RH-40) The current findings show the potential of VitE-TPGS/RH-40 polymeric micelles in ocular drug administration due to their capacity to improve CyA solubility and residence time in tear fluid, particularly when used as an in situ gelling method.[63]

3.9 Ethosomes:

Ethosomes are non-invasive devices for drug delivery that allow drugs to reach deep skin layers or the systemic circulation. These are soft, pliable vesicles that have been produced for increased active drug distribution. They are mostly made up of phospholipids (phosphotidlycholine, phosphotidyl serine, and phosphotidic acid), ethanol, and water. Ethosomes can range in size from tens of micrometers to microns. It is a minor modification of well-known drug carrier liposomes. Ethanol acts as a skin penetration booster. The method by which it improves penetration is well understood. Ethanol penetrates intracellular lipids, increasing the fluidity of the lipid membrane and decreasing the density of the lipid multilayer of the mobileular membrane. According to the components incorporated into their formula, the known ethosomal system can be divided into three distinct types: classic or conventional ethosomes, binary ethosomes, and transethosomes. Traditional or classical ethosomes are the first ethosomal systems produced, which altered the liposomal composition by incorporating a rather high amount of ethanol, up to 45%, along with phospholipids and water. Binary ethosomes are modifications of classic ethosomes caused by the inclusion of several types of alcohol, and transethosme being the most recent generation of ethosomes.[64] Short biological half-life, low oral bioavailability, and high lipophilicity are ideal pharmacological characteristics for ethosomes.[65] The beta-adrenoreceptor blocker Timolol maleate is a commonly used pharmaceutical agent for the management of glaucoma. Conventional eye drops have limitations due to biological factors. Burcu Uner has developed

Timolol- loaded ethosomes for ophthalmic delivery for the reduction of intraocular pressure. This formulation shows similar pharmacological response with lowered application frequencies. Therefore it can be proved that the novel TML-loaded ethosomes could be a safe and efficient alternative for glaucoma treatment.[66]

3.10 Bilosomes:

Bilosomes are nanotechnology based products consists of Non-ionic surfactant and bile salt. They are chemically stable and no special conditions are required for their storage.[67] Abdelbary et al. developed terconazole loaded bilosomes using cholesterol, span 60, and edge activator. The resulted formula showed great entrapment, improved permeation, and enhanced activity.[68] Acetazolamide bilosomes were synthesized using Span 60, cholesterol, and different bile salts (sodium cholate, sodium deoxycholate, sodium taurocholate, and sodium tauroglycocholate) in two molar ratios (1:1:0.1 and 1:1:0.2) which showed improved corneal permeation and ocular bioavailability.[69]

Table 2: Nanotechnology based drug delivery carriers used in opthalmic research

Sr.no	Drug	Carrier platform	Outcomes	Refs
1.	Brinzolamide	Nanocrystal	It shows improved absorption behaviour with effectivelydecrease IOP	70
2.	Dexamethasone	Nanocrystal	Enhanced retention time and safety	71
3.	Gentamycin	Niosomes	High retention of gentamicin sulphate inside the vesicles such that their *in vitro* release was slower compared to the drug solution.	68
4.	Acetazolamide	Niosomes	Overcome the problems ofconventional ocular therapy, such as short residence time, loss of drug through nasolacrimal drainage,impermeability of corneal epithelium	72
5.	Moxifloxacin	Leciplex	It improves the therapeuticefficacy of hydrophilic drugs	73
6.	Ibuprofen	Nanostructuredlipid carrier	It enhances drug loading and permeation of the lipophilicmolecules	37
7.	Riboflavin	Nanostructured lipid carrier	Superior corneal residential time, permeation and safety	74
8.	Dexamethasone	Nanosponges	It shows greater ocular retention and permeation	42
9.	Baicalin	Solid lipid nanoparticle	It prolongs the drug release and Enhance the apparentpermeation coefficient of drug	54
10.	Acyclovir	Liposome	It increases the residential time on ocular surface	33

Conclusion:

Nanotechnology based ophthalmic drug delivery system represent a promising approach in the field of ocular therapeutics. The utilization of all Nano drug carriers offers several advantages, including improved drug solubility, sustained release and enhanced bioavailability. These nanoscale delivery systems have the potential to address the limitations of the conventional ophthalmic drug delivery methods, such as poor drug retention and limited efficacy. Several methodologies and technologies have been used to reduce dosing intervals, administered doses, and undesirable effects while increasing ocular retention time, drug permeation efficacy, and ocular bioavailability using a regulated and sustained drug delivery system.

Conflict of interests:

The authors declare that there are no conflicts of interests.

References:

1. Ahmed S, Amin MM, Sayed S. Ocular Drug Delivery: a Comprehensive Review. AAPS PharmSciTech. 2023 Feb 14;24(2):66. https://doi.org/10.1208/s12249-023-02516-9 PMid:36788150

2. Willoughby CE, Ponzin D, Ferrari S, Lobo A, Landau K, Omidi Y. Anatomy and physiology of the human eye: effects of mucopolysaccharidoses disease on structure and function - a review. Clin Experiment Ophthalmol. 2010 Aug;38(s1):2-11. https://doi.org/10.1111/j.1442-9071.2010.02363.x

3. Wadhwa S, Paliwal R, Paliwal S, Vyas S. Nanocarriers in Ocular Drug Delivery: An Update Review. Curr Pharm Des. 2009 Aug 1;15(23):2724-50. https://doi.org/10.2174/138161209788923886 PMid:19689343

4. Wankhede TM, Wankhede AM. Ocular Drug Delivery System: Review. 21.

5. Rahul J, Namrata H, Raykar M, Goi H. Occular Drug Delivery System. 2022;10(3).

6. Raj VK, Mazumder R, Madhra M. OCULAR DRUG DELIVERY SYSTEM: CHALLENGES AND APPROACHES. Int J Appl Pharm. 2020 Aug 11;49-57. https://doi.org/10.22159/ijap.2020v12i5.38762

7. Lee DA, Higginbotham EJ. Glaucoma and its treatment: A review. Am J Health Syst Pharm. 2005 Apr 1;62(7):691-9. https://doi.org/10.1093/ajhp/62.7.691 PMid:15790795

8. Alasil T, Wang K, Yu F, Field MG, Lee H, Baniasadi N, et al. Correlation of Retinal Nerve Fiber Layer Thickness and Visual Fields in Glaucoma: A Broken Stick Model. Am J Ophthalmol. 2014 May;157(5):953-959.e2. https://doi.org/10.1016/j.ajo.2014.01.014 PMCid:PMC4423422

9. Grzybowski A, Och M, Kanclerz P, Leffler C, De Moraes CG. Primary Open Angle Glaucoma and Vascular Risk Factors: A Review of Population Based Studies from 1990 to 2019. J Clin Med. 2020 Mar 11;9(3):761. https://doi.org/10.3390/jcm9030761 PMid:32168880 PMCid:PMC7141380

10. Patel K, Patel S. Angle-closure glaucoma. Dis Mon. 2014 Jun;60(6):254-62. https://doi.org/10.1016/j.disamonth.2014.03.005 PMid:24906670

11. Wright C, Tawfik MA, Waisbourd M, Katz LJ. Primary angle-closure glaucoma: an update. Acta Ophthalmol (Copenh). 2016 May;94(3):217-25. https://doi.org/10.1111/aos.12784

12. Qummar S, Khan FG, Shah S, Khan A, Shamshirband S, Rehman ZU, et al. A Deep Learning Ensemble Approach for Diabetic Retinopathy Detection. IEEE Access. 2019;7:150530-9. https://doi.org/10.1109/ACCESS.2019.2947484

13. Ung L, Bispo PJM, Shanbhag SS, Gilmore MS, Chodosh J. The persistent dilemma of microbial keratitis: Global burden, diagnosis, and antimicrobial resistance. Surv Ophthalmol. 2019 May;64(3):255-71. https://doi.org/10.1016/j.survophthal.2018.12.003 PMid:30590103 PMCid:PMC7021355

14. Austin A, Lietman T, Rose-Nussbaumer J. Update on the Management of Infectious Keratitis. Ophthalmology. 2017 Nov;124(11):1678-89. https://doi.org/10.1016/j.ophtha.2017.05.012 PMid:28942073 PMCid:PMC5710829

15. Koganti R, Yadavalli T, Naqvi RA, Shukla D, Naqvi AR. Pathobiology and treatment of viral keratitis. Exp Eye Res. 2021 Apr;205:108483. https://doi.org/10.1016/j.exer.2021.108483 PMid:33556334 PMCid:PMC8043992

16. Bourcier T, Sauer A, Dory A, Denis J, Sabou M. Fungal keratitis. J Fr Ophtalmol. 2017 Nov;40(9):e307-13. https://doi.org/10.1016/j.jfo.2017.08.001 PMid:28987448

17. Azari AA, Barney NP. Conjunctivitis: A Systematic Review of Diagnosis and Treatment. JAMA. 2013 Oct 23;310(16):1721. https://doi.org/10.1001/jama.2013.280318 PMid:24150468 PMCid:PMC4049531

18. Høvding G. Acute bacterial conjunctivitis. Acta Ophthalmol (Copenh). 2008 Jun 28;86(1):5-17. https://doi.org/10.1111/j.1600-0420.2007.01006.x PMid:17970823

19. Gupta V, Rajagopala M, Ravishankar B. Etiopathogenesis of cataract: An appraisal. Indian J Ophthalmol. 2014;62(2):103. https://doi.org/10.4103/0301-4738.121141 PMid:24618482 PMCid:PMC4005220

20. Allen D, Vasavada A. Cataract and surgery for cataract. BMJ. 2006 Jul 15;333(7559):128-32. https://doi.org/10.1136/bmj.333.7559.128 PMid:16840470 PMCid:PMC1502210

21. Lang JC. Ocular drug delivery conventional ocular formulations. Adv Drug Deliv Rev. 1995 Aug;16(1):39-43. https://doi.org/10.1016/0169-409X(95)00012-V

22. Sultana Y, Jain R, Aqil M, Ali A. Review of Ocular Drug Delivery. Curr Drug Deliv. 2006 Apr 1;3(2):207-17. https://doi.org/10.2174/156720106776359186 PMid:16611007

23. Kumar A, Malviya R, Sharma PK. Recent Trends in Ocular Drug Delivery: A Short Review. 2011;

24. Majeed A, Khan NA. Ocular in situ gel: An overview. J Drug Deliv Ther. 2019 Jan 15;9(1):337-47. https://doi.org/10.22270/jddt.v9i1.2231

25. Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug Discov Today. 2003 Dec;8(24):1112-20. https://doi.org/10.1016/S1359-6446(03)02903-9 PMid:14678737

26. Mudgil M, Gupta N, Nagpal M, Pawar P. NANOTECHNOLOGY: A NEW APPROACH FOR OCULAR DRUG DELIVERY SYSTEM. 4(2).

27. Liu S, Jones L, Gu FX. Nanomaterials for Ocular Drug Delivery. Macromol Biosci. 2012 May;12(5):608-20. https://doi.org/10.1002/mabi.201100419 PMid:22508445

28. Sharma A. Liposomes in drug delivery: Progress and limitations. Int J Pharm. 1997 Aug 26;154(2):123-40. https://doi.org/10.1016/S0378-5173(97)00135-X

29. Maurer N, Fenske DB, Cullis PR. Developments in liposomal drug delivery systems. Expert Opin Biol Ther. 2001 Nov;1(6):923-47. https://doi.org/10.1517/14712598.1.6.923 PMid:11728226

30. Samad A, Sultana Y, Aqil M. Liposomal Drug Delivery Systems: An Update Review. Curr Drug Deliv. 2007 Oct 1;4(4):297-305. https://doi.org/10.2174/156720107782151269 PMid:17979650

31. Meisner D, Mezei M. Liposome ocular delivery systems. Adv Drug Deliv Rev. 1995 Aug;16(1):75-93. https://doi.org/10.1016/0169-409X(95)00016-Z

32. Sahoo S, Dilnawaz F, Krishnakumar S. Nanotechnology in ocular drug delivery. Drug Discov Today. 2008 Feb;13(3-4):144-51. https://doi.org/10.1016/j.drudis.2007.10.021 PMid:18275912

33. Law SL, Huang KJ, Chiang CH. Acyclovir-containing liposomes for potential ocular delivery Corneal penetration and absorption. J Controlled Release. 2000; https://doi.org/10.1016/S0168-3659(99)00192-3 PMid:10640587

34. Khosa A, Reddi S, Saha RN. Nanostructured lipid carriers for site-specific drug delivery. Biomed Pharmacother. 2018 Jul;103:598-613. https://doi.org/10.1016/j.biopha.2018.04.055 PMid:29677547

35. Salvi VR, Pawar P. Nanostructured lipid carriers (NLC) system: A novel drug targeting carrier. J Drug Deliv Sci Technol. 2019 Jun;51:255-67.

https://doi.org/10.1016/j.jddst.2019.02.017

36. Obeidat WM, Schwabe K, Müller RH, Keck CM. Preservation of nanostructured lipid carriers (NLC). Eur J Pharm Biopharm. 2010 Sep;76(1):56-67. https://doi.org/10.1016/j.ejpb.2010.05.001 PMid:20452422

37. Li X, Nie S fang, Kong J, Li N, Ju C yi, Pan W san. A controlled-release ocular delivery system for ibuprofen based on nanostructured lipid carriers. Int J Pharm. 2008 Nov;363(1-2):177-82. https://doi.org/10.1016/j.ijpharm.2008.07.017 PMid:18706987

38. Araújo J, Nikolic S, Egea MA, Souto EB, Garcia ML. Nanostructured lipid carriers for triamcinolone acetonide delivery to the posterior segment of the eye. Colloids Surf B Biointerfaces. 2011 Nov;88(1):150-7. https://doi.org/10.1016/j.colsurfb.2011.06.025 PMid:21764568

39. Nikam PL. NANOSPONGES: A BENEFICATION FOR NOVEL DRUG DELIVERY. World J Pharm Res. 9(5).

40. Shringirishi M, Prajapati SK, Mahor A, Alok S, Yadav P, Verma A. Nanosponges: a potential nanocarrier for novel drug delivery-a review. Asian Pac J Trop Dis. 2014 Sep;4:S519-26. https://doi.org/10.1016/S2222-1808(14)60667-8

41. Bhowmik H, Venkatesh DN, Kuila A, Kumar KH. NANOSPONGES: A REVIEW. Int J Appl Pharm. 2018 Jul 7;10(4):1. https://doi.org/10.22159/ijap.2018v10i4.25026

42. Pillai MK, Jain P, Pillai S. Fabrication and evaluation of nanosponges of besifloxacin hydrochloride for ocular drug delivery. J Med Pharm Allied Sci. 2022 Mar 30;11(2):4657-60. https://doi.org/10.55522/jmpas.V11I2.2586

43. Diebold Y, Jarrín M, Sáez V, Carvalho ELS, Orea M, Calonge M, et al. Ocular drug delivery by liposome-chitosan nanoparticle complexes (LCS-NP). Biomaterials. 2007 Mar;28(8):1553-64. https://doi.org/10.1016/j.biomaterials.2006.11.028 PMid:17169422

44. Patel A. Ocular drug delivery systems: An overview. World J Pharmacol. 2013;2(2):47. https://doi.org/10.5497/wjp.v2.i2.47 PMid:25590022 PMCid:PMC4289909

45. Araújo J, Vega E, Lopes C, Egea MA, Garcia ML, Souto EB. Effect of polymer viscosity on physicochemical properties and ocular tolerance of FB-loaded PLGA nanospheres. Colloids Surf B Biointerfaces. 2009 Aug;72(1):48-56. https://doi.org/10.1016/j.colsurfb.2009.03.028 PMid:19403277

46. Garhwal R, Shady SF, Ellis EJ, Ellis JY, Leahy CD, McCarthy SP, et al. Sustained Ocular Delivery of Ciprofloxacin Using Nanospheres and Conventional Contact Lens Materials. Investig Opthalmology Vis Sci. 2012 Mar 13;53(3):1341. https://doi.org/10.1167/iovs.11-8215 PMid:22266514 PMCid:PMC3339908

47. Prajapati SK, Maurya SD, Das MK, Tilak VK, Verma KK, Dhakar RC, Dendrimers in drug delivery, diagnosis and therapy: basics and potential applications. Journal of Drug Delivery and Therapeutics, 2016;6(1),67-92. https://doi.org/10.22270/jddt.v6i1.1190

48. Yadav JD, Kulkarni PR, Vaidya KA, Shelke GT. Available online through www.jpronline.info NIOSOMES: A REVIEW. J Pharm Res. 2011;(3).

49. Lohumi A. A NOVEL DRUG DELIVERY SYSTEM: NIOSOMES REVIEW. J Drug Deliv Ther. 2012;2(5). https://doi.org/10.22270/jddt.v2i5.274

50. Badri S, P S, Annagowni NR, Lunjala RS, B BN, B SKR, et al. A review on niosomes as novel drug delivery system. Int J Indig Herbs Drugs. 2022 Sep 29;87. https://doi.org/10.46956/ijihd.v7i5.352

51. Hasan AA. Design and in vitro characterization of small unilamellar niosomes as ophthalmic carrier of dorzolamide hydrochloride. Pharm Dev Technol. 2014 Sep;19(6):748-54. https://doi.org/10.3109/10837450.2013.829095 PMid:23964893

52. Zubairu Y, Negi LM, Iqbal Z, Talegaonkar S. Design and development of novel bioadhesive niosomal formulation for the transcorneal delivery of anti-infective agent: In-vitro and ex-vivo investigations. Asian J Pharm Sci. 2015 Jul;10(4):322-30. https://doi.org/10.1016/j.ajps.2015.02.001

53. Maurya SD, Prajapati S, Gupta A, Saxena G, Dhakar RC, Formulation development and evaluation of ethosome of stavudine, Int J Pharm Edu Res, 2010;13:16

54. Liu Z, Zhang X, Wu H, Li J, Shu L, Liu R, et al. Preparation and evaluation of solid lipid nanoparticles of baicalin for ocular drug delivery system in vitro and in vivo. Drug Dev Ind Pharm. 2011 Apr;37(4):475-81. https://doi.org/10.3109/03639045.2010.522193 PMid:21054217

55. Kalam MohdA, Sultana Y, Ali A, Aqil Mohd, Mishra AK, Chuttani K. Preparation, characterization, and evaluation of gatifloxacin loaded solid lipid nanoparticles as colloidal ocular drug delivery system. J Drug Target. 2010 Apr;18(3):191-204. https://doi.org/10.3109/10611860903338462 PMid:19839712

56. Wang F, Chen L, Zhang D, Jiang S, Shi K, Huang Y, et al. Methazolamide-loaded solid lipid nanoparticles modified with low-molecular weight chitosan for the treatment of glaucoma: vitro and vivo study. J Drug Target. 2014 Nov;22(9):849-58. https://doi.org/10.3109/1061186X.2014.939983 PMid:25045926

57. Abdellatif MM, Josef M, El-Nabarawi MA, Teaima M. Sertaconazole-Nitrate-Loaded Leciplex for Treating Keratomycosis: Optimization Using D-Optimal Design and In Vitro, Ex Vivo, and In Vivo Studies. Pharmaceutics. 2022 Oct 18;14(10):2215. https://doi.org/10.3390/pharmaceutics14102215 PMid:36297650 PMCid:PMC9611087

58. Ibrahim MM, Abd-Elgawad AEH, Soliman OAE, Jablonski MM. Pharmaceutical Nanotechnology Nanoparticle-Based Topical Ophthalmic Formulations for Sustained Celecoxib Release. J Pharm Sci. 2013 Mar;102(3):1036-53. https://doi.org/10.1002/jps.23417 PMid:23293035

59. Dave RS, Goostrey TC, Ziolkowska M, Czerny-Holownia S, Hoare T, Sheardown H. Ocular drug delivery to the anterior segment using nanocarriers: A mucoadhesive/mucopenetrative perspective. J Controlled Release. 2021 Aug;336:71-88. https://doi.org/10.1016/j.jconrel.2021.06.011 PMid:34119558

60. Vaishya RD, Khurana V, Patel S, Mitra AK. Controlled ocular drug delivery with nanomicelles. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2014 Sep;6(5):422-37. https://doi.org/10.1002/wnan.1272 PMid:24888969 PMCid:PMC4155159

61. Mandal A, Bisht R, Rupenthal ID, Mitra AK. Polymeric micelles for ocular drug delivery: From structural frameworks to recent preclinical studies. J Controlled Release. 2017 Feb;248:96-116. https://doi.org/10.1016/j.jconrel.2017.01.012 PMid:28087407 PMCid:PMC5319397

62. Hughes P, Olejnik O, Changlin J, Wilson C. Topical and systemic drug delivery to the posterior segments. Adv Drug Deliv Rev. 2005 Dec 13;57(14):2010-32. https://doi.org/10.1016/j.addr.2005.09.004 PMid:16289435

63. Terreni E, Zucchetti E, Tampucci S, Burgalassi S, Monti D, Chetoni P. Combination of Nanomicellar Technology and In Situ Gelling Polymer as Ocular Drug Delivery System (ODDS) for Cyclosporine-A. Pharmaceutics. 2021 Feb 1;13(2):192. https://doi.org/10.3390/pharmaceutics13020192 PMid:33535607 PMCid:PMC7912864

64. Mohanty D, Mounika A, Bakshi V, Akiful Haque M, Keshari Sahoo C. Ethosomes: A Novel Approach For Transdermal Drug Delivery. Int J ChemTech Res. 2018;11(8):219-26. https://doi.org/10.20902/IJCTR.2018.110826

65. Dave V, Kumar D, Lewis S, Paliwal S. Ethosome for enhanced transdermal drug delivery of aceclofenac. Int J Drug Deliv. 2010 Mar 16;2(1):81-92. https://doi.org/10.5138/ijdd.2010.0975.0215.02016

66. Sun Y, Du L, Yang M, Li Q, Jia X, Li Q, et al. Brain-targeted drug delivery assisted by physical techniques and its potential applications in traditional Chinese medicine. J Tradit Chin Med Sci. 2021 Jul;8(3):186-97. https://doi.org/10.1016/j.jtcms.2021.07.003

67. Bilosomes Based Drug Delivery System. 2015;

68. Abdelbary AA, Abd-Elsalam WH, Al-mahallawi AM. Fabrication of novel ultradeformable bilosomes for enhanced ocular delivery of terconazole: In vitro characterization, ex vivo permeation and in vivo safety assessment. Int J Pharm. 2016 Nov;513(1-2):688-96. https://doi.org/10.1016/j.ijpharm.2016.10.006 PMid:27717916

69. Mohsen AM, Salama A, Kassem AA. Development of acetazolamide loaded bilosomes for improved ocular delivery: Preparation, characterization and in vivo evaluation. J Drug Deliv Sci Technol. 2020 Oct;59:101910. https://doi.org/10.1016/j.jddst.2020.101910

70. Tuomela A, Liu P, Puranen J, Rönkkö S, Laaksonen T, Kalesnykas G, et al. Brinzolamide nanocrystal formulations for ophthalmic delivery: Reduction of elevated intraocular pressure in vivo. Int J Pharm. 2014 Jun;467(1-2):34-41. https://doi.org/10.1016/j.ijpharm.2014.03.048 PMid:24680962

71. Romero GB, Keck CM, Müller RH, Bou-Chacra NA. Development of cationic nanocrystals for ocular delivery. Eur J Pharm Biopharm. 2016 Oct;107:215-22. https://doi.org/10.1016/j.ejpb.2016.07.005 PMid:27388629

72. Guinedi AS, Mortada ND, Mansour S, Hathout RM. Preparation and evaluation of reverse-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. Int J Pharm. 2005 Dec;306(1-2):71-82. https://doi.org/10.1016/j.ijpharm.2005.09.023 PMid:16263229

73. Albash R, Abdellatif MM, Hassan M, M Badawi N. Tailoring Terpesomes and Leciplex for the Effective Ocular Conveyance of Moxifloxacin Hydrochloride (Comparative Assessment): In-vitro, Ex-vivo, and In-vivo Evaluation. Int J Nanomedicine. 2021 Aug;Volume 16:5247-63. https://doi.org/10.2147/IJN.S316326 PMid:34376978

74. Aytekin E, Öztürk N, Vural İ, Polat HK, Çakmak HB, Çalış S, et al. Design of ocular drug delivery platforms and in vitro - in vivo evaluation of riboflavin to the cornea by non-interventional (epi-on) technique for keratoconus treatment. J Controlled Release. 2020 Aug;324:238-49. https://doi.org/10.1016/j.jconrel.2020.05.017 PMid:32413453