



Ocular Drug Delivery: a Comprehensive Review

Sadek Ahmed¹ · Maha M. Amin¹ · Sinar Sayed¹

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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, intravitreal, intraocular, juxtasclear, subconjunctival, intracameral, and retrobulbar. More than 95% of marketed products exist 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 carriers is resulted from their capabilities to entrap both hydrophilic and lipophilic drugs, enhance ocular permeability, sustain residence time, improve drug stability, and augment 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. This review also discusses different nanostructured platforms and their characterization approaches. Strategies to enhance ocular bioavailability are also explained. Finally, recent advances in ocular delivery are described.

Keywords corneal barriers · *in situ* gel · nanocarriers · ocular delivery · retention time

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].

✉ Sadek Ahmed
sadek.sadek@pharma.cu.edu.eg

¹ Department of Pharmaceutics and Industrial Pharmacy,
Faculty of Pharmacy, Cairo University, Kasr El-Aini,
Cairo 11562, Egypt

Ocular formulations are intended to be applied on the anterior surface (topical route) of the eye, delivered intraocularly (inside the eye), periocularly (subtenon or juxtasclear), or in combination with ocular devices. Ocular dosage forms could be liquid, semi-solid, solid, or mixed. Liquid dosage forms include drops, suspension, and emulsion. Eye drops represent more than 95% of the marketed ocular products [7]. They are used for delivering the medication into the anterior part of the eye but with short residence time [5]. Ocular suspensions and emulsions have the ability to deliver hydrophobic drugs, but may lead to blurred vision. Ocular gels and ointments (semi-solid) could significantly enhance residence time. Solid dosage forms could be used to deliver water-sensitive drugs (powder), provide zero order release model (insert), or sustain residence time (therapeutic contact lens) [7].

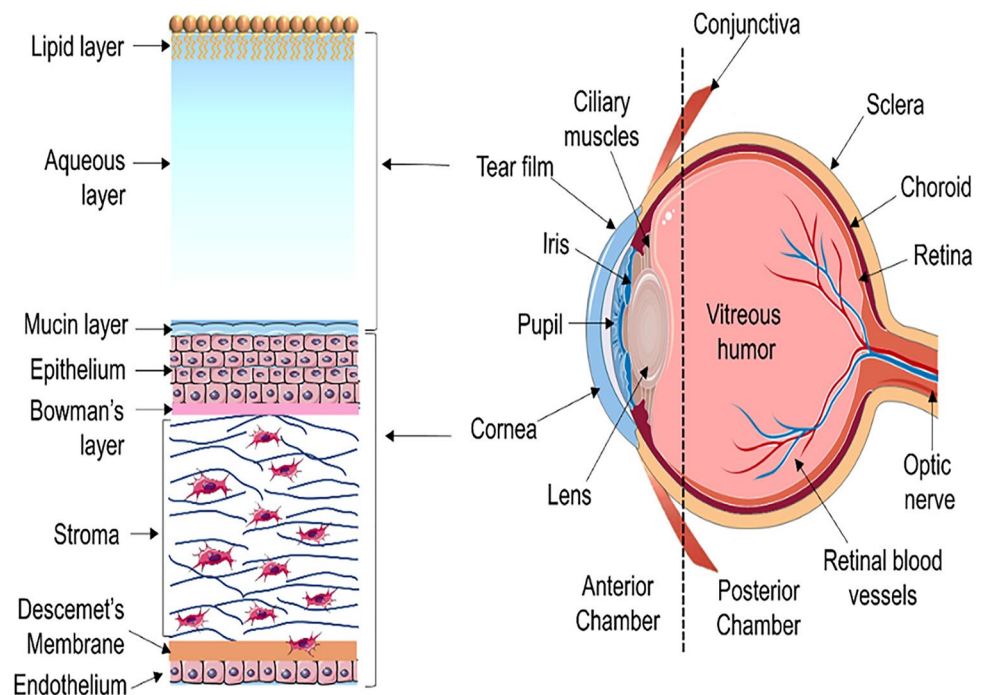
Effective ocular absorption necessitates appropriate corneal penetration along with effective precorneal residence time, so as to reach and preserve an acceptable drug concentration with the minimum quantity of the active therapeutic constituent. Nanosystems are innovative technologies developed to get through ocular obstacles, shield the drug from the biological environment, sustain drug residence time, and improve corneal permeation across biological barriers [8]. Characterization of the constructed nanosystems is of great importance to ensure its ability to accomplish the required activity. There are many approaches for characterization such as visual appearance, stability, size, zeta potential, possible interactions, pH measurement, and other important *ex vivo* and *in vivo* evaluations [6]. This review highlights the gaps in other published reviews regarding the ocular

drug delivery. It described comprehensively ocular drug delivery from different points such as the various anatomical features of the eye, different ocular diseases, obstacles to ocular delivery, different routes of ocular administration, classification of dosage forms, numerous nanostructured platforms, characterization approaches, strategies to improve ocular delivery, and future technologies.

Anatomy of the Eye

Human eye is a very sensitive and complex organ. Figure 1 illustrates the anatomy of human eye [6]. Human eye is composed of anterior and posterior chambers. The anterior segment is composed of tear film, cornea, pupil, lens, and ciliary body. The posterior segment is composed of conjunctiva, sclera, choroid, retina, vitreous humor, and optic nerve. The structure and quantity of tears are controlled by orbital glands and epithelial secretions. Cornea is the front portion of the eye that conveys and focuses light into the eye. It is divided into epithelium, stroma, and endothelium. The epithelium is made of five to seven layers of firmly connected cells. Stroma is a water-based compact layer. The endothelium preserves the transparency of the cornea [6]. Iris is the colored portion of the eye which controls the quantity of light penetrating the eye. The dark center opening in the middle of the iris is called pupil. The pupil changes its size according to the available light. Lens is transparent portion that focuses the light into retina. The ciliary body is made of pigmented and non-pigmented ciliary epithelia, a

Fig. 1 Anatomy of the eye [6]



stroma, and ciliary muscles. Capillaries of ciliary body allow communication between anterior and posterior segments [7]. Vitreous humor is a gel-like, clear, avascular connective tissue that exists between the eye lens and the retina. It is made of 99.9% water, hyaluronic acid, ions, and collagen [7]. The conjunctiva is a delicate transparent membrane lining inside the eyelids and shelter the frontal surface of the sclera. It is a mucous membrane that is composed of three layers, an outer epithelium, a substantia propria enclosing nerves, lymphatic and blood vessels, and a submucosa layer linked to the sclera [9]. The sclera is a continuous of cornea. It is made of collagen and mucopolysaccharides. Choroid is vascular layer that is located between retina and sclera. The retina is thin film of tissue composed of neural and glial cells covering the back of the eye. It produces electrical impulses that are delivered through the optic nerve to the brain [7].

Ocular Diseases

Cataract

Cataract is chief cause of loss of vision worldwide. About 40–60% of blindness in the world is caused as a complication of cataract [1]. As said by the National Programme for Control of Blindness and Visual Impairment, the major reason of avoidable blindness in India is cataract (62.6%) [2]. Cataract could be defined as the development of cloudiness/opacification in the eye lens. The risk factors include exposure to UV light, diabetes, bad nutrition, genetic determinism, and smoking. Cataract could be divided into three types: cortical, nuclear, or posterior subcapsular. The clearness and transparency of lens is regulated by crystallin protein [10]. Alterations in α , β , and γ crystallin and its associated genes are responsible for the early cataract development. Triggers to cataract are glycation, oxidative stress, and exposure to lipophilic compounds which result in increasing calcium level in the lens plus crystallin accumulation. Oxidative stress is mediated by hyperglycemia and hydroxyl radicals. Nowadays, surgical removal of opaque lens is the treatment choice. However, the early employment of anti-cataract agent may minimize surgical treatment. Anti-cataract agents are multifunctional antioxidants with radical hunting and chelation ability [10]. Examples of anti-cataract agents include curcumin, lanosterol, resveratrol, and metformin [11].

Glaucoma

Glaucoma is a famous optic neuropathy disease. Symptoms start with blurred vision that progresses into irreversible blindness in the late stage. It leads to blindness as a result of

slow deterioration of optic nerve axon and fatality of retinal ganglion cells [3]. It is commonly connected with elevation in intraocular pressure (IOP) because of irregular formation or obstruction of the aqueous humor [12]. Risk factors include age, race, diabetes, genetics, nearsightedness, migraine, and retinal vascular caliber. Glaucoma is more common in women population as they represent 55% of open angle glaucoma, 70% of angle closure glaucoma, and 59% of all forms of glaucoma in 2010 [1]. Worldwide incidence is estimated at 76 million at 2020 and is expected to elevate to 112 million by 2040 [13]. There are two types of glaucoma: open angle and closed angle. Open angle glaucoma has no symptoms and is characterized by enlarging optic disc cupping and visual field that results in elevated prevention of drainage of aqueous humor through trabecular meshwork. However, closed angle is characterized by the elevated pressure resulted from the blockage of outflow pathways [3]. About 76 million people suffered from glaucoma and the number is expected to reach 112 million by 2040 [14]. Glaucoma developed as a result of oxidative and nitrative processes. There are many antioxidant enzymes in aqueous humor for example superoxide dismutase, catalase, and glutathione peroxidase. Their level is decreased as a result of aging and that leads to elevated IOP. Change the equilibrium between oxidants and antioxidants influence the progression of glaucoma [15]. Anti-glaucoma drugs help to adjust either aqueous humor formation or drainage. Many studies were published to enhance glaucoma treatment [12, 16–18]. Abd-Elsalam and ElKasabgy developed topical agomelatin-loaded olaminosomes with remarkable anti-glaucoma activity [12]. Eldeep *et al.* developed topical proniosomal gel-derived niosomes to improve ocular retention and activity of brimonidine tartrate [18].

Age-Related Macular Degeneration (AMD)

AMD is one of the main causes of loss of vision in developed countries. It is more frequent above the age of 50 years. [3]. About 8.7% of worldwide blindness is initiated by AMD AMD [19]. Nearly 196 million people suffered from AMD at 2020 and the number is expected to reach 288 million by 2040 [20]. It is a multifactorial degenerative complaint involving the posterior segment of the eye. Risk factors include aging, smoking, bad nutrition, high blood pressure, and immobility. There is no remedy for AMD till now, but its progression may be reduced by proper medications [21]. AMD could be divided into two types, dry (atropic or non-exudative) and wet (neovascular or emulative). Irregular angiogenesis (development of new blood vessels) in the retinal epithelium is the main character of AMD and results in drusen (yellow deposits under the retina), atropy, and separation of bruch's membrane [22]. Many cellular growth factors are increased during angiogenesis due to

the irregularities in corresponding metabolic pathways as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), and epithelial growth factor (EGF). A new approach for treatment of AMD involves juxtasceral injections of anecortave cortisone that showed prolonged release for 6 months in the choroid and retina [23]. Moreover, intravitreal injection of the biodegradable Rho kinase and protein kinase C inhibitor for handling diabetic macular edema and neovascular age-related macular degeneration exhibited prolonged release for about 6 months [24].

Conjunctivitis

Conjunctivitis is generally the most frequent ocular complaint. It is simply the inflammation of conjunctival tissue. It affects all ages, races, and genders [25]. According to the cause, it may be classified into infectious or non-infectious. Infectious conjunctivitis results from microbial infection, while non-infectious conjunctivitis results from allergens and irritants [25]. Symptoms of conjunctivitis include eye redness, eye discomfort, tears, and elevated eye secretions. Prevalence of allergic conjunctivitis is nearly 40% of the global population [26]. Treatments of conjunctivitis include topical administration of antimicrobial (infectious) or anti-inflammatory agents (non-infectious).

Diabetic Retinopathy (DR)

Diabetic retinopathy is a particular vascular complication related to both types of diabetes mellitus. About 60% of patients of type II and all patients of type I diabetes have a certain extent of retinopathy after 20 years of diabetes. Oxidative stress and inflammation result from the upregulation of proinflammatory mediators initiated by hyperglycemic disorders and are the cause of development of DR. It is the third major trigger to blindness in the USA. After cataract and corneal blindness, the first and second triggers to blindness. It is avoidable if distinguished and cured early plus the effective management of blood glucose and blood pressure [27]. It has two types, proliferative and non-proliferative and both of them result eventually in progressive damage to the retina. Nowadays, diabetic retinopathy is managed through laser photocoagulation, vitrectomy, and pharmacological treatments. Laser photocoagulation works by closing the leaky blood vessels and possibly avoids blindness, but results in laser scar. Vitrectomy is a surgical removal of vitreous gel and blood from leaking vessels in the back of the eye, but this procedure provides only short-term relief and does not obstruct further leaking of blood [1]. Pharmacological treatments include intravitreal injections of corticosteroids to decrease the swelling of macula. Also, sustained release corticosteroids implant that interferes the inflammatory pathways. Modern management with anti-VEGF agents (Ranibizumab and Aflibercept) prevents the expression of VEGF and thus reduce blood leakage and edema [28].

Retinoblastoma

Retinoblastoma is a malignant tumor distressing the retina and mainly prevails in children younger than 5 years old. Untreated retinoblastoma leads to blindness and finally mortality (99%). Its frequency is about 1 out of 20,000 live births [29]. Its occurrence rate is equal in both gender. It is caused due to mutation in tumor suppressor gene RB1 encoding for retinoblastoma protein. It could be unilateral (60%) or bilateral (40%) [1]. The handling choices of retinoblastoma include radiotherapy, cryotherapy, systemic chemotherapy, and surgery. Latest studies propose that release of compensatory proangiogenic factors and angiogenic blood vessels development are the vital phases for treating retinoblastoma [30].

Fungal Keratitis

Fungal keratitis occurs only in traumatic cornea, since healthy cornea would not allow any fungal infection. It is caused by different fungus like *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, and *Candida parapsilosis* [31]. Fungal keratitis represents 40% of the contagious keratitis in developing countries of third world [1]. Risk factors may be ocular (trauma, contact lens, prior corneal surgery, and topical corticosteroids) or systemic (diabetes, HIV positivity, and leprosy). Fungal keratitis leads to impaired wound healing, corneal ulceration, and stromal inflammatory infiltration. The corneal inflammation may alter miRNA expression [32]. Oral or topical antifungal drugs are used to treat fungal keratitis. Corneal surgery approach could be required when the medicines are useless. In some situations, vision may not be restored even after surgery. Many papers consider the treatment of fungal keratitis. Younes *et al.* developed topical Sertaconazole nitrate loaded cubosomes and mixed micelles with enhanced safety and antifungal activity [33–37]. Figure 2 illustrates various ocular diseases [1].

Obstacles to Ocular Delivery

Precorneal Barriers

Capacity of Cul-de-sac

Figure 3 explains different ocular barriers. Cul-de-sac is a shallow pocket in the lower eyelid where palpebral and bulbar conjunctiva meet in the lower eyelid and the deeper recess in the upper eyelid. The maximum capacity of cul-de-sac is 30 μ L in humans. The movement of the lower eyelid to its regular place would reduce this capacity to 70–80%. Inflammation and allergic response of the eye would also minimize capacity of the cul-de-sac [6]. Since the activity of any drug is directly related to its residence time and concentration. The low capacity of cul-de-sac would reduce the

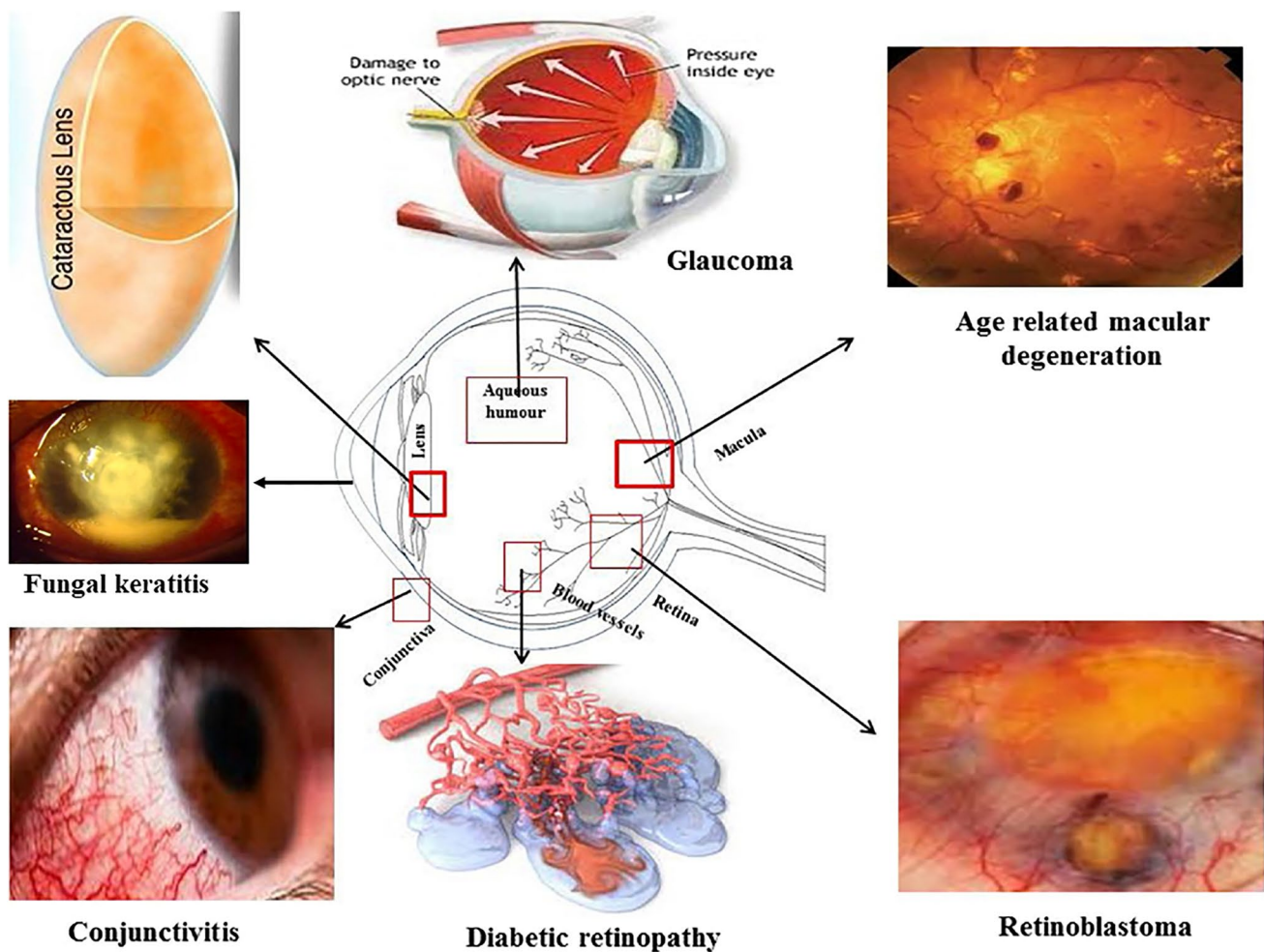


Fig. 2 Various ocular diseases affecting the two segments of the eye [1]

concentration of the drug in the eye, thereby reducing the therapeutic activity.

Loss of Drug from Lacrimal Fluid

Drainage of the administered ocular solution is a major barrier in precorneal region. Loss of drug from lacrimal fluid could happen as a result of lacrimation, solution drainage, and non-productive absorption in the conjunctiva [38]. Also, drug metabolism and protein binding would further obstruct drug absorption [6]. Continuous renewal of lacrimal fluid helps maintaining eye hydration, preventing pathogens or dust from retaining on the eye. In order to maintain effective drug activity, residence time of the administered formula must be sustained which could be achieved by different mechanisms.

Corneal Barriers

The cornea provides a resistant obstacle to different chemical and mechanical injuries. It also supports light convergence

on the retina. It is divided into epithelium, stroma, and endothelium. The epithelium is formed of five to seven layers of firmly linked cells. Stroma is a water-based compact layer. The epithelium is a barrier for hydrophilic drugs and large molecules, whereas the stroma is a barrier for lipophilic drugs [5]. The endothelium preserves the transparency of the cornea and provides selective access for hydrophilic drugs and macromolecules into the aqueous humor. As a general rule, drug molecular weight, charge, degree of ionization, and hydrophobicity influence the corneal permeation. Hence, the trans-corneal permeation is known as rate limiting step for drug transfer from the lachrymal fluid into the aqueous humor [6].

Blood-Ocular Barriers

They prevent the entry of foreign compounds into the blood stream. They are classified into blood-aqueous barrier (BAB) and blood-retinal barrier (BRB). BAB is an anterior portion of the eye that prevents the access of many compounds in the

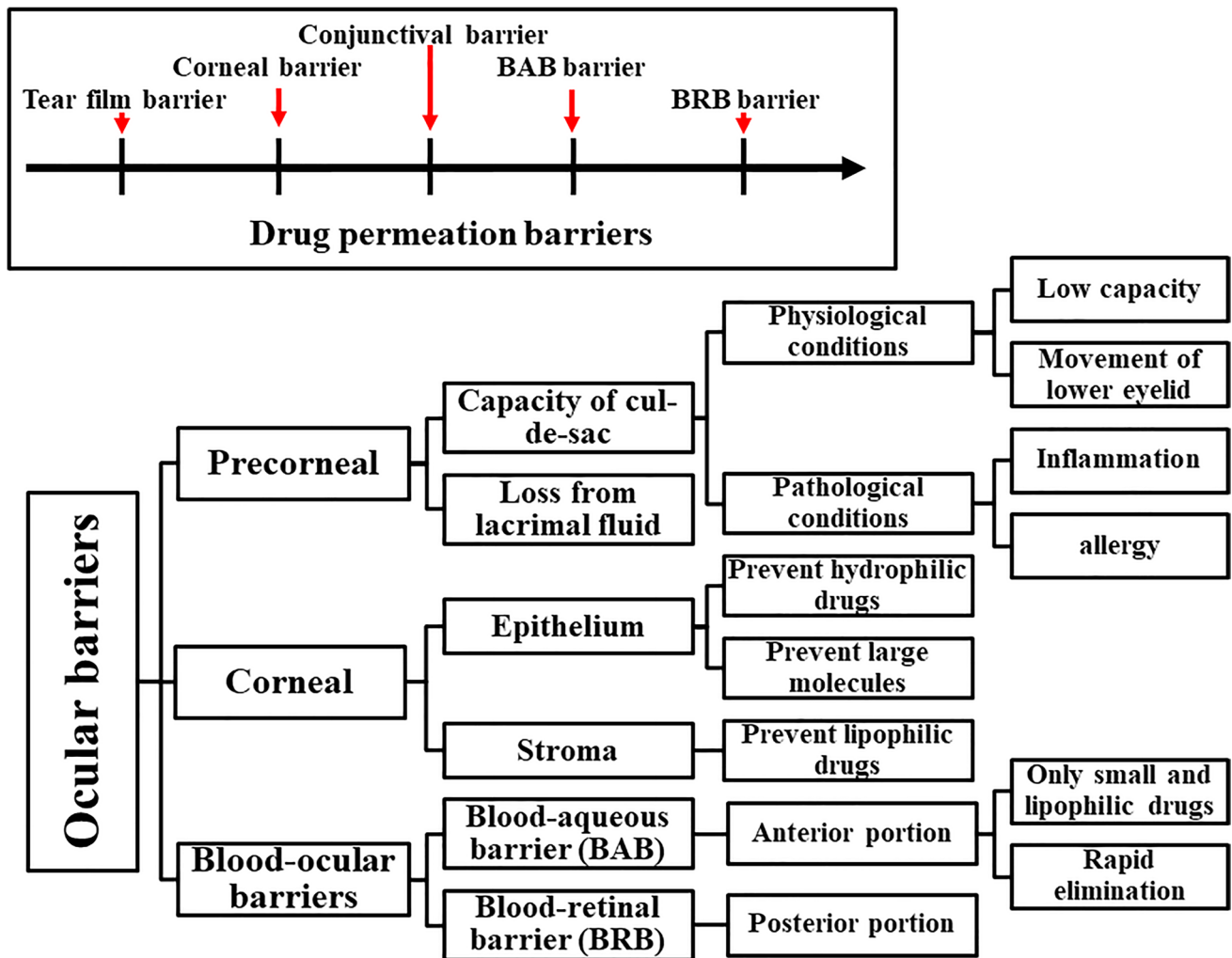


Fig. 3 Schematic diagram of physiological ocular barriers

intra-ocular milieu. BAB allows the passage of lipophilic and small drugs. These drugs are eliminated from the anterior compartment faster than hydrophilic and larger molecules. For example, the clearance rate of pilocarpine was found to be faster than inulin [6]. BRB is a posterior portion of the eye that is made of the retinal endothelial cells and the retinal pigment epithelial cells. It prevents the access of dangerous materials, water, and plasma components into the retina [39].

Routes for Ocular Drug Delivery

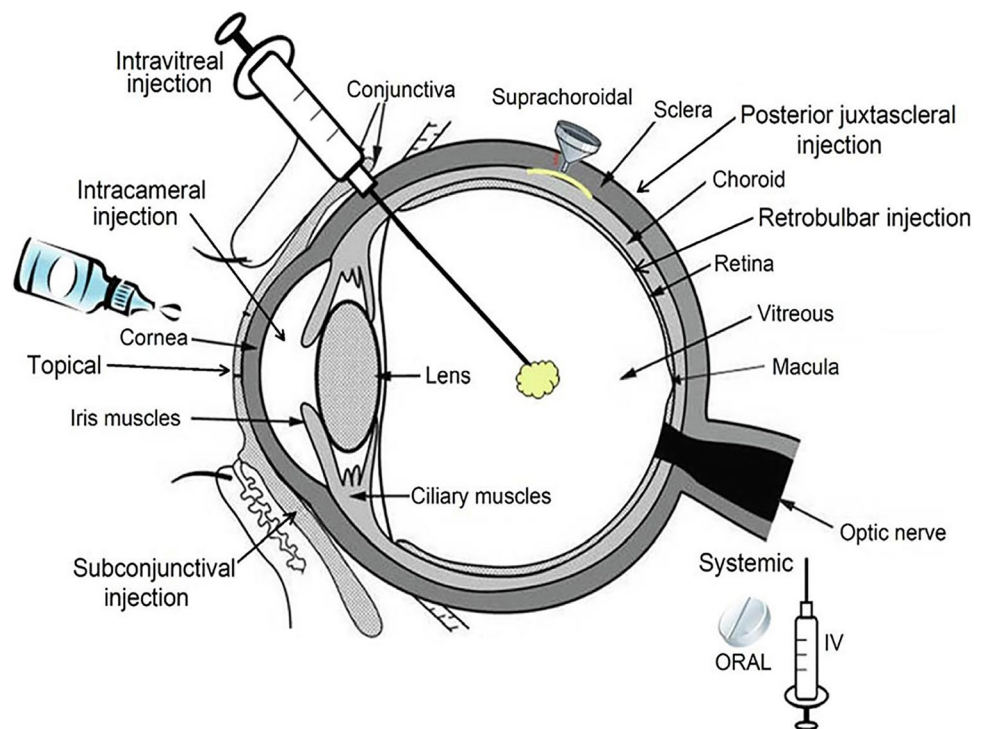
Figure 4 illustrates different routes for ocular drug delivery [7].

Topical Administration

Topical administration is the most common route for ocular drug delivery that represents more than 95% of marketed

ocular products. It is non-invasive route, but with low bio-availability (<5%) due to insufficient corneal permeation and short residence time [4]. Moreover, bioavailability is reduced by tear drainage, blinking and entering the systemic circulation through the nasolacrimal pathway. Topical delivery necessitates frequent and high dose concentration, which could result in serious side effects. Also, frequent dosing could influence the patient compliance [4, 5]. Topical route is unsuitable for handicapped and elder patients [7]. The topical administration of terconazole in the form of bilosomes showed enhanced drug permeation and safety [40]. Topical administration of sertaconazole nitrate as mixed micelles or cubosomes revealed high corneal uptake and corneal retention [33, 34]. β -cyclodextrin-based micellar system demonstrated higher ex vivo and *in vivo* permeation of itraconazole and higher antifungal activity [35]. The topical administration of dorzolamide hydrochloride in the form of proniosomal gels showed controlled ex vivo permeation, increased

Fig. 4 Different routes for ocular drug delivery [7]



stability, and improved bioavailability [16]. Table I reveals more examples of topical administration.

Intracameral Injections

Intracameral injections involve injection of antibiotic directly into the anterior segment of the eyeball or in the vitreous cavity. It is done usually subsequent to cataract surgery to avoid endophthalmitis initiated by a contagion of the eye that can occur after cataract surgery. Recently, the application of intracameral injection for treatment of glaucoma using hydrogel functionalized with vinyl sulfone and thiol groups was published [73].

Intravitreal Injections/Implants

Intravitreal injection is a delivery of medicine into the vitreous that is close to the retina at the back of the eye. A new approach for treatment of glaucoma includes a single intravitreal injection of vitamin E/poly-lactic-co-glycolic acid microspheres enclosing glial cell line derived neurotrophic factor. This approach provided a prolonged release for 6 months. Similar results was obtained after intravitreal injection of polymer-free dexamethasone dimer implants [52]. Intravitreal injection of the biodegradable Rho kinase and protein kinase C inhibitor for handling diabetic macular edema and neovascular age-related macular degeneration exhibited prolonged release for about 6 months [24]. Additional examples are mentioned in Table I.

Juxtасcleral Injections

Juxtасcleral injections are used for treatment of some posterior part complaints that cannot be handled through conventional topical route. It is used for the treatment of cystoid macula edema, trauma, and diabetic-related conditions. A new approach for treatment of AMD involves juxtасcleral injections of anecortave cortisone that showed prolonged release for 6 months in the choroid and retina [23]. Advanced trans-scleral microneedles have been formulated to carry adeno-associated viruses for retinal gene treatment [55]. Table I shows further examples.

Retrolbulbar Injection

Retrolbulbar route involves the injection of a needle through the eyelid and orbital fascia to deliver the medication behind the globe into the retrolbulbar space. Retrolbulbar injection of amphotericin B showed higher antifungal efficacy than intravenous injection [58]. Retrolbulbar injection of chlorpromazine is used to manage blind painful eyes [59]. Retrolbulbar injection of triamcinolone is utilized to handle macular edema resulted from retinal vein occlusion [60].

Subconjunctival Injection

Subconjunctival injection is frequently used in cases of very low drug penetration into the anterior part of the eye after topical administration. Subconjunctival injection of steroids

Table 1 Examples of Different Routes of Ocular Drug Delivery. Description of the Investigated Drug, Route of Administration, and Major Outcomes

Model drug	Route of administration	Major outcome	Reference(s)
Terconazole	Topical	Enhanced drug permeation and safety	[40]
Sertaconazole nitrate	Topical	high corneal uptake and corneal retention	[33, 34]
Itraconazole	Topical	higher ex vivo and in vivo permeation	[35]
Dorzolamide hydrochloride	Topical	controlled ex vivo permeation, increased stability and improved bioavailability	[16]
Agomelatine	Topical	Sustained drug activity and prolonged drug retention	[12]
Ketoconazole	Topical	Improved corneal permeation, prolonged ocular action, and increased bioavailability	[41]
Voriconazole	Topical	Increased drug solubility, efficacy, stability, and duration of action	[36, 37]
Dorzolamide hydrochloride	Topical	Higher penetration, enhanced safety, and bioavailability	[42]
Cyclosporine	Topical	Enhanced drug retention, permeation, and efficacy	[43]
Hesperetin	Topical	Improved permeation and bioavailability	[44]
Rebamipide	Topical	Improved stability and drug retention	[45]
Posaconazole	Topical	Higher antifungal activity and prolonged activity	[46]
Coenzyme Q10	Topical	Prolonged activity and improved efficacy	[47]
Fluconazole	Topical	Enhanced drug entrapment, permeation, and activity	[48]
Gatifloxacin	Topical	Improved safety, permeation, and efficacy	[49]
Rifampicin	Topical	Higher stability and enhanced antimicrobial activity	[50]
Dexamethasone	Topical	Enhanced retention time and prolonged release	[51]
Dexamethasone	Intravitreal injections	Prolonged release for 6 months	[52]
Rho kinase and protein kinase C inhibitor	Intravitreal injections	Prolonged release for 6 months	[24]
Methotrexate	Intravitreal injections	Reduced intraocular inflammation, pain, and macular edema	[53]
Vancomycin	Intravitreal injections	Sustained release and prolonged drug retention	[54]
Anecortave cortisone	Juxtasceral injections	Prolonged release for 6 months	[23]
Adeno-associated viruses	Juxtasceral injections	For retinal gene treatment	[55]
Fluocinolone	Juxtasceral injections	Delivering the drug up to 2.5 years for treatment of posterior uveitis	[56]
Anti-VEGF	Juxtasceral injections	Forming a depot on the episcleral surface and was used for treatment of macular degeneration and diabetic retinopathy	[57]
Amphotericin B	Retrobulbar injection	Higher antifungal efficacy	[58]
Chlorpromazine	Retrobulbar injection	Manage blind painful eyes	[59]
Triamcinolone	Retrobulbar injection	Handle macular edema resulted from branch retinal vein occlusion	[60]
Steroids	Subconjunctival injection	Sustained anti-inflammatory activity and targeting	[61]
Brinzolamide	Subconjunctival injection	Successful handling of IOP for 10 days	[62]
Human mesenchymal stromal cells	Subconjunctival injection	Significant lowering in corneal inflammation and squamous metaplasia	[63]
Voriconazole	Subconjunctival injection	Sustained drug release for >21 days and increased antifungal efficacy	[64]
Dorzolamide	Subconjunctival injection	Prolonged reduction in IOP for 35 days	[65]
Ketorolac and phenylephrine	Irrigation solutions	Minimizing the cataract surgical duration and avoiding pupil miosis	[66]
Povidone iodine	Irrigation solutions	Reduced frequency of microbial contamination during surgery in anterior segment (used every 20 s)	[67]
Hydrogen	Irrigation solutions	Protection of the corneal endothelial subsequent to cataract surgery	[68]
Acyclovir	Iontophoresis	higher permeation and bioavailability	[69]
Dexamethasone	Iontophoresis	higher efficacy in managing non-infectious anterior uveitis	[70]
Besifloxacin	Iontophoresis	Increased bioavailability	[71]
Pilocarpine	Iontophoresis	Reduced doses and increased permeability	[72]

Abbreviations: VEGF, vascular endothelial growth factor

fabricated as PEGylated liposome for handling of uveitis showed sustained anti-inflammatory activity and targeting the required ocular tissue for 1 month as minimum [61]. The administration of PLGA nanoparticle of brinzolamide by subconjunctival injection showed successful handling of IOP for 10 days [62]. Significant lowering in corneal inflammation and squamous metaplasia was ensured via subconjunctival injection of human mesenchymal stromal cells in mice with graft *versus* host disease [63]. Table I shows extra examples.

Irrigating Solutions

They are solutions made under aseptic condition without the inclusion of preservatives. They are used as balanced salt by surgeons to eradicate blood, cellular waste, and maintain the appropriate hydration volume of the eye [74]. There are many examples that intensifies the importance of these solutions. For example, minimizing the cataract surgical duration and avoiding pupil miosis by using ketorolac (0.3% w/v) and phenylephrine (1% w/v) in the irrigation solutions [66]. Table I shows more examples.

Iontophoresis

Iontophoresis is a technique used to carry medications into the posterior segment of the eye. It involves the usage of voltage gradient. Novel systems involve the employment of microneedle-based instruments. They had doubled the amount of formula delivered to the back of the eye compared to suprachoroidal injection [75]. The combinations of iontophoretic delivery and contact lens results in 550–1300-times shorter duration than drug uptake into choroidal capillaries [76]. Short-duration iontophoresis of acyclovir produg resulted in higher permeation and bioavailability [69]. Ocular iontophoresis of dexamethasone phosphate revealed higher efficacy in managing non-infectious anterior uveitis [70]. Table I shows more examples.

Dosage Forms

Liquid Dosage Forms

Eye Drops

Eye drops represent more than 95% of the marketed ocular products. They deliver the medication into the anterior part of the eye. Their advantages include easy administration and accepted stability. However, their disadvantages include low retention time (<5 min.), poor bioavailability, and serious side effect resulted from the frequent administration of high concentration [77]. Several nanosystem platforms had been

developed to solve their drawbacks. Cyclosporine was formulated as a mucoadhesive nanosystem utilizing poly (D-L-lactide)-b-dextran. Nanoprecipitation technique was adopted for the formulation. The final product demonstrated small particle size, enhanced permeability, and drug retention [43]. Formulation of the antibacterial hesperetin as micellar system showed minute particle size, high percentage entrapment efficacy, greater penetration, and enhanced efficacy [44]. More examples are illustrated in Table II. Figure 5 illustrates different ocular dosage forms.

Eye Suspensions

Ocular suspensions represent dispersions of hydrophobic drug in aqueous solvent. They have enhanced contact time because of drug retention in the conjunctival cul-de-sac. Particle size, solubility, and dissolution rate in the tear fluid are extremely important during the preparation process [102]. Generally, particle size <10 µm has greater solubility, enhanced dissolution rates, and poor retention on the ocular surface. However, particles of >10 µm could result in ocular irritation and stimulated tearing [103]. Disadvantages of ocular suspension include poor stability. They cannot be stored in freezer as the particles tend to agglomerate and fail to disperse easily. Also, change in crystal size during the storage will influence both solubility and bioavailability of the drug. A blurred vision after their administration could also result. Improved ocular administration of posaconazole in polymer system of carbopol 974P and xanthan gum using high pressure homogenizing technique showed enhanced stability, antifungal activity, and prolonged retention [46]. High speed liquid–liquid shear technique was adopted to formulate ultra-fine rebamipide ophthalmic suspension. This formula showed enhanced transparency, small particle size, and improved stability [45]. Table II states more examples.

Eye Emulsions

An emulsion is a solubilized biphasic system due to the inclusion of surfactants or stabilizers. Advantages of eye emulsions include ability to deliver hydrophobic drugs; oil-in water (O/W) emulsion is less irritant to the eye, enhanced contact time and bioavailability [104]. The ocular delivery of dexamethasone acetate and polymyxin B sulfate was enhanced by the formation of nanoemulsion by high-pressure homogenization. A positive charge inducer was incorporated to enhance ocular adhesion. The resulted formula showed enhanced stability, reduced particle size, and enhanced retention time [84]. Water titration method was adopted for the construction of triamcinolone acetonide microemulsion. It showed minimized particle size and improved permeability [85]. Additional results are clarified in Table II.

Table II Examples of Different Ocular Dosage Forms. Description of the Studied Drug, Dosage Form, Carrier Platform, and Essential Results

Model drug	Dosage form	Carrier platform	Essential results	Reference(s)
Cyclosporine	Eye drops	Mucoadhesive nanosystem	Small particle size, enhanced permeability, and drug retention	[43]
Hesperetin	Eye drops	micellar system	Greater penetration and enhanced efficacy	[44]
Acetazolamide	Eye drops	Hybridized vesicle	Prolonged drug release >24 h, Sustained reduction in IOP for 24 h	[78]
Tacrolimus	Eye drops	Solution	Increased drug solubility and enhanced ocular permeation	[79]
Nepafenac	Eye drops	cyclodextrin nano-aggregate	Improved the solubility and permeability of the drug	[80]
Posaconazole	Eye suspension	polymer system	Enhanced stability, antifungal activity, and prolonged retention	[46]
Olopatadine	Eye suspension	Nanosuspension	Reduced particle size, enhanced drug retention time, and prolonged drug release	[81]
Amphotericin B	Eye suspension	Nanosuspension	Improved drug stability	[82]
Diclofenac	Eye suspension	Nanosuspension	Higher drug entrapment, sustained release and improved activity	[83]
Dexamethasone acetate	Eye emulsion	Nanoemulsion	Enhanced stability, reduced particle size and enhanced retention time	[84]
Triamcinolone acetonide	Eye emulsion	Microemulsion	Minimized particle size and improved permeability	[85]
Erythromycin	Eye emulsion	Microemulsion	Improved transparency, particle size, and permeation	[86]
Cyclosporine A	Eye emulsion	Nanoemulsion	Improved drug retention, safety, and activity	[87]
Ketotifen	Eye emulsion	Nanoemulsion	Enhanced corneal permeation and prolonged release	[88]
Rifampicin	Eye emulsion	Nanoemulsion	Improved permeation and antibiotic activity	[50]
Curcumin	Eye gel	Proniosomal gel	Effective reduction in PS and improvement of anti-inflammatory activity	[89]
Pilocarpine	Eye gel	Liquid crystalline gel	increase in the ex vivo permeability and retention time	[90]
Ketoconazole	Eye gel	Proniosomal gels	Increased bioavailability and ocular permeation	[41]
Brimonidine tartrate	Eye gel	Proniosomal gels	Improved ocular bioavailability and sustained drug release	[18]
Dorzolamide hydrochloride	Eye gel	Proniosomal gels	Enhanced drug efficacy and permeation	[16]
Beclomethasone dipropionate	Eye gel	Cubosomal gels	Reduced particle size and increased drug permeation	[91]
Dorzolamide hydrochloride	Eye gel	Cubogel	Higher penetration, enhanced safety, and bioavailability	[42]
Acyclovir and loteprednol etabonate	Eye ointment	Ointment	Enhanced corneal penetration and drug release	[92]
Triamcinolone acetonide	Ocular insert	Nanofiber	Reduced particle size, systemic absorption, and side effects	[93]
Ketorolac	Ocular insert	Microsphere	Prolonged drug release (over several months)	[94]
Tenoxicam	Ocular insert	Nanostructured formulation	Superior drug diffusion, ex vivo and in vivo permeation	[4]
Timolol	Therapeutic contact lens	Gold nanoparticles	Encouraged outcomes in animal model to treat glaucoma	[95]

Table II (continued)

Model drug	Dosage form	Carrier platform	Essential results	Reference(s)
Flurbiprofen	Therapeutic contact lens	Nanoaggregates	Sustained release of the drug	[96]
Phomopsidione	Therapeutic contact lens	Nanoparticles	Sustained release of drug for 48 h	[97]
Ciprofloxacin	<i>In situ</i> gel	Nanoparticles	Enhanced residence time and sustained drug release	[98]
Hydrocortisone butyrate	<i>In situ</i> gel	Nanoparticles	Extended drug release and avoided burst release	[99]
Bimatoprost	<i>In situ</i> gel	Solid lipid nanoparticle	Improved drug retention time and permeation	[100]
Tenoxicam	<i>In situ</i> gel	Nanostructured formulation	Enhanced drug permeation and safety	[4]
Vancomycin	<i>In situ</i> gel	Niosomes	Sustained release and enhanced activity of drug	[101]

Semisolid Dosage Forms

Eye Gels

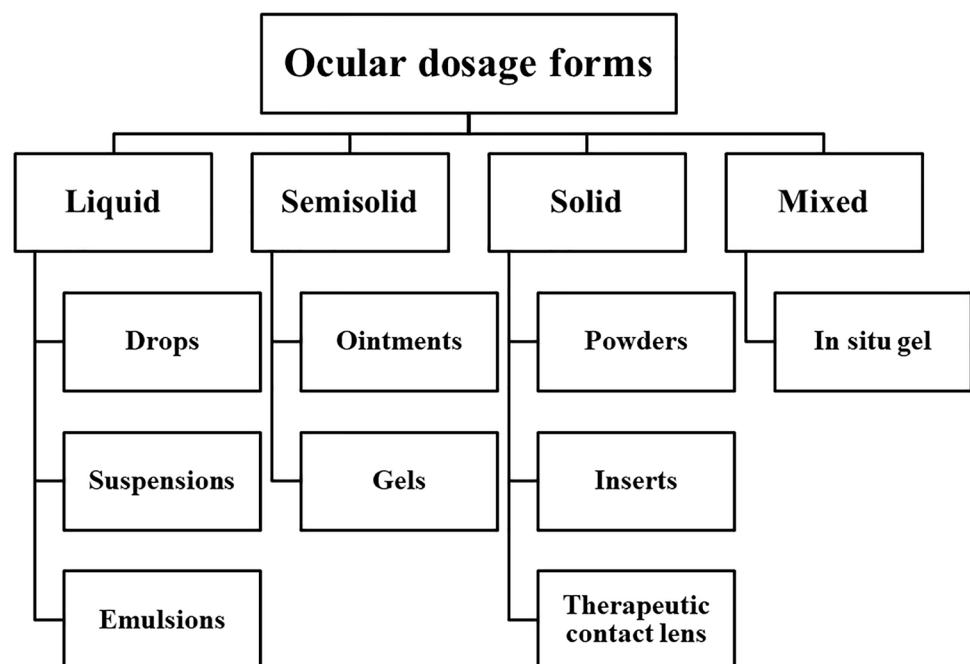
Eye gels are a semisolid dosage form containing high water quantity. They have enhanced retention time and bioavailability because of their viscosity. Although gels contain large quantity of water, blurred vision could still result. Various polymers could be used to prepare ocular gels like polyacrylic acid, acrylic acids, hydroxypropyl methylcellulose, and carboxymethyl cellulose [105]. Coacervation technique was used to prepare a proniosomal gel of curcumin with effective reduction in particle size and improvement of anti-inflammatory activity [89]. An increase in the *ex vivo* permeability and retention time of pilocarpine was demonstrated via formation of phytantriol-based lyotropic

liquid crystalline gel. That gel was formed by vortex method [90]. Additional examples are mentioned in Table II.

Eye Ointments

Eye ointments are semisolid dosage form containing white petrolatum and mineral oil. They are administrated to the lower eyelid only at bedtime due to its interference with vision. They are commonly used among young patients. They have anhydrous nature making them a good choice for lipophilic and moisture sensitive drugs. They have higher retention time and bioavailability in comparison with solutions [106]. Avaclyr® is an ocular ointment enclosing the antiviral acyclovir that was approved in 2019 for herpetic keratitis. Also, Lotemax® enclosing the anti-inflammatory

Fig. 5 Classification of ocular dosage forms



loteprednol etabonate. Both of them showed enhanced corneal penetration and drug release [92].

Solid Dosage Forms

Eye Powders

They are sterile solid dosage form of water-sensitive drugs. They are administrated in injectable forms as intracameral injection of cefuroxime, moxifloxacin, and voriconazole. Cefuroxime and moxifloxacin are reconstituted in saline, while voriconazole is reconstituted in water. Both cefuroxime and voriconazole solutions are stable for 7 days after reconstitution. However, moxifloxacin solution is stable for 24 weeks [107, 108].

Ocular Inserts

Ocular inserts are solid dosage form of biodegradable polymers. They show zero order drug release model. Advantages of inserts include high residence time, sustain drug delivery, constant release, and reduced side effects [109]. Electrospinning technique was adopted for the construction of triamcinolone acetonide-loaded nanofibers. They showed reduced particle size, systemic absorption, and side effects [93]. Also, sustained bimatoprost activity for many months was proved after incorporation of its insert [110]. Table II shows more examples.

Therapeutic Contact Lens

New studies showed that therapeutic contact lens could enhance bioavailability by >50% as a consequence to sustained residence time and close contact with the cornea [111]. Their residence time is 10 folds the conventional eye drops [112]. They also reduce required doses, interval between doses and systemic absorption [113]. There are many techniques to enclose the drug inside contact lens as molecular imprinting, ion ligation, soaking, and use of nanoparticles [77, 114, 115]. Obstacles to their clinical use include protein attachment, ion and oxygen permeation, drug loss during manufacture or storage, transmittance, and swelling of the lens [7]. Dexamethasone contact lens was prepared by encapsulation technique. It showed 200-fold drug retention in the retina matching with conventional eye drops [116]. In order to reduce rapid drug release, chips of either timolol, bimatoprost, or hyaluronic acid have been used [111]. Extra examples are given in Table II.

Mixed Dosage Forms

In Situ Gel

They are polymeric solutions of low viscosity. They converted into pseudo-plastic gels in contact with tear fluid. They have

sustained contact time compared to simple solutions [117]. There are three types of *in situ* gel according to the transition properties: temperature, ionic, or pH sensitive [118]. *In situ* gel of ciprofloxacin with hydroxypropyl methylcellulose and sodium alginate (ion-sensitive) showed enhanced residence time and sustained drug release [98]. Thermosensitive *in situ* gel of hydrocortisone butyrate revealed extended drug release and avoided burst release [99]. Thermosensitive *in situ* gel of ketorolac tromethamine showed improved mucoadhesive properties with prolonged release of drug up to 12 h [119]. Table II shows more examples about *in situ* gel.

Nanostructured Platforms

Liposomes

They were discovered in the mid-1960s [120]. Advantages of liposomes include safety, biodegradation, simple preparation techniques, and improved bioavailability [121]. They are spherical nanocarriers made of one or more concentric lipid bilayers. They could carry lipophilic drug in the lipid area, while the interior could entrap hydrophilic drugs. Changing the formation technique and their composition could alter their surface charge, sensitivity to ion or pH, or temperature changes and the resulted particle size [120]. Generally, the corneal epithelium has a negative charge; therefore, a positively charged liposomes would have high adherence, longer retention time, and better absorption. These outcomes will reduce the interval between doses and improve patient satisfaction [122]. Zhang and Wang created a liposomal system composed of phosphatidylcholine, cholesterol, α -tocopherol, and chitosan. The resulted formula showed high percent entrapment, sustained activity, and enhanced efficacy [47]. Lin *et al.* used phosphatidylcholine, stearylamine, cholesterol, and hyaluronic acid. The finished product revealed better corneal uptake, high drug targeting, improved percent entrapment, and prolonged penetration [123]. Cheng *et al.* constructed liposomal system formed of soybean phosphatidylcholine, cholesterol, chitosan, and dicetylphosphate. This formula showed superior corneal permeation and improved activity [124]. Vicario-de-la-Torre *et al.* used phosphatidylcholine, cholesterol, sodium hyaluronate, trehalose, borate, and vitamin E to form a stable formula with enhanced safety, ocular adhesion, and hydration [125]. Other studies are briefly described in Table III. Figure 6 shows different nanostructured platforms [8].

Niosomes

Niosomes are bilayered nanocarriers composed of self-aggregated non-ionic surfactants. They are biodegradable, biocompatible, enclose both hydrophilic and lipophilic drugs

and non-immunogenic. They could prolong drug release and enhance its permeability and efficacy [161, 162]. Disadvantages of niosomes include chemical instability and possible hydrolysis, accumulation or loss of drug [18]. Cholesterol or its derivative is added to improve rigidity and stability of niosomes [8]. Elmotasem and Awad developed a niosomal system composed of span 60, cholesterol, poloxamer 407, hydroxypropyl methylcellulose, cyclodextrin, and chitosan. The resulted formula showed high drug entrapment, enhanced corneal permeation and activity [48]. Kaur *et al.* studied niosomal system composed of span 60, cholesterol, and chitosan. The finished product revealed higher activity, reduced side effects, and prolonged release [129]. Aggarwal *et al.* improved the duration of action and efficacy of acetazolamide using span 60, cholesterol, and Carbopol® 934P [130]. Zubairu *et al.* developed a niosomal system of gatifloxacin composed of span 60, cholesterol, and chitosan. The optimized formula showed enhanced antimicrobial activity, no toxicity, and superior ocular permeation [49]. More investigations are concisely mentioned in Table III.

Nanoemulsions

They are potential carriers for ocular delivery. Oils in water nanoemulsions are composed of dispersed oil phase that is stabilized by surfactants in an aqueous medium. They provide a reservoir for lipophilic drugs and interact with the lipids of tear film providing a sustained drug release [87, 163]. Surfactants are important for the interaction with the surface of the cornea, plus enhancing drug solubility [8]. Drawbacks of nanoemulsions include blurred vision if the particle size exceeds 100 nm due to development of milky formulation and reduced ocular tolerance due to high surfactant concentration [163]. Akhter *et al.* developed nanoemulsions system of cyclosporine A. Many oils, chitosan, Carbopol®, and Transcutol® P were incorporated. The resulted formula revealed enhanced drug retention, safety, and efficacy [87]. Oleic acid, polysorbate 80, poloxamer 188, chitosan, and polymyxin B were used by Bazán Henostroza *et al.*, to improve stability, mucoadhesion, and antibiotic activity of rifampicin [50]. Soltani *et al.* constructed nanoemulsions of ketotifen fumarate utilizing Eudragit® RL 100 and polyvinyl alcohol. Enhanced corneal permeation and sustained release were obtained [88]. Additional findings are listed in Table III.

Nanosuspensions

They are colloidal nanocarriers constituted of lipophilic or semi-lipophilic drugs, suspended in a dispersion medium and stabilized by surfactants or polymers [121]. Their advantages include sustained drug release, increased residence time, and enhanced drug solubility and bioavailability

[161]. The most commonly used mucoadhesive agents in nanosuspensions are Eudragit® polymers. Pignatello *et al.* developed a nanosuspensions of cloricromene composed of Eudragit® RS and RL 100 and Tween 80. The resulted formula showed enhanced stability, corneal residence time, and permeation [136]. Ahuja *et al.* used Eudragit® S100 and poloxamer 188 to form nanosuspensions of diclofenac with enhanced percent entrapment, prolonged release, and increased anti-inflammatory activity [83]. Khan *et al.* employed Eudragit® RL100 to increase percent entrapment, sustain drug release, and enhance pilocarpine activity [137]. Extra results are briefly listed in Table III.

Nanomicelles

They are nanocarriers composed of anionic, cationic, or zwitterionic surfactants. They may be spherical, cylindrical, or star-shaped. They could entrap both hydrophilic and lipophilic drugs. They have simple preparation techniques, reduced toxicity, increased bioavailability, increased stability, and enhanced permeation. They could deliver drugs to both segments of the eye (anterior and posterior portions) [161]. Yingfang *et al.* developed nanomicelles of pimecrolimus using polyethylene glycol and poly (ϵ -caprolactone) as co-polymers. The resulted formula showed enhanced percent entrapment, sustained release, and enhanced activity [141]. Liu *et al.* enhanced ocular permeation and prolonged release of tacrolimus utilizing amino-terminated poly(ethylene glycol)-block-poly(D,L)-lactic acid and hydroxypropyl methylcellulose [142]. Terreni *et al.* used hyaluronic acid to sustain the release, increase permeation, and activity of cyclosporine A [143]. Table III briefly lists additional studies.

Polymeric Nanoparticles

Polymeric nanoparticles could be divided according to their structure and preparation method into nanospheres and nanocapsules. Nanospheres are small solid spheres composed of a dense polymeric network. They have a matrix type composition with a great surface area. The drug could be adsorbed on the surface or entrapped within the particle. However, nanocapsules are a small liquid core enclosed by a polymeric membrane. The drug could be adsorbed on the capsule surface or entrapped within the liquid core [121]. Polymeric nanoparticles could reach both segments of the eye. They improve patient compliance particularly in chronic complaints due to their small particle size. They have a prolonged drug release, improved permeation, and reduced elimination rate [161]. Yu *et al.* developed polymeric nanoparticles for dexamethasone utilizing glycol chitosan, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, and N-hydroxysuccinimide. They showed

Table III Examples of Different Nanostructured Platforms. Description of the Examined Drug, Other Components, Nanostructured Platform, and Important Results

Model drug	Other components	Nanostructured platform	Important results	Reference(s)
Coenzyme Q10	Phosphatidylcholine, cholesterol, α -tocopherol and chitosan	Liposomes	Sustained activity and enhanced efficacy	[47]
Hyaluronic acid	Phosphatidylcholine, stearylamine, cholesterol	Liposomes	Improved entrapment and prolonged penetration	[123]
Triamcinolone acetonide	Soybean phosphatidylcholine, cholesterol, chitosan and dicytlylphosphate	Liposomes	Showed superior corneal permeation and improved activity	[124]
Fluconazole	Hyaluronic acid and Carbopol® 940	Liposomes	Increased corneal uptake, improved the antifungal activity	[126]
Timolol maleate	Chitosan	Liposomes	Improved ocular permeation, precorneal residence time and bioavailability	[127]
Ibuprofen	Lipoid® S100; stearylamine; cholesterol; silk fibroin	Liposomes	Sustained corneal permeation and improved safety	[128]
Fluconazole	Span 60, cholesterol, poloxamer 407, and chitosan	Niosomes	Enhanced corneal permeation and activity	[48]
Timolol maleate	Span 60, cholesterol, and chitosan	Niosomes	Reduced side effects and prolonged release	[129]
Acetazolamide	Span 60, cholesterol, and Carbopol® 934P	Niosomes	Improved the duration of action and efficacy	[130]
Gatifloxacin	Span 60, cholesterol, and chitosan	Niosomes	Enhanced antimicrobial activity	[49]
Lomefloxacin	Poloxamer 188, poloxamer 407, and hydroxypropyl methylcellulose	Niosomes	Increased antimicrobial activity and enhanced corneal permeation	[131]
Natamycin	Carboxymethylcellulose or hydroxypropyl methylcellulose-E4	Niosomes	Increased drug entrapment and increased bioavailability	[132]
Tacrolimus	Hyaluronic acid	Niosomes	Sustained release and enhanced activity	[133]
Cyclosporine A	Chitosan, Carbopol®, and Transcutol® P	Nanoemulsions	Enhanced drug retention, safety, and efficacy	[87]
Rifampicin	Polysorbate 80, poloxamer 188, and chitosan	Nanoemulsions	Improved stability, mucoadhesion and antibiotic activity	[50]
Ketotifen	Eudragit® RL 100 and polyvinyl alcohol	Nanoemulsions	Enhanced corneal permeation and sustained release	[88]
Timolol	Chitosan, hydroxyethylcellulose, polyvinylalcohol and polyethylenglycol	Nanoemulsions	Increased permeability and activity	[134]
Terbinafine hydrochloride	Surfactants, co-surfactant and gellan gum	Nanoemulsions	Sustained release and improved bioavailability	[135]
Cloricromene	Eudragit® RS and RL 100 and Tween 80	Nanosuspensions	Enhanced stability, corneal residence time and permeation	[136]
Diclofenac	Eudragit® S100 and poloxamer 188	Nanosuspensions	Prolonged release and increased activity	[83]
Pilocarpine	Eudragit® RL100	Nanosuspensions	Sustained drug release and enhanced activity	[137]
Itraconazole	Chitosan, lysine and poloxamer 188	Nanosuspensions	Increased corneal permeation and stability	[138]
Piroxicam	Eudragit® RS 100 and polyvinyl alcohol	Nanosuspensions	Sustained release and improved efficacy	[139]
Methylprednisolone acetate	Eudragit® RS 100 and polyvinyl alcohol	Nanosuspensions	Prolonged release and enhanced activity	[140]
Pimecrolimus	Using polyethylene glycol and poly (ϵ -caprolactone)	Nanomicelles	Sustained release and enhanced activity	[141]

Table III (continued)

Model drug	Other components	Nanostructured platform	Important results	Reference(s)
Tacrolimus	Amino lactic acid and hydroxypropyl methylcellulose	Nanomicelles	Enhanced ocular permeation and prolonged release	[142]
Cyclosporine A	Hyaluronic acid	Nanomicelles	Improved release and permeation	[143]
Itraconazole	β -cyclodextrin and polyethylene oxide	Nanomicelles	Improved drug stability, permeation and activity	[35]
Dexamethasone	Chitosan	Nanomicelles	Sustained activity and enhanced permeability	[144]
Dexamethason	Glycol chitosan	Polymeric nanoparticles	Enhanced retention time and sustained release	[51]
Acetazolamide	Chitosan and span 60	Polymeric nanoparticles	Enhanced ocular permeation and efficacy	[145]
5-Fluorouracil	Quaternary ammonium-chitosan conjugates, sodium tripolyphosphate and hyaluronic acid	Polymeric nanoparticles	Increased ocular residence time and bioavailability	[146]
Cyclosporine A	Span 80 and hyaluronic acid	Polymeric nanoparticles	Increased cellular uptake and efficacy	[147]
Norflloxacin	Chitosan, sodium tripolyphosphate and Carbopol® 934P	Polymeric nanoparticles	Prolonged residence time, Sustained release and improved efficacy	[148]
Etoposide	Gelucire® 44/14 and Compritol® ATO 888	Solid lipid nanoparticles	Sustained release, improved safety and activity	[149]
Triamcinolone acetonide	Pluronic® F-68 and gellan gum	Solid lipid nanoparticles	Improved residence time and increased delivered concentration	[150]
Tobramycin	Stearic acid, Epikuron 200 and sodium taurocholate	Solid lipid nanoparticles	Higher concentration in both segments of the eye	[151]
Indomethacin	Hydroxypropyl- β -cyclodextrin and chitosan	Solid lipid nanoparticles	Improved ocular permeation, drug entrapment and delivery to both eye segments	[152]
Riboflavin	Compritol® ATO 888 and Gelucire® 44/14,	Nanostructured lipid carriers	Superior corneal residence time, permeation and safety	[153]
Etoposide	Glyceryl stearyl citrate and chitosan	Nanostructured lipid carriers	Sustained and improved activity	[154]
Ibuprofen	Many solid and liquid lipids and Pluronic® F-127	Nanostructured lipid carriers	Increased corneal retention time, permeation and stability	[155]
Ofloxacin	Compritol® HD5 ATO, oleic acid, Tween 80 and chitosan	Nanostructured lipid carriers	Extended release and enhanced efficacy	[156]
Brinzolamide	Poloxamer F68/ F127 and polysorbate 80	Nanocrystals	Immediate dissolution and improved efficacy	[157]
Dexamethasone	Benzalkonium chloride and cetylpyridinium chloride	Nanocrystals	Enhanced retention time and safety	[158]
Acyclovir	Cysteamine HCl	Dendrimers	Sustained release and improved stability	[159]
Antisense oligonucleotides	Penetratin, hyaluronic acid	Dendrimers	Enhanced retention time, permeability and distribution in the posterior segment	[160]
Brimonidine tartrate	Glyceryl monooleate and poloxamer 407	Cubosomes	Improved permeation and bioavailability	[17]
Sertaconazole nitrate	Pluronic® F127, Brij® 58 and pluronic® F108	Cubosomes	Improved permeation, stability and efficacy	[33]
Agomelatine	Oleic acid and oleylamine	Olaminosomes	Enhanced permeation and activity	[12]
Terconazole	Cholesterol, span 60 and edge activator	Bilosomes	Improved permeation and activity	[40]

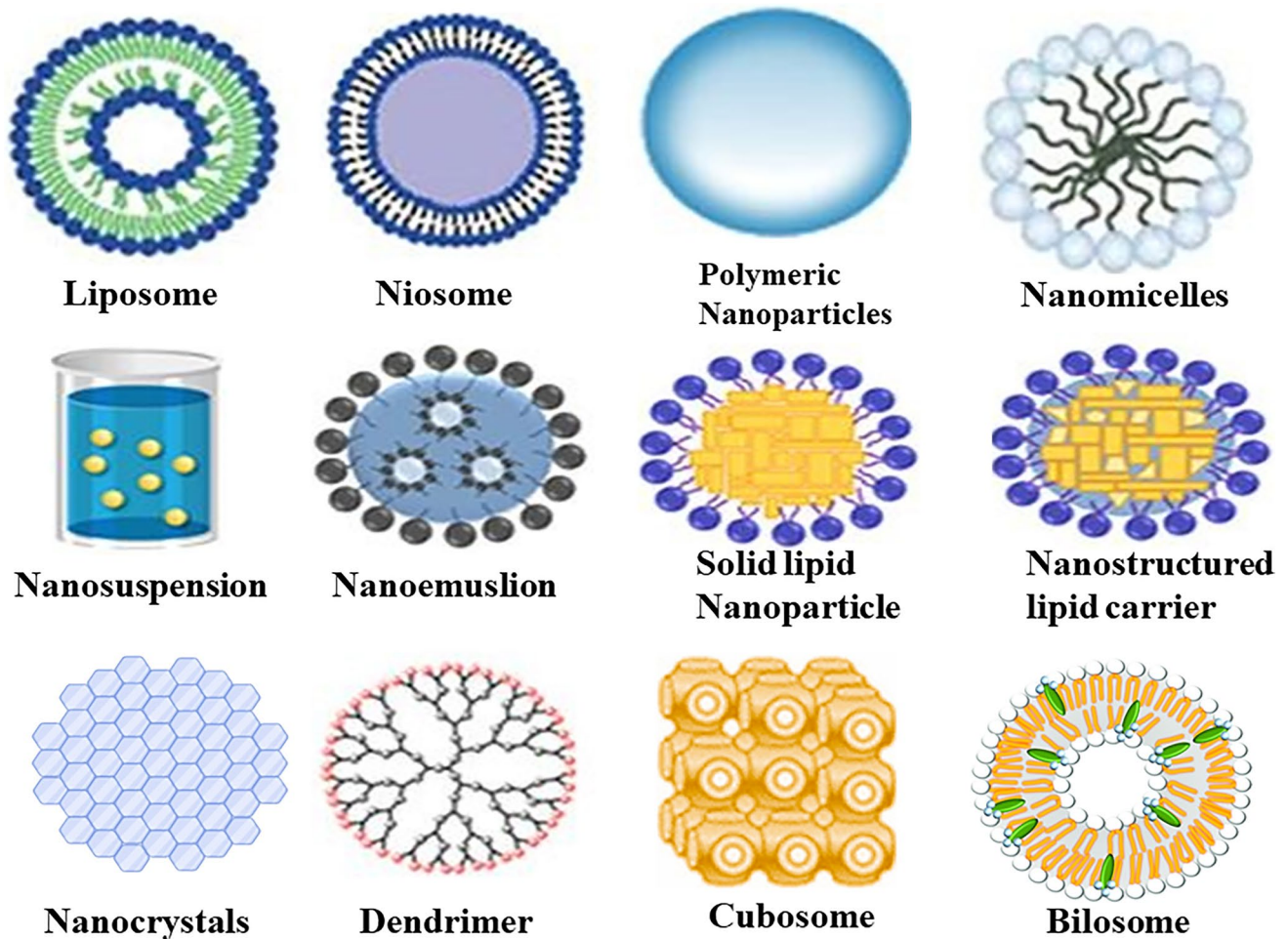


Fig. 6 Illustration of numerous nanostructured platform [8]

enhanced retention time, sustained release, and small particle size [51]. Bodoki *et al.* sustained the release and enhanced the efficacy of lutein using poly(lactic-co-glycolic acid), tween 80, and Poloxamer 407 [164]. Abdel-Rashid *et al.* enhanced ocular permeation and efficacy of acetazolamide employing chitosan, span 60, Tween® 80/20, and sodium tripolyphosphate [145]. More examples are concisely mentioned in Table III.

Solid Lipid Nanoparticles

They are a solid lipid matrix enclosing hydrophilic and lipophilic drugs [161]. Examples of lipids used to prepare solid lipid nanoparticles include triglycerides, fatty acids, steroids, and waxes. They do not require organic solvents since surfactants stabilize the lipid dispersion [165]. They are biodegradable, biocompatible, safe, and of low-cost preparation [165]. They showed enhanced ocular retention time, permeability, prolonged release, and

improved bioavailability [161]. Ahmad *et al.* developed solid lipid nanoparticles loaded with etoposide employing Gelucire® 44/14 and Compritol® ATO 888. The resulted formula demonstrated sustained release, improved safety, and activity [149]. Tatke *et al.* constructed triamcinolone acetone-loaded solid lipid nanoparticles utilizing Pluronic® F-68 and gellan gum. The finished formula ensured improved residence time and increased delivered concentration [150]. A mucoadhesive solid lipid nanoparticles of tobramycin was successfully examined by Chetoni *et al.* The system composed of stearic acid, Epikuron 200, and sodium taurocholate. Higher concentration of tobramycin in both segments of the eye was demonstrated [151].

Nanostructured Lipid Carriers

They are considered a second generation of lipid nanoparticles, composed of around 30% of liquid lipids but the finished formula is solid, with no crystalline structure [161]. The liquid oil

droplets provide additional space for drug in lipid matrix leading to higher drug content compared to solid lipid nanoparticles. They show controlled release, small toxicity, and enhanced activity. Aytekin *et al.* studied nanostructured lipid carriers loaded with riboflavin utilizing Compritol® ATO 888, Gelucire® 44/14, Miglyol® 812, Cremophor® EL, Transcutol® P, and stearylamine. The finished product demonstrated superior corneal residence time, permeation, and safety [153]. Pai and Vavia constructed etoposide-loaded nanostructured lipid carriers using many solid and liquid lipids, glyceryl stearyl citrate, and chitosan. The resulted formula revealed sustained and improved activity [154]. Yu *et al.* used Compritol® 888 ATO, Miglyol® 812 N, Cremophor® EL, soy lecithin, carboxymethyl chitosan, genipin, and poloxamer F127 to formulate nanostructured lipid carriers of baicalin. Investigations showed increased corneal permeation, retention time, and safety [166]. More investigations are succinctly stated in Table III.

Nanocrystals

The drug represents a major composition of nanocrystals, being enclosed and stabilized by other excipients. They have small particle size, simple formation techniques, high mucoadhesion properties, and improved bioavailability [162]. Tuomela *et al.* created brinzolamide-loaded nanocrystals using poloxamer F68/F127, polysorbate 80, and hydroxypropyl methylcellulose. The finished formula revealed immediate dissolution and improved efficacy [157]. Romero *et al.* developed cationic nanocrystals of dexamethasone and polymyxin B using benzalkonium chloride and cetylpyridinium chloride. The resulted preparation revealed small particle size, enhanced retention time, and safety [158]. Orasugh *et al.* formulated a cellulose nanocrystals of pilocarpine. Sustained drug release and safety were demonstrated [167]. Nanocrystals could be promising nanocarriers to be investigated in the near future in details.

Dendrimers

They are star-shaped or tree-shaped highly branched 3D structure, composed of repetitive molecules enclosing a central core [162]. They are suitable for delivery of both hydrophilic and lipophilic drugs due to their several terminal groups [161]. They showed increased residence time, prolonged activity, improved bioavailability, targeted delivery, and antimicrobial properties. They could transfer medications to both segments of the eye [8]. Lancina *et al.* developed brimonidine tartrate-loaded dendrimers using methoxy-polyethylene glycol. Sustained release and improved activity were achieved [168]. Mishra and Jain studied dendrimers entrapping acetazolamide. Increased residence time, prolonged release, and activity were confirmed [169]. Holden *et al.* developed timolol maleate-loaded dendrimers utilizing polyethylene glycol. The finished formula showed

improved permeation and increased cellular uptake [170]. Table III clarifies briefly more studies about dendrimers.

Cubosomes

They are bicontinuous cubic liquid crystalline nanocarriers constructed by emulsification of lipids in water with the aid of stabilizer. They are stable, entrap high amount of drugs due to its large surface area, easy to prepare, biodegradable, and relatively safe [17]. El deep *et al.* formulated brimonidine tartrate-loaded cubosomes utilizing glyceryl monooleate and poloxamer 407. The resulted formula revealed sustained release, improved permeation, and bioavailability [17]. Younes *et al.* developed sertaconazole nitrate-loaded cubosomes using DL- α -Monoolein, pluronic® F127, Brij® 58, pluronic® F108, Tween 80, and polyvinyl alcohol. Improved permeation, stability, and efficacy were achieved [33]. Gaballa *et al.* developed cubosomal system of beclomethasone dipropionate employing glyceryl monooleate. Improved corneal permeation and anti-inflammatory activity were demonstrated [91].

Olaminosomes

Olaminosomes are mainly formed of oleic acid, oleylamine, and surfactant. Oleic acid is natural unsaturated free fatty acid. Oleic acid is safe, biodegradable, and biocompatible. Thus, oleic acid is often used in the preparation of ocular nanocarriers [12]. Oleylamine is an unsaturated fatty amine derived from oleic acid. It has the extensively used as surfactant or co-stabilizer. It is generally used in food and drug products as a result of its well-accepted safety [171]. Olaminosomes have a small particle size, high drug entrapment ability, improved corneal permeation, safety, and activity. Abd-Elsalam and ElKasabgy developed agomelatine-loaded olaminosomes. The optimum formula showed enhanced permeation and improved activity [12].

Bilosomes

Bilosomes are bilayered nanocarriers containing bile salts. They have high drug entrapment, minute particle size, accepted zeta potential, accepted safety, enhanced corneal permeation, and activity. 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 [40].

Characterization of Nanocarriers

Visual Appearance

Figure 7 shows briefly the approaches used to characterize ocular nanocarriers. Visual appearance depends on the particle

size, surfactant, and oil concentration and type. Nanosystems could be transparent, translucent to milky white. Transparency is estimated by percentage transmittance (% T) using a UV spectrophotometer at 520 nm [6]. Small particles permit light transmission resulting in translucent or transparent appearance. High % T indicates absence of visual disturbance. However, gelation would reduce the transparency by 15% [172].

Stability

Stability of different nanosystems could be determined through short-term stability (3 months), centrifugation test, heating–cooling cycle, freeze–thaw cycles, and storage at elevated temperatures. All tests are followed by visual evaluation [6, 36]. The structure of the constructed formula determine the storage condition which could be at ambient temperature ($25 \pm 2^\circ\text{C}$) [33, 34, 36] or refrigerated ($4\text{--}8^\circ\text{C}$) [31, 173].

Size and Uniformity Analysis

Particle size (PS) and poly-dispersity index (PDI) are the determined variable. They are estimated by dynamic light scattering (DLS) or photon correlation spectroscopy (PCS) using either Zetasizer devices (Malvern) or Coulter Counter particle size analyzer [6]. The ratio of the standard deviation to the mean droplet size is known as a PDI. Regarding PDI, a value of 0 indicates homogenous system, while a value of 1 indicates heterogeneous system [174]. Generally, small PS and PDI are desirable for ocular drug delivery since they increase patient compliance and enhance corneal permeability and corneal bioavailability [33]. PS is affected by homogenization time, surfactants type, surfactants amount, lipids type, and lipids quantity. Using high amount of lipid would increase the viscosity of the medium resulting in high difficulty to break the particles and hence large PS [33]. However, high surfactant concentration would allow more coverage for the surface of nanosystem; consequently prevent additional growth in the PS [12]. Using surfactant with low hydrophilic-lipophilic balance (HLB) value would increase the hydrophobicity of the medium and decrease the free energy resulting in smaller PS [41]. Increasing the homogenization time would reduce the PS [33]. However, the efficacy of sonication process might be reduced if the fatty acid had a high melting point as a result of the increased viscosity of the formula [175].

Zeta Potential

Zeta potential (ZP) is an indicator of physical stability of the formed nanosystem. It is determined through electrophoretic movement of particles in an electrical field. Generally, ZP

around ± 20 mV is appropriate for electrostatic attachment with the cornea surface. In addition, ZP ensures the stability because of electrostatic repulsion between the particles. It is high recommended to dilute the formed nanosystem prior to ZP determination [6]. Effective precorneal retention time is achieved when the absolute value of ZP lies between 20 and 40 mV. It has been demonstrated that ZP value +40 mV of Catioprost (Latanoprost — cationic emulsion) revealed a comparable effect as Xalatan (commercial eye solution) for reducing IOP but have a superior ocular tolerance profile [176]. Also, cubosomal formula with ZP = -30.2 mV showed better bioavailability and activity compared to Alphagan P® eye drops [17].

Morphological

Transmission electron microscopy (TEM) and atomic force microscopy (AFM) approaches are valuable to ensure the results of dynamic light scattering (DLS) or photon correlation spectroscopy (PCS) [173]. TEM of the nanoemulsion referred by Tayel *et al.* showed spherical and homogenous structure with no aggregates. TEM was in harmony with the results obtained by PCS [135]. In addition to, the AFM examination of the nanoemulsion referred by Dukovski *et al.* revealed spherical structure with the same size as resulted from PCS [177]. TEM of the mixed micelles constructed by Younes *et al.* revealed spherical shape, with no accumulation and was comparable to DLS [34].

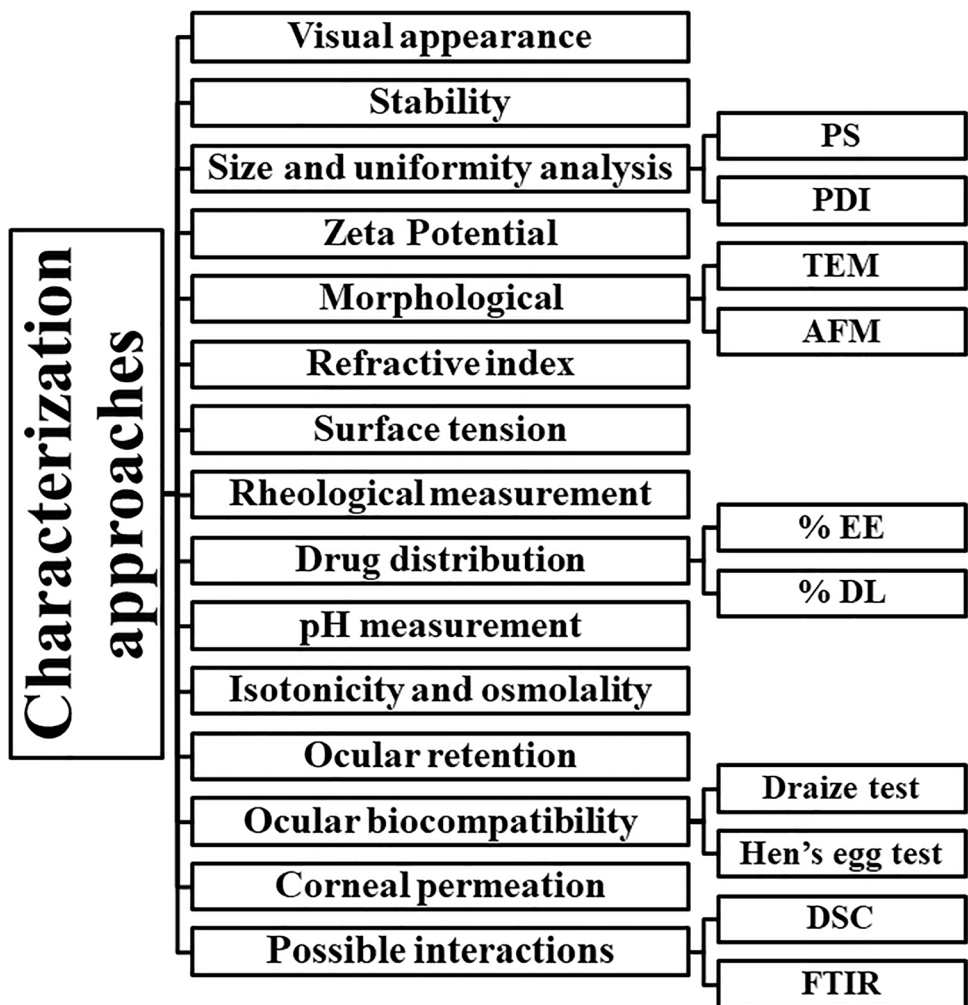
Refractive Index

The refractive index (RI) is detected by Abbe's refractometer and employed to detect the water content of soft contact lenses. It is important to confirm that the nanosystem will not cause a blurred vision [178]. The optimum RI for ocular delivery is <1.476 since the RI of tear fluid ranged from 1.34 to 1.36 [178]. Ismail *et al.* obtained acceptable RI (1.334 to 1.338) for the formed nanoemulsion [179]. The mixed micelles constructed by Fahmy *et al.* showed adequate RI (1.348) [36].

Surface Tension

Tate's law indicates that there is a direct relation between drop volume and surface tension. The volume of the drop regulates the amount of drug that reaches the eye. Surface tension is measured by tensiometer. Generally, the most appropriate dose for ocular delivery is 5–15 μL . However, commercial eye drops give 25.1 and 56.4 μL . Surfactants could condense the droplet size [180]. A surface tension below 35 mN/m results in painful ocular administration, while high surface tension leads to minor film stability. For ocular delivery, surface tension between 40 and 50 mN/m is

Fig. 7 Approaches to characterize ocular nanocarriers



required [181]. Dukovski *et al.* discovered that both chitosan and ibuprofen could reduce surface tension as a result of their surface-active properties [177].

Rheological Measurement

Low viscosity nanosystem allows beneficial compliance with minor blinking pain. However, high viscosity nanosystem could prolong contact time, reduce frequency of dose, and increase bioavailability, but also results in patient discomfort [177]. The appropriate viscosity for ocular preparation is between 2 and 3 mPa.s [6].

Drug Distribution

Both percent entrapment efficiency (% EE) and percent drug loading (% DL) are used to examine diffusion of drug inside the nanosystems. % DL indicates the mass ratio of drugs to the mass of the nanosystem; however, % EE reflects the incorporation of drugs within the nanosystem during the

formulation process. Generally, % DL depends on the structure and physical and chemical properties of the carrier material; however, % EE depends on drug hydrophobicity, molecular weight, and structure. Additionally, obtaining high %DL is more difficult than high % EE for most nanosystems [182]. Prior to determination of amount of the drug, the formula may be subjected to ultrafiltration, ultracentrifugation, gel filtration, or microdialysis [6, 34, 36]. Said *et al.* determined % EE of voriconazole-loaded cubosomes after ultracentrifugation [37]. % EE of rifampicin-loaded nanoemulsion and ibuprofen-loaded nanoemulsion was conducted after ultrafiltration [50, 177] Lin *et al.* estimated both % EE and % DL for the constructed micellar system [183].

pH Measurement

pH determination is important to ensure safety and efficacy of nanosystems. Acidic (pH < 4) or alkaline (pH > 10) solution would harm the eye [37]. Also, pH from 4 to 8 would significantly enhance drug permeation [31]. The pH of

ocular preparation usually ranged from 3.50 to 8.50 [37]. pH of the formed cubosomes referred by Said *et al.* was (6.20 ± 0.01) [37]. Micellar system constructed by Fahmy *et al.* revealed acceptable pH value (7.41 ± 0.01) [36].

Isotonicity and Osmolality

Osmolality measurements are based on the colligative properties of tears or ocular nanosystem known as the freezing point, boiling point, vapor pressure, and osmotic pressure. Osmolality of open eyes is ranged from 231 to 446 mOsm/kg due to fluid evaporation. Ocular preparation with osmolality lower than 100 mOsm/kg or greater than 640 mOsm/kg was considered an eye irritant. Osmolality is restored within 1 or 2 min subsequent to administration of the non-isotonic preparation [6].

Ocular Retention

Ocular retention is important since it will reduce the frequency of doses and improve drug bioavailability. Ocular retention largely depends on surface area of nanosystem, since large surface area will enhance residence time. Ocular retention is determined by texture analysis method, modified balance method, fluorescence retention method, γ -scintigraphy, and rheological synergism after mixing with mucoadhesive polymer [6]. As a general rule, the force needed to detach eyelid during normal blink is about 0.2 N and 0.8 N during strong blink [184]. For chitosan-coated cyclosporine nanoemulsions, the resulted force of detachment was 0.153 N [87].

Ocular Biocompatibility

Draize Test

It's a traditional *in vivo* test to detect possible irritation potential of the formed nanosystems. It may be also used for cosmetics [185]. Draize test relays on scoring system from 0 (no irritation) to 3 (inflammation and redness) for the cornea, iris, and conjunctivae [18]. For example, Ismail *et al.* utilized the test on rabbits to compare between nanoemulsions of travoprost and Travatan® eye drops. Safety of the constructed formula was confirmed [179]. Also Eldeep *et al.* used Draize test to confirm safety of the topically applied niosomes of brimonidine tartrate against Alphgan P® [18].

Hen's Egg Test

Because of the existence similarities between chorioallantoic membrane (CAM) and vascularization of mucosal tissue of humans, this technique is used to detect possible

ocular irritation from nanosystem. The score is given based on clotting, bleeding, and hyperemia on CAM blood vessels [186]. For example, Mahboobian *et al.* examined the safety of the formed nanoemulsion *versus* negative control (PBS, pH = 7.4) and positive control (sodium dodecyl sulfate). Study was accomplished on freshly fertilized hens egg at $37 \pm 0.5^\circ\text{C}$ and relative humidity of $67 \pm 5\%$ RH for 10 days with regular rotation every 12 h. Irritation consequences such as hemorrhage or hypermia were evaluated by visual inspection. Safety of the nanoemulsion was demonstrated by the end of the experiment [186].

Corneal Permeation

Ability of the nanosystem to penetrate through cornea is studied through various *in vivo*, *ex vivo*, and *in vitro* tests. The *in vivo* models usually utilized the rodents (rabbit, rat, or mouse); however, *in vitro* and *ex vivo* models used epithelial cells layer cultures, reconstructed cornea, or excised cornea [6]. Also, different permeation chambers are available like Franz-type diffusion cell, modified Franz diffusion cell, modified using chamber, horizontal perfusion cells, modified Erlenmeyer flask diffusion cell, and polycarbonate corneal perfusion chamber [6]. Different permeation parameters are estimated to evaluate the permeation potential of nanosystem. Permeation parameters include the amount of drug permeated per unit area ($\mu\text{g}/\text{cm}^2$), average flux (J_{max}), permeability coefficient, and the enhancement ratio (ER) [5, 34].

Possible Interactions

Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) are important techniques to detect possible interaction between the components of nanosystems [173]. They also assure complete entrapment of the drug. For example, the specific peaks of vancomycin, poly (d, l-lactide- coglycolide), and Eudragit® RS 100 were preserved ensuring the absence of chemical interactions [187], while complete entrapment of dorzolamide hydrochloride was confirmed by disappearance of its characteristic peak from DSC thermogram [16].

Approaches to Enhance Ocular Delivery

Improvement of Corneal Permeability

Figure 8 shows concisely the approaches used to enhance ocular delivery. One of the approaches to enhance drug bioavailability following topical administration is increasing corneal permeability. For example, changing membrane components and/or disrupting epithelial tight junctions using surfactants, permeation enhancers, calcium chelating

agents [188], and modifying physicochemical characters of the ionized drug using ion pairs [189]. On the other hand, enzymatic transformation of prodrug would convert it into the active after appropriate permeation [190]. Finally, applying a low-intensity electrical current (iontophoresis) would enhance drug permeation by electrorepulsion and electroosmosis effects.

Improvement of Corneal Retention Time

One of the techniques to increase corneal retention time is inclusion of excipients. Excipients could be a viscosity increasing polymers. However, high viscous eye drops are irritating for many patients, do not provide an accurate dose and result in blurred vision [191]. *In situ* gel has sustained contact time compared to simple solutions [117]. There are three types of *in situ* gel according to the transition properties: temperature, ionic, or pH sensitive [118]. *In situ* gel of ciprofloxacin with hydroxypropyl methylcellulose and sodium alginate (ion-sensitive) showed enhanced residence time and sustained drug release [98]. More examples of *in situ* gel were previously mentioned in Table II. The mucus gel layer covering the ocular surface is made of mucins, a class of at least 20 O-glycosyl proteins with anionic charge. Excipients permitting attachment to this mucus gel layer provide a sustained residence time [191]. Chitosan is a commonly used mucoadhesive polymer by virtue of its polycationic nature and the existence of many reactive amino groups capable of interacting with mucin layer. Kaur *et al.* studied niosomal system composed of span 60, cholesterol, and chitosan which revealed higher activity, reduced side effects, and prolonged release [129]. Cyclodextrins are widely used cyclic glycopyranose oligosaccharides. They have the ability to enhance drug solubility and to attach covalently to mucoadhesive polymers to prolong residence time [191]. Sayed *et al.* used β -cyclodextrin to enhance ocular delivery of itraconazole [35]. Many colloidal delivery nano-systems have been employed to enhance ocular delivery. They have the ability to carry different drugs, increase bioavailability, reduce frequency and potential side effects, and improve patient's compliance. Different ocular nano-systems were previously stated in Table III. Also, solid polymeric devices have been developed as authorized sustained release ocular dosage forms. However, solid strategies are frequently not accepted by patients because of discomfort and interference with vision. Sustained bimatoprost activity for many months was proved after incorporation of its insert [110]. Dexamethasone contact lens was prepared by encapsulation technique. It showed 200 fold drug retention in the retina matching with conventional eye drops [116]. More examples of solid dosage forms were formerly listed in Table II.

Future Technologies

Smart Nano-Micro Platforms

Smart denotes to nano-micro matrix that can considerably change their mechanical, thermal, and/or optical properties in a manageable or expectable means, and they can achieve sensing triggering roles with stimuli-responsive features. Unlike conventional nanocarriers, the smart nano-micro platforms can reveal precise reaction to exogenous (light, sound, and magnetic field) or endogenous (pH, reactive oxygen species, and biological molecules such as DNA and enzymes) factors resulting in accomplishing many functions, e.g., site-specific drug delivery, bio-imaging, and detection of bio-molecules. These fascinating techniques have extended into ocular delivery in recent years. Generally, these revolutionary systems have been used for cancer diagnosis and management, to enhance the bioavailability of drugs/agents, minimize side effects, and augment safety and efficacy [192, 193]. Tsujinaka *et al.* successfully delivered sunitinib microparticles that effectively inhibit the intraocular inflammation in mice model up to 6 months [194]. Rodriguez *et al.* constructed solid lipid nanoparticles that carry miRNA as gene therapy [195]. Basuk *et al.* demonstrated photo-modulated release of pre-loaded bevacizumab using visible light [196].

Extracellular Vesicles (Exosomes)

Extracellular vesicles are a sort of organelle that is produced by different cell types. Various bioactive compounds for example proteins, lipids, RNAs, and DNAs are enclosed within extracellular vesicles. They have a nano-size behave as a strong intercellular trigger that can start different physiological and pathological consequences. Under pathological situations, they could be produced by immune cells and control the inflammation progressions. They have a well-recognized role in immune-mediated eye diseases, such as Sjogren's syndrome and corneal allograft rejection [197]. Also, they could encourage renewal of corneal tissue by stimulating the production of different matrix components. Additional investigations are required to develop ocular delivery systems based on exosomes. Tang *et al.* constructed exosomes of pluripotent stem cell-derived mesenchymal stem cells to hasten the restorative process of the corneal epithelium [198]. Zhu *et al.* developed exosomes derived from lens epithelial cells to load doxorubicin to prevent posterior capsular opacification [199].

Tissue Engineering

Tissue engineering investigations are classified into two types. First type is additive tissue engineering which substitutes cells or tissue or tries to permit the growth of

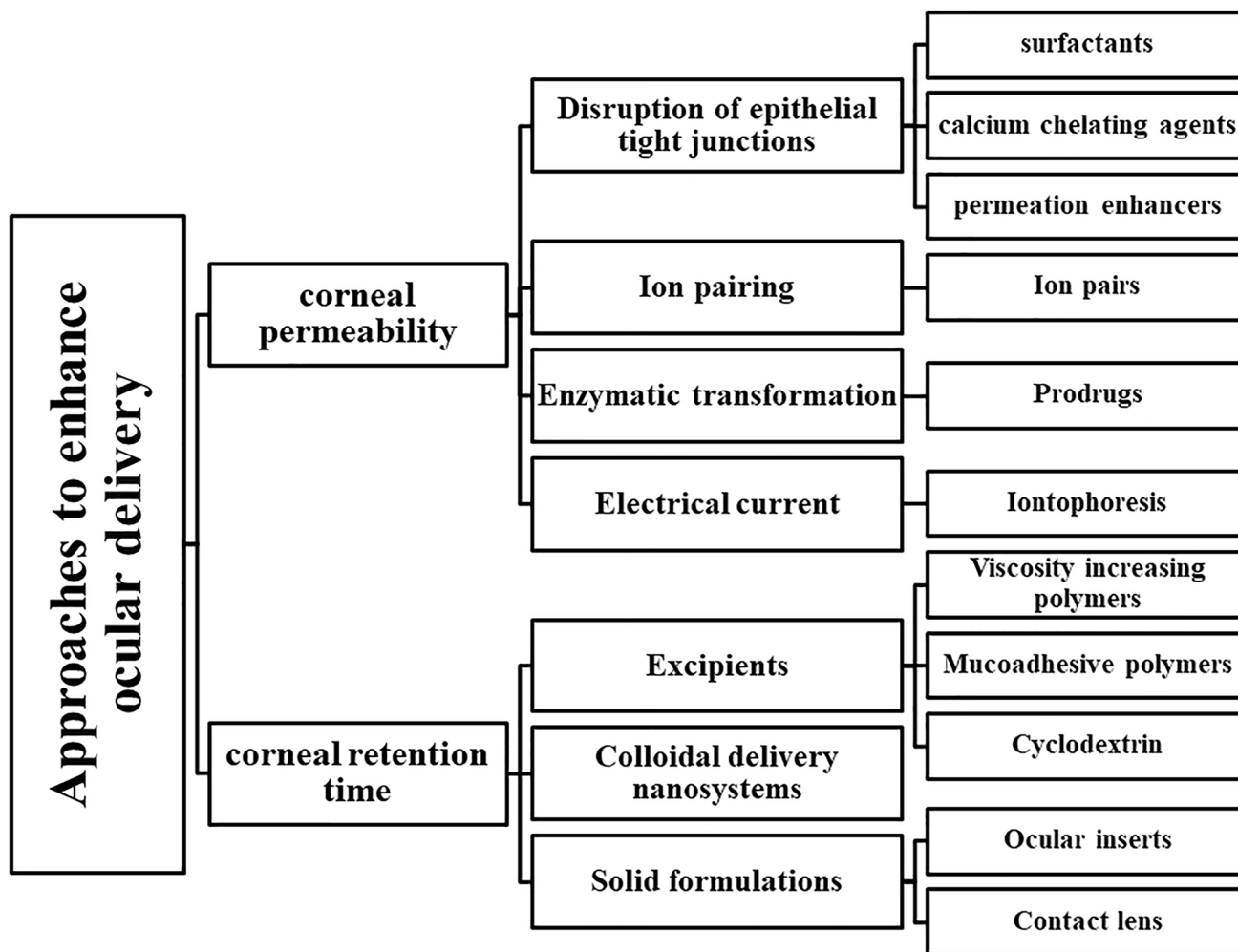


Fig. 8 Approaches to enhance ocular delivery

something that is no longer there. The second type is arrestive tissue engineering that prevents irregular growth. Both additive and arrestive tissue engineering could be performed utilizing nanosystems. Examples of nanosystem-based tissue engineering include check of retinal ganglion cell viability [200], retinal ganglion cell repair [201], formulation of nanofiber scaffolds [202], corneal endothelial cell transplantation [203], and inhibition of retinal cell apoptosis [204]. Scientists begun to examine if nanotools and nanomaterials could be used to restore neural function of eye’s nerve cells.

Innovations in Clinical Trials

Continuous clinical trials for different dosage forms give the lead for pioneer treatment. For example, pilocarpine topical cream (semi-solid) for the treatment of presbyopia. It is a multicenter, randomized, double-masked, placebo-controlled, parallel group phase 2 trial evaluating the safety and efficacy of the cream. The study starts at January 3, 2022

and will continue till May 2023. Moreover, Cequa™ (Cyclosporine) ophthalmic emulsion (twice daily). This is a phase 4, multicenter, single arm, and 12-week study. An example of solid dosage form includes Dextenza 0.4 Mg (dexamethasone) ophthalmic insert. The study is performed to assess the efficacy and safety of Dextenza insert for the treatment of pain and inflammation following corneal transplant surgery.

Conclusions

The effective management of ophthalmic diseases remains a difficult mission as a result of existence of many ocular obstacles in the anterior and posterior sections of the eye. There are many ocular routes of administration that are used in order to deliver the medication into the targeted site of action such as topical, intraocular, periocular, or in conjunction with ocular devices. Several approaches and technologies have been adopted in order to minimize dosing interval,

administered dose, and unwanted effects and to enhance ocular retention time, drug permeation efficacy, and ocular bioavailability via controlled and sustained drug delivery systems. These advanced technologies have improved drug efficacy and shown good biocompatibility which suggest that they might have wide applications in the management and treatment of ocular diseases. In the future, more innovations are predicated in the ocular drug delivery systems in order to enhance and preserve the health of the eye, to improve patient compliance, and to accomplish superior results in the management of ocular diseases.

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Data Availability Data is available within the article.

Declarations

Conflict of Interest The authors declare no competing interests.

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