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REVIEW ARTICLE

A review on ophthalmic delivery systems containing flavonoids for the treatment of eye diseases

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HIGHLIGHTS

> Flavonoids have very beneficial effects on eye health, and also in the treatment of the eye diseases.
> A decreased antioxidant capacity, oxidative stress and inflammatory mechanisms have a significant role in the development and progression of the ocular diseases.
> Ophthalmic delivery systems can increase the ocular bioavailability of flavonoids.

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ABSTRACT

Flavonoids, polyphenolic compounds, have many biological effects, including antioxidant, free-radical scavenging properties, antiviral, antibacterial, anti-inflammation, anti-allergic, and anti-carcinogenic effects, anti-platelet, anti-thrombotic, and vasodilating actions. A decreased antioxidant capacity, oxidative stress, and inflammatory mechanisms in the ocular tissues are considered to have a significant role in the development and progression of the ocular diseases. Flavonoids have very beneficial effects on eye health, and also the treatment of the eye diseases due to their antioxidant, anti-inflammatory and ocular blood flow enhancing properties. Most flavonoids have low bioavailability associated with low water solubility. It is important to develop effective ocular drug delivery systems containing flavonoids for application directly to the eye. This delivery systems can increase ocular bioavailability and enable flavonoids to reach the internal structures of the eye more effectively. Furthermore, considering the sensitive nature of flavonoids as antioxidant agents, especially nano-sized formulations have in particular become potential carriers for preserving them and improving their bioavailability and therapeutic efficacy. This review will focus the published studies that have investigated the development of delivery systems containing flavonoids for the treatment of eye diseases. In addition, within the scope of this review, flavonoids, common eye diseases, and the materials used in the preparation of the ophthalmic delivery systems containing flavonoids are briefly mentioned.

1. Introduction

Flavonoids are a big family of plant-derived polyphenolic compounds with diphenylpropane skeletons that are widely distributed in vegetables and fruits, thus, regularly consumed in the human diet. The number of different flavonoids identified until now is over 4000 [1]. Flavonoids, polyphenolic compounds, have several subgroups depending on the positions of the substitutes present on the parent molecule, which include flavonols, flavanones, flavones, isoflavones, flavanols or catechins, and chalcones [2,3]. These compounds have many biological effects, including antioxidant and free-radical scavenging properties, anti-platelet, anti-thrombotic, and vasodilating actions, antiviral, antibacterial, anti-inflammation, anti-allergic, and anti-carcinogenic effects [1,3–5]. They are also capable of strengthening capillary walls and reducing fluid retention [6].

In a study, the *in vitro* antioxidant, anti-inflammatory, and antibacterial activities of the flavonoid fraction extracted from the leaves of *Abutilon theophrasti Medic.* (*A. theophrasti*), commonly used for the treatment of inflammation and joint pain in China, was evaluated. Their obtained results showed that the fraction has *in vitro* antibacterial, antioxidant, and anti-inflammatory effects and

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it might be beneficial in the adjuvant treatment of oxidative stress and also, inflammatory and bacterial diseases [7].

In another study, the extracts (ethanol, ethyl acetate and heptane) *of Euphrasia officinalis L.*, which is traditionally used in folk medicine and especially in the treatment of eye disorders, were obtained. Later, the effects of these extracts on human corneal epithelial cells were investigated *in vitro*. After 24 hours of incubation, the extracts (ethanol or ethyl acetate) reduced pro-inflammatory cytokine expression (TNF-α IL-6, and IL-1β) of human corneal cells. The biological effects of these extracts are based on the presence of highly active compounds such as flavonoids, essential oils, iridoids, phenolic acids. It was stated that the application of the extracts of *Euphrasia officinalis L.* as a complementary therapy for eye disorders is promising [8].

In addition, it has been shown a select group of flavonoids (quercetin, luteolin, fisetin, 3,7-dihydroxyflavone, and baicalein, etc.) protect retinal pigment epithelial cells from oxidative stress-induced death with low toxicity and high potency, and also many of these flavonoids induce the expression of phase-2 detoxification proteins that may serve as an additional protection against oxidative stress [9].

The previously published studies reported that flavonoids cause beneficial effects on reduction of the growth of malignant carcinomas, on inhibition of tumor angiogenesis, and on protection from cardiovascular disease, coronary heart disease, menopause syndrome, hypertension, and cerebral thrombosis [1,5,10].

Recently, in *in vitro* and preclinical studies, it has been reported that decreased antioxidant capacity, oxidative stress, and inflammatory mechanisms in the ocular tissues are considered to have a remarkable role in the development and progression of the ocular diseases with etiology including hypoxia, decreased blood supply to ocular tissues, free radical mediated oxidative damage and in certain conditions, increased vascular permeability, angiogenesis, and leakage of vascular contents (diabetic retinopathy, age-related macular degeneration etc.). Therefore, some phytochemicals such as flavonoids may be useful due to their antioxidant, anti-inflammatory and ocular blood flow enhancing properties in the treatment of the ocular diseases [6]. Xiao et al. [11] evaluated the suppression effect of daidzin, an isoflavone found in some plants, including kudzu root and soy plants, on corneal inflammation and oxidative stress in the dry eye rat model developed by removing the lacrimal gland of rats. They found that oxidative stress in the cornea was reduced due to the tyrosyl radical scavenging activity of daidzin. Daidzin improved corneal erosion and also restored tear volume in the dry eye rat model. Xiao et al. [11] emphasized that daidzin might be useful in the treatment of dry eye due to protection of the cornea by the suppression of oxidative stress and inflammation in a dry eye rat model. In another study, which is a population-based prospective cohort study included 2856 adults aged 49 y and over at baseline for prevalence analysis and 2037 adults re-examined (follow-up) 15 y later for incidence analysis, the independent associations between the prevalence and 15-y incidence of age-related macular degeneration (AMD) with dietary intake of flavonoids (the median intake of total flavonoids: 875 mg/d) were assessed. This study reported that a higher intake of flavonoids (especially flavanones and flavonols) was associated with reduced odds of the prevalence of AMD, thus, the intake of flavonoids might have a role in the prevention and progression of AMD [12]. Baicalin is a flavonoid found in *Scutellaria baicalensis Georgi*, an herb that has been used in traditional Chinese medicine for many years. It has various biological activities such as antibacterial, antiviral, anti-inflammatory, and anti-cataract effects that may be beneficial in the treatment of eye diseases [13,14].

On the other hand, Pawlowska et al. [15] emphasized that most of the evidence for the effect of dietary polyphenols on the progression of AMD comes from *in vitro* and animal studies. Therefore, the necessity of conducting prospective interventional studies to confirm these results was stated by the authors.

In addition, Davinelli et al. [16] conducted a systematic review (16 studies included after literature search) and meta-analysis (11 intervention trials involving 724 participants) to evaluate the effect of dietary flavonoids on primary eye disorders. They stated that flavonoids could improve the clinical manifestations related to ocular diseases, but further clinical studies are needed to examine and confirm the effect of flavonoids on different eye disorders.

There are enzymatic [glutathione peroxidase (GSH-Px), super oxide dismutase (SOD) and catalase (CAT)] and non-enzymatic (such as β-carotene, vitamin C and E) antioxidant defences responsible for scavenging free radical [17]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the most important oxidants generated by various metabolic pathways, biological factors, and pathological conditions [18]. The mitochondria is one of the main sources of cellular ROS and an imbalance between antioxidant defenses and ROS causes to oxidative stress [19]. Oxidative stress leads to damage lipids, proteins, DNA, and mitochondria and is associated with some age-related disease, because, with age, mitochondria become gradually more incompetent [20]. In addition, an excess amount of ROS can lead to functional and morphological impairments in retinal pigment epithelium (RPE), endothelial cells, and retinal ganglion cells (RGCs). Oxidative stress can initiate and develop ocular tissue/cell (cornea, endothelial cells, retinal pigment epithelium, and retinal ganglion cells etc.) damages resulting in a decrease in visual acuity, or even vision loss [20,21]. The one of major target of the ROS/RNS attack is the eye, because, it (especially, its anterior segment, mainly the cornea) is exposed to a number of environmental factors such as oxygen, ionizing radiation, UV light, visible light, air pollution, irritant, environmental toxins, cigarette smoke, and pathogenic microbes, which are able to alter the redox status of a cell to oxidizing conditions [18,19,21]. On the other hand, the retina is also highly sensitive to oxidative damage, because, (a) there are an abundance of the polyunsaturated fatty acids, whose double bonds are primary targets for peroxidation reactions, in its membrane bilayers, (b) free radical formation and peroxidation reactions can be initiated by photoexcitation as a result of the periodical exposure of the retina to continuous light, and (c) the retina that is a highly metabolic tissue requires a high rate of blood flow for sufficient oxygen supply [6]. Atmospheric oxygen, environmental chemicals, constant light irradiation, and physical abrasion contribute to

oxidative stress which is responsible for disruption of blood–retinal barrier (BRB), microvascular abnormalities, retinal neovascularization, increased vascular permeability, and apoptotic loss of retinal capillary cells [22]. As a result, the oxidative stress has a significant role in the development and progression of ocular diseases such as AMD, cataract, retinopathy of prematurity (ROP), and diabetic retinopathy (DR) [20,21].

When the antioxidant defense systems are depleted/dysfunctional, visual impairment can be observed. Therefore, antioxidants are important agents in the prevention/treatment of oxidative diseases [22].

1.1. Age-related macular degeneration (AMD)

AMD, which is caused by the loss of RPE cells and photoreceptors in large zones of the macula, is a multifactorial disease of the retina [15,23]. It is a leading reason for blindness and the number of people affected by AMD will increase to 288 million by 2040 [24]. AMD especially affects people over 65 and is the main cause for legal blindness and vision loss in the elderly in developed countries. It affects the macula which is a highly specialized area of the central retina responsible for color and fine vision [15]. Oxidative stress, age, gender, race, diabetes, obesity, hypertension, smoking, hyperopia, pyroptosis, iris-color, genetics, and sun-light are risk factors for AMD [24]. AMD is characterized by drusen accumulating between the RPE and Burch's membrane. In this accumulation, carboxyethylpyrrole adducts, which is produced by the oxidative modification of fatty acids in photoreceptor tips, and advanced glycation end-products, a transmembrane receptor that applies pro-inflammatory functions thru nuclear factor-κB (NF-κB) signaling, have been found [23]. Therefore, oxidative stress and oxidative stress-induced inflammation play a major role in the pathogenesis and progression of AMD [15,23,24].

1.2. Retinopathy of prematurity (ROP)

ROP, which is a retinal vasoproliferative disease and frequently found in prematurely born infants, is the significant cause of visual impairment and blindness in these infants. Its incidence rate is about 98% among babies born with very low birth weight (<750 g) and about 68% among infants born with birth weight <1200 g [25].

It is a retinal vasoproliferative disease [26,27]. ROP might be divided into an early retinal ischemic stage and a late retinal neovascular stage [27]. Birth weight, gestational age, oxidative stress, prolonged mechanical ventilation, bronchopulmonary dysplasia, pulmonary complications, deficiency of vitamin E, maternal diabetes mellitus, hypertensive disorders of pregnancy, smoking, gender, blood transfusion, race/ethnicity, anemia, bacterial and fungal sepsis, medical interventions, intraventricular hemorrhage, and genetic factors are risk factors for the development and progression of ROP in premature infants [28]. High supplemental oxygen must be given to premature infants due to their immature cardiopulmonary system [29]. Oxygen has a critical role in the development of ROP, because, it causes tissue injury through the formation of ROS and lipid peroxidation [27,28,30].

1.3. Cataract

Cataract, which is a multifactorial eye disease associated with several risk factors such as oxidative stress, age, ultraviolet (UV) radiation, low antioxidant defence capacity, diabetes mellitus, obesity, female gender, smoking, and steroid consumption, is one of the leading causes of preventable blindness in the world today [31–33]. It refers to lens degradation characterized by clouding, with consequent blurred vision. It is stated that 35.1 million out of 191 million people with visual impairment globally have this debilitating disease. The prevalence of cataracts increases exponentially after the age of 40, and it is 3.9% in the 55-64 age group, while it is 92.6% for 80 years and older [31]. ROS produced by H_2O_2 causes protein degradation and epithelial cell damage. In cataract, there are the aggregation of oxidatively damaged proteins, and thus, oxidation of lens proteins is a main risk factor in cataract formation. Using antioxidant supplements is a protective strategy against oxidative stress. It was shown that ghrelin, which is a growth hormone-releasing peptide and may reduce ROS, may protect human lens epithelial cells against oxidative stress and prevent the progression of cataract [34].

1.4. Diabetic retinopathy (DR)

DR is one of the leading reasons for acquired blindness in working-age adults in the world. In DR, there are structural and functional changes in the retina [35]. The retina's oxygen uptake and glucose oxidation are higher than that of other tissues; which makes it more susceptible to oxidative stress. Atmospheric oxygen, physical abrasion, environmental chemicals, and, continuous light radiation contribute to oxidative stress [22]. Multiple factors such as hyperglycemia, and oxidative stress are included in DR pathophysiology. Hyperglycemia promotes changes in neuronal and vascular structures through ischemic/hyperosmotic damage, it also heads oxidative stress. Neovascularization is the major clinical change in proliferative DR [36]. Oxidative stress plays a significant role in the development and pathogenesis of DR. NADPH oxidase 2 is one of the isomers activated in the retina of person with diabetes. Ras-related C3 botulinum toxin substrate 1 (Rac1) is an obligatory component of the multicomponent cytosolic NADPH oxidase 2. Activation of Rac-1-NADPH oxidase 2-mediated cytosolic ROS production causes to mitochondrial damage, and the development of diabetic retinopathy [37].

1.5. Oral bioavailability of flavonoids

Flavonoids, which has a central ring (C-ring) in their structure and are largely decomposed by bowel flora, have poor bioavailability [38]. The bioavailability of flavonoids may be even lower and vary severely among different flavonoid classes due to their complex structures and larger molecular weights. Their bioavailability depends primarily on the type and position of sugar moiety in their structure and also their dietary source [39]. The flavonoids, which are in the ingested matrix after consumption of foods/beverages containing flavonoids, should pass from the gut lumen to the circulatory system for their absorption

[40]. Flavonoids are substrates for conjugating and hydrolyzing enzymes in liver, small intestine, and colon. Their conjugation first becomes in the small intestine and then in the liver where they are metabolized and the produced sulfate and glucuronides derivatives facilitates their excretion through urine and bile [39]. However, most of the flavonoids, except flavan-3-ols, exist as glycosides, thus, the attached sugar in their structure must be removed before their absorption [40]. The glycosides are generally hydrolyzed to their aglycones to show effects *in vivo* [41]. Flavonoid-O-glycosides that are commonly too large and polar structure to be absorbed are converted into an aglycone through hydrolysis by bacterial enzymes. Then, the aglycones can be absorbed or continue breakdown by a C-ring fission process to give smaller ring fission products that can be readily absorbed [38]. The chemical structure and molecular weight of flavonoids and also their glycosylation and esterification are significant factors for flavonoid absorption [39].

There are several approaches to improve the bioavailability of active compounds; these are changing their absorption site, improving their metabolic stability [such as quercetin, it is rapidly cleared after oral intake due to undergoing extensive metabolism [42], increasing their intestinal absorption, use of different routes for their administration, etc. Drug delivery systems (microparticles, nanoparticles, microemulsion, solid dispersions etc.) are commonly used to achieve these purposes [39].

2. The studies on the development of drug delivery systems containing flavonoids for eye diseases

The human eye is anatomically divided into two parts: the anterior segment (cornea, aqueous humor, iris, and lens) and the posterior segment (the back of the sclera, choroid, retina, and vitreous body). After systemic administration of drug/compound, it can be delivered to the anterior segment of the eye with very low ocular bioavailability due to the presence of the anterior blood-aqueous barrier (BAB), and also a systemically administered drug/compound must cross the posterior blood-retinal barrier (BRB) to reach the posterior segment of the eye. On the other hand, although the topical application of drugs to the eye surface is more convenient and simpler, the drug must pass the corneal barrier consisting of different layers (primarily epithelium, stroma, and endothelium) to reach the inner segments of the eye; the hydrophobic epithelium restricts the penetration of hydrophilic drugs into the cornea, while the more hydrophilic stroma limits the passage of lipophilic drugs. However, topically applied ophthalmic drugs can enter the anterior segment of the eye after absorption through the conjunctiva/sclera (compared to the cornea, they have a larger surface area and high permeability) [13]. Furthermore, other factors limiting the passage of the drug into the inner segments of the eye include the possible elimination of the drugs by lymphatic and conjunctival blood flow, and the size of drug molecules. Besides, ophthalmic bioavailability of drugs is also reduced by metabolic degradation, removal of drug from the surface of the eye due to tear clearance or nasolacrimal drainage. Other alternative routes used for drug administration to the eye (intracameral and subconjunctival, intravitreal routes) have some disadvantages such as discomfort and pain that may limit patient compliance [13]. As mentioned above, several treatment options for eye diseases are available, but multiple factors (the existence of anatomical barriers in the eye, the disadvantage of the alternative ocular routes) could limit their efficacy. The development of ophthalmic drug delivery systems (particularly nano-sized systems) has been useful to overcome these limitations of existing ocular drug application methods. Antioxidant agents such as flavonoids, which are used in ophthalmology due to their capacity to scavenge free radicals, prevent cellular and tissue damage caused by oxidative stress [13]. Previously published studies suggest that the flavonoids have very beneficial effects for eye health, and also the treatment of the eye diseases [1,42–44]. The flavonoids such as quercetin, genistein, and chrysin are rapidly cleared following oral ingestion due to undergoing extensive metabolism, and thus, they have limited systemic effects [42]. Therefore, it is important to develop effective ocular drug delivery systems containing flavonoids for application directly to the eye. This delivery systems can increase ocular bioavailability and enable flavonoids to reach the internal structures of the eye more effectively. Furthermore, considering the sensitive nature of antioxidant agents, nano-sized formulations have in particular become potential carriers for preserving antioxidant agents and improving their bioavailability and therapeutic efficacy [22]. A nano-sized delivery system such as like nanoliposomes, polymeric nanoparticles, or micelles can prevent premature degradation or removal of the antioxidant agents by the eye's protective mechanisms. These nano-carrier systems carry the antioxidant agents towards the internal structures of the eye that are generally difficult to reach using the conventional formulations of antioxidant agents [22,43,45].

This review will focus the published studies that have investigated the development of delivery systems containing flavonoids for eye diseases. In addition, within the scope of this review, the materials used in the preparation of the ophthalmic delivery systems containing flavonoids are briefly mentioned.

The design and preparation/synthesis of effective modern delivery systems is of great importance in fields such as pharmaceutics, food, and cosmetics. Advances in especially nanotechnology and the production of new materials have synergistically fueled advances in the design/preparation of these systems. The preparation of biocompatible, biodegradable, targeted and environmentally friendly delivery systems has been made possible by innovations in material chemistry [46]. Materials such as polymers, lipids, and metals are often used in the preparation of these delivery systems due to their high biocompatibility and biodegradability properties, synthetic polymers (poly (lactic-co-glycolic acid), poly-L-lactic acid, etc.) and natural polymers (alginate, chitosan, etc.) are widely used in the preparation of the delivery systems [47]. Delivery of drug/biologically active compounds/nutraceuticals is a vital issue for healthcare. Advantages such as the modified release of drugs/biologically active compounds, increasing/improving their stability and bioavailability, overcoming the solubility problem of hydrophobic compounds, and targeting of drugs/the compounds have been achieved especially with the development of nano-sized delivery systems [46,48].

Cyclodextrin (CD) complexes, liposomes, polymeric micelles, nanocomplexes, and polymer-/lipid-based nanoparticles as delivery systems are frequently prepared, to overcome the limitations of especially hydrophobic drugs/compounds.

2.1. Polymeric delivery systems

Developments in polymer science are very important for the design and preparation of polymeric delivery systems. Most flavonoids have low bioavailability associated with low water solubility, poor stability, extensive metabolism, limiting the activity and potential health benefits of flavonoids. There are different approaches to increase the solubility of active substances/compounds with poor water solubility; the use of water-soluble complexing agents is one of these approaches. Various bonds/interactions (covalent bonds or non-covalent forces such as electrostatic interactions, hydrophobic interactions, dipole forces, hydrogen bonds or van der Waals forces) are involved in the formation of these complexes. CDs and polyvinylpyrrolidone (PVP) are complexing and solubilizing agents commonly used in pharmaceutical formulations. PVP is a hydrophilic polymer that can form intermolecular cross-links with active substance/compounds and is suitable for the formulation and therapeutic applications of poorly water-soluble active substance/compound. PVP is also used in some ophthalmic suspensions and solutions due to its functions as a viscosity increaser and stabilizer [49].

Wang et al. [49] prepared nanocomplex containing naringenin using polyvinylpyrrolidone (PVP) K-17 PF (Kollidon® 17 PF). Naringenin, a flavanone with anti-inflammatory, anti-cancer, antioxidant, and antiviral effects widely found in some fruits such as citrus, cherries, tomatoes, bergamot, and cocoa [50,51]. Naringenin's therapeutic potential is limited due to its hydrophobic nature, which leads to poor water solubility and very low bioavailability. It rapidly converts to its crystalline form with low absorption from the gastrointestinal tract and has a short half-life. Furthermore, naringenin in an aqueous solution has the potential for oxidative modification and degradation, limiting its therapeutic use. Recently, it has been shown that naringenin may have potential use in the treatment of eye diseases (inhibition of corneal neovascularization, prevention of retinal damage in diabetic retinopathy, and treatment of uveitis, etc.) due to its antioxidant and anti-inflammatory activities [50]. PVP can improve its water solubility by forming complexes with poorly water-soluble naringenin. For this purpose, Wang et al. [49] firstly dissolved naringenin and PVP 17 PF in ethanol for the preparation of nanocomplex. After the evaporation of solvent, thin dry film was hydrated with a buffer solution (pH 6.5) under normal pressure. Later, the non-complexed naringenin was removed by passing the prepared mixture through a 0.22 μm filter and then re-filtered using 0.22 μm filter to obtain a sterile ophthalmic nanocomplex formulation containing naringenin. It was determined that the optimum formulation obtained using PVP 17 PF and naringenin at a ratio of 20:1 (w/w) had a complexation efficiency of 98.51%, had a small mean particle size of 6.73 nm, and showed a homogeneous size distribution (PDI:0.254). It was determined that the *in vitro* antioxidant activity, *in vitro* membrane permeability, and *in vivo* anti-inflammation efficacy of naringenin were significantly improved with the use of naringenin-containing nanocomplex. Besides, they evaluated the ocular biodistribution of the naringenin-containing nanocomplex administered topically to the rabbits'eyes and found that the levels of naringenin in the cornea, aqueous humor, conjunctiva, and iris-ciliary body after application of the nanocomplex to the rabbit's eye were 5.22-, 10.16-, 7.43-, and 34.02-fold higher at 30 min, and 2.31-, 8.33-, 1.54-, and 1.57-fold higher at 60 min, respectively, when compared with the use of free naringenin solution [49].

CDs are relatively large molecules consisting of (α-1,4)-linked α-d-glucopyranose units. They are cyclic oligosaccharides with a hydrophilic outer surface and a hydrophobic central cavity and form water-soluble inclusion complexes with many lipophilic compounds. α-Cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, which contain six, seven, and eight glucopyranose units, respectively, are commonly found as natural cyclodextrins and differ in cavity size, their molecular weight, and solubility. Its low cost and complexing ability make β-cyclodextrin a very useful pharmaceutical complexing agent. Their toxicity especially at high concentrations limits the use of cyclodextrin complexes and thus the dose level. As the cyclodextrin complexes' formation requires specific molecular properties this approach may not work for some compounds [52]. CDs can be easily modified to change their physicochemical properties [53]. Cyclodextrin derivatives [hydroxypropyl (HP)-β-CD, sulfobutyl ether (SBE)-β-CD, HP-γ-CD, etc.] with improved properties are available but tend to be expensive [52]. They are also versatile oligosaccharides that can be used in combination with other excipients such as polymers to achieve a synergistic effect. CDs have been shown to be compatible with many polymers (synthetic or natural) [53]. By preparing CD complexes of poorly soluble active substances/compounds, their water solubility and dissolution characteristics can be changed/improved. Thus, CDs play an important role in improving the oral bioavailability of active substances/compounds whose absorption is limited by the dissolution rate. Also, in recent years, CD inclusion complexes have been investigated for ocular delivery. CD complexes have been shown to be useful in the treatment of eye diseases such as glaucoma, eye infection, corneal inflammation and AMD. For example, HP-β-CD has been extensively researched for its potential to show lower toxicity, improve the solubilization and stability of drugs/compounds, reduce ocular irritation, and increase ocular drug/compound permeability and bioavailability [53]. A study in which the ocular pharmacokinetics of baicalein was evaluated after topical application. Baicalein, a flavone originally extracted from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora*, is a poorly water-soluble compound, thus, HP-β-CD that form inclusion complex with hydrophobic drug molecule was used to improve the solubility of baicalein. After the administration topically of baicalein suspension (1%) or baicalein-HP-β-CD formulation (1%) to rabbits'eye, cornea and aqueous humor were collected to determine baicalein concentrations using HPLC. It was found that compared with baicalein suspension, baicalein- HP-β-CD formulation caused significant solubilization of baicalein in the precorneal area, thereby providing a significant increase

in baicalein levels in the rabbit's cornea and aqueous humor [54].

For the effective ocular delivery of hesperidin, changes in its physicochemical properties and *in vitro* ocular tissue permeability were investigated by preparing the complex of hesperidin with various ratios of HP-β-CD by Majumdar and Srirangam [55]. Hesperidin has potential in the treatment of cataracts, diabetic retinopathy and AMD. However, it shows poor water solubility. The poor solubility of hesperidin was dramatically improved with the use of HP-β-CD. In addition, Majumdar and Srirangam [55] performed a corneal permeation study using a side-by-side diffusion apparatus and various ocular tissues (cornea, sclera and sclera with RPE) isolated from the rabbits. The permeability of hesperidin in the presence of HP-β-CD across the sclera was about ten-fold higher than that across the cornea and sclera with RPE. It was observed that the corneal permeability of hesperidin in the presence of HP-β-CD from apical to basolateral direction and vice versa was not statistically different and as a result, no carrier-mediated process (*influx* or *efflux*) was involved in the corneal permeation of hisperidine [55].

In addition, poly(ethylene glycol) (PEG), a synthetic polymer with hydrophilic properties, PEG has been used both alone or in combination with other polymers such as PLGA to prepare ocular delivery systems [56]. PEG nanocomplexes can be prepared to obtain long-acting and sustained-release formulations of active substances/compounds [57]. In a study on the use of catechin, a naturally occurring flavonol, in dry eye disease, the therapeutic effect of the nanocomplex of catechin and PEG in the treatment of dry eye disease in a dry eye mouse model was investigated. Catechin and PEG nanocomplexes containing different ratios of PEG (catechin:PEG=1:1, 1:5, and 1:10 w/w) were prepared. They stated that the ratio of PEG is important for the effectiveness of nanocomplexes and the highest catechin-PEG weight ratio (1:10) is the most convenient system for the treatment of dry eye model. It was found that catechin:PEG nanocomplex (1:10) increased tear production and anti-inflammatory activity, and also stabilized corneal epithelium in the dry eye model. Catechin, a potent antioxidant, its propensity to act as a dose-dependent prooxidant, and its low bioavailability attributed to poor solubility in water can be enhanced by the use of PEG-catechin nanocomplexes [57].

Biopolymers are attracting great interest in many application fields such as food or pharmaceutics. In this context, proteins and polysaccharides are widely used for drug delivery/nutraceuticals [58]. Chitosan nanoparticles have been commonly prepared as delivery systems for active substances, nutraceuticals, gene, and protein delivery. Chitosan, a polyaminosaccharide obtained by N-deacetylation of chitin, is used in various fields (pharmaceutical, biomedical, food, etc.) due to its, biocompatibility, biodegradability, safety profile, bacteriostatic, and mucoadhesive properties. Ionotropic gelation is the mostly used method for the preparation of chitosan NPs. It is a method based on the electrostatic interaction between negatively charged polyanions (tripolyphosphate, hexametaphosphate, dextran sulfate, etc.) and positively charged amino sugar monomeric units of chitosan. While chitosan NPs have many benefits as drug delivery systems, there are many hurdles that need to be resolved to realize the clinical potential of these NPs [59].

Another study was conducted in which naringenin-containing sulfobutylether-β-cyclodextrin/chitosan ophthalmic nanoparticles were prepared for topical application. For this purpose, naringenin was first complexed with sulfobutylether-β-cyclodextrin, which can significantly increase the solubility of poorly soluble compounds. Secondly, chitosan nanoparticles were prepared as a result of the ionic gelation of the obtained complex with chitosan. The average particle size of the prepared nanoparticles was about 446 nm and their zeta potential value was +22.5 mV. It was observed that the nanoparticles were non-irritant for the rabbit eye and increased the residence time of naringenin in the eye compared to the naringenin suspension [60].

Gelatin, obtained by partial hydrolysis of collagen, is a natural biopolymer and has been widely used for the encapsulation of drugs/nutraceuticals/biologically active compounds to treat various disease such as cancer, eye diseases [43,61,62]. Gelatin nanoparticles for topical application are preferred because gelatin is biodegradable and biocompatible and also collagen, which is the source of obtaining gelatin, is the main component of the corneal stroma [62]. Tseng et al. [63] prepared cationic gelatin nanoparticles for ocular delivery and evaluated the nanoparticles *in vitro* and *in vivo*. They showed that the cationic gelatin nanoparticles were non-toxic to human corneal epithelium cells in *in vitro* study, and non-irritating to the eyes of rabbits. The cationic gelatin nanoparticles efficiently adsorbed on the negatively charged cornea of the rabbits and retained in the cornea longer than other ophthalmic solutions [63].

Chuang et al. [43] prepared kaempferol containing-gelatin nanoparticles by a two-step desolvation method using glutaraldehyde (GA) as a cross-linker for the treatment of corneal neovascularization that is one of the main causes of vision loss. Kaempferol is a dietary flavonoid and has antioxidant and antitumor effects. The particle size, zeta potential, and encapsulation efficiency of the prepared nanoparticles in optimum condition (0.4% (v/v) GA for 3 h; 1% (*w/v*) gelatin Type A) were about 85 nm, +25.6 mV, and 95%, respectively. The authors also investigated the effects of kaempferol containing-gelatin nanoparticles on corneal neovascularization model induced in mice. They reported that the mice treated with kaempferol containing-gelatin nanoparticles showed a lower corneal neovascularization ratio that indicates a better therapeutic condition for inhibition of vessel formation and the use of nano-formulation as eye drops may be useful for effectively treating corneal neovascularization [43].

The epigallocatechin gallate, is a major flavonoid in green tea, has antioxidant, anti-inflammatory, and pleiotropic effects [13,64]. It is therapeutic in various inflammatory diseases (dry eye syndrome, atherosclerosis, and arthritis) and inhibits inflammation-related autoimmune disorders [62]. Epigallocatechin gallate is effective on the condition of the eye and the physiology of vision [62]. The symptoms of dry eye syndrome can be summarized as an unstable tear film, visual disruption, and discomfort. There is inflammation of the ocular surface, tear hyperosmolality, and potential damage to the ocular surface. Inflammatory cytokines (such as IL1β, IL6, TNFα, and IFNγ) are known

to play a role in the ocular inflammation associated with dry eye syndrome [62]. Nano-sized systems have been developed for epigallocatechin gallate to protect it against undesirable environmental factors (oxygen, humidity, light), avoid degradation, extend its shelf life, and provide a modified release [13]. Huang et al. [62] developed epigallocatechin gallate-containing gelatin nanoparticles with surface decoration by hyaluronic acid for the treatment of dry-eye syndrome. The mean particles size and zeta potential values of the obtained nanoparticles with different concentrations (0-250 μg/mL) of hyaluronic acid ranged from about 142-323 nm and (+)23.2-(-)35.2 mV. The zeta potential values decreased proportionally with the addition of hyaluronic acid (the zeta potential values of the nanoparticles were (+)9.2 mV and (−)35.2 mV at the hyaluronic acid concentrations of 62.5 μg/mL and 250 μg/mL, respectively). The encapsulation efficiency values were more than 97%. The authors selectively used the nanoparticles with added 62.5 μg/mL hyaluronic acid for further experiments to maintain the cationic surface charge of the NPs. The anti-inflammatory effect of the selected nanoparticles on lipopolysaccharide-stimulated human corneal epithelium cells were evaluated *in vitro*. It has been reported that the nanoparticles down-regulate gene expression of IL6, TNFα, and IL8 in inflamed human corneal epithelium cells. Besides, they examined the therapeutic effect of these nanoparticles in a dry-eye syndrome rabbit's model. The ocular surface of the rabbits treated with nanoparticles topically twice daily exhibited normal corneal architecture with no appreciable change in inflammatory cytokine levels in corneal lysate, improving associated clinical signs such as tear secretion. Therefore, it was emphasized by the authors that epigallocatechin gallate-containing gelatin nanoparticles with surface decoration by hyaluronic acid have the potential to be used as eye drops (the suspension of nanoparticles) for the treatment of dry-eye syndrome [62].

Polymeric micelles are delivery systems prepared using amphiphilic block copolymers. They are characterized by a core-shell structure resulting from the self-assembly of in aqueous solutions [65,66]. Polymeric micelles have lower critical micelle concentration and higher kinetic stability compared to micelles formed by low molecular weight surfactants. Easy preparation, nano-size, and good solubilization properties of polymeric micelles are beneficial factors for their administration by different routes. Polymeric micelles are used in the pharmaceutical field to increase the solubility of drugs with poor water solubility, improve the bioavailability of drugs, provide modified drug release and reduce their side effects. Amphiphilic diblock copolymers such as PEG and polystyrene, and triblock copolymers such as poloxamers, and ionic copolymers such as PEG-poly(ε-caprolactone)-g-polyethyleneimine) are widely used for the preparation of polymeric micelles. There is a nanomicellar formulation of cyclosporine (CEQUA™) for ocular administration approved by the FDA in 2018 to increase tear production [66].

Myricetin, a natural flavonol compound, has beneficial bioactivities such as anti-inflammatory, antioxidant, and antimicrobial activities. However, its clinical use is limited due to the characteristics of myricetin such as poor water solubility, poor stability in aqueous/physiological media, and poor bioavailability [67]. Sun et al. [67] developed myricetin-containing polyvinyl caprolactam–polyvinyl acetate–PEG graft copolymer micelles using the thin-film hydration method to increase the efficacy of myricetin in eye disease treatments. The size, zeta potential, and encapsulation efficiency of the selected polymeric micelle formulation (polymer:myricetin weight ratio=18:1) containing myricetin for further studies were 60.72 nm, (-)2.29 mV, and 99.5%, respectively. They found that micelles significantly increased the water solubility and stability of myricetin, which provides flexibility in the design of eye drops for myricetin. Sun et al. [67] reported that myricetin-containing polymeric micelles greatly enhanced the *in vitro* cellular uptake, *in vivo* corneal permeation (in mouse eyes), and *in vivo* anti-inflammatory activity (in rabbit eyes with the inflammation induced by sodium arachidonate solution) of myricetin.

2.2. Lipid-based delivery systems containing flavonoids

Besides, the use of lipid-based delivery systems (liposomes, solid lipid nanoparticles, nanoemulsion, etc.) provides improvements/increases in the solubility, absorption and bioavailability of poorly water-soluble drugs/compounds [68]. Liposomes contain a phospholipid bilayer surrounding an aqueous core. Liposomes, biodegradable and biocompatible, are delivery systems that can be prepared from nano size to micro size using different preparation methods such as thin-film method, reverse phase evaporation method, membrane extrusion, sonication, microfluidic technique [69,70]. Liposomes with different compositions [using different phospholipids (such as egg or soybean phosphatidylcholine, dipalmitoylphosphatidylcholine, phosphatidylserine) and cholesterol content], structure (large unilamellar vesicle, small unilamellar vesicle, multilamellar vesicle*)* and charge (e.g. using phospholipids with different charges) can be prepared. Cholesterol is added to the formulation to increase the stability by improving the rigidity of the membrane. They can contain a wide variety of hydrophilic and hydrophobic diagnostic, active substances or biologically active compounds, protecting the encapsulated agents from environmental conditions and metabolic processes [69,71]. Because of their versatile nature, liposomes offer some advantages for the treatment of both anterior and posterior segment eye disorders. By binding to the corneal surface and increasing residence time, they can improve the permeation of poorly absorbed compounds/active substances and increase the therapeutic effect and reduce higher dose-related toxicity [72].

Other common lipid-based delivery systems are solid lipid nanoparticles and nanostructured lipid carriers [73]. Lipid-based nanoparticles have been developed to overcome some of the limitations of polymeric nanoparticles, such as the high cost and the scarcity of safe polymers with legal approval. These lipid nanoparticles have the potential to improve the performance of pharmaceuticals, neutraceuticals, and other compounds due to their small size with large surface area, and interaction of phases at interfaces [74]. Solid lipid nanoparticles are prepared by dispersing physiological lipids in water or an aqueous surfactant solution. Potential disadvantages were seen with solid lipid nanoparticles, such as the relatively high water content of the dispersions (≥70%), poor drug loading capacity, and active substance/compound expulsion

during storage. The structure of the lipid matrix, the solubility of the active substance/compound in the lipid melt, and the polymorphic state/arrangement of the lipid matrix limit the drug loading capacity of the conventional solid lipid nanoparticles. Therefore, higher drug loading requires the use of more complex lipids [74]. Solid lipid nanoparticles are particularly useful in ocular delivery as they can improve the ocular bioavailability of hydrophilic and lipophilic drugs/compounds by increasing their corneal absorption. Another advantage of solid lipid nanoparticles is that they allow autoclave sterilization. Sterilization is necessary step for the ophthalmic formulations [75]. Nanostructured lipid carriers were developed to overcome potential difficulties with solid lipid nanoparticles. Biodegradable and compatible solid lipids (such as steroids, fatty acids, monoglyceride, diglyceride, triglyceride, and waxes) and liquid lipids (such as oleic acid, castor oil, Miglyol® 812, olive oil) and surfactants for their preparation were used [74,76]. The presence of liquid lipids in the formulation leads to structural imperfections of solid lipids and a less regular crystal arrangement, thereby preventing drug/compound leakage, and providing a high drug/compound loading. They are promising delivery systems for oral, ocular, parenteral, pulmonary, topical and transdermal use [76].

Nanoemulsions, kinetically stable system, have nanosized (generally about 200-600 nm) droplet size. Nanoemulsion formulations are prepared using different surfactants, oil phases, and aqueous phases. Their composition and structure might be controlled for the encapsulation and efficient delivery of active substances/compounds. Nanoemulsions have potential application in the pharmaceutical, cosmetic and food fields. They are widely used for the delivery of active substances/compounds and nutraceuticals. By preparing nanoemulsion formulations of poor-water soluble active substances/compounds, the solubility and bioavailability of these compounds are increased [77]. Nanoemulsions are potent delivery systems for ophthalmic use due to their high ability of active substances/compounds penetration into the deeper layers of the ocular structure and the aqueous humor [78].

Quercetin, a common flavonol, has been found to have potent anti-inflammatory, antioxidant, and anti-fibrotic effects in various tissues in *in vitro* and *in vivo* studies. Especially, studies evaluating the efficacy of quercetin for the treatment of dry eye, corneal inflammation, keratoconus, and the neovascularization of the cornea draw attention [42]. It protects eye cells from oxidative damage [79]. After oral administration, its exposure to intense metabolism limits the systemic effects of quercetin [42]. For this reason, some studies have been carried out on the preparation of different dosage forms containing quercetin to be administered by different application routes.

In a study, quercetin-containing lipid-based nanoparticles (solid lipid nanoparticles and nanostructured lipid carriers) and quercetin-containing hot melt cast films were prepared and also evaluated the permeability of quercetin for nanostructured lipid carrier and hot melt cast film formulations across rabbit cornea in a side-by-side diffusion apparatus. The particle sizes, zeta potentials, and the entrapment efficiencies of nanostructured lipid carriers and solid lipid nanoparticles were 46.1 and 65.4 radius in nm, (-)16.2 mV and (-)12.3 mV, and 93.4% and 90.9%, respectively. Transcorneal flux values were found to be 0.026 μg/min/cm^2 for quercetin (control), about 0.036 μg/min/cm^2 for quercetin-containing nanostructured lipid carrier, and about 0.144 μg/min/cm^2 for quercetin-containing hot melt cast films. As the result of this study, quercetin-containing hot melt cast films showed a better transcorneal permeability. It was stated that lipid-based nanoparticles and hot melt cast films might be beneficial for topical application of quercetin to the eye [45].

Wang et al. [80] prepared puerarin and scutellarin-loaded cationic lipid nanoparticles for ophthalmic application. Puerarin, an isoflavonoid compound, is derived from the root of *Pueraria lobata* (Willd.) Ohwi, commonly known as Gegen (Chinese name) in traditional Chinese medicine. It is widely used in the treatment of cancer, cerebrovascular disorders, cardiovascular diseases, diabetes and diabetic complications, Parkinson's disease, and Alzheimer's disease. It also has protective effects against oxidative damage, inflammation, osteonecrosis, hyperlipidemia, fever and disorders caused by alcohol and reduce intraocular pressure [80,81]. Scutellarin, a flavonoid, is derived from *Erigeron breviscapus* (Vant.) Hand.-Mazz, and is used in the traditional Chinese medicine. Breviscapine, a flavonoid extract of *Erigeron breviscapus*, contains ≥90% scutellarin and ≤10% apigenin-7-O-glucronide and is classified as a prescription drug in China. Data from clinics and experimental studies have demonstrated the benefits and efficacy of breviscapine and scutellarin in the treatment of cardiovascular diseases, cerebrovascular diseases, and diabetic complications. It has also been shown to be effective in regulating intraocular pressure. However, the low bioavailability of scutellarin due to its low solubility and its short half-life in biological systems limit the efficacy of scutellarin in some clinical applications [82]. Puerarin and scutellarin are used to treat retinopathy and glaucoma [80]. Wang et al. [80] stated that scutellarin can help protect the optic nerve and improve optic nerve microcirculation, and puerarin can reduce intraocular pressure, and therefore, with the co-administration of these two compounds, it can be a focal point in relief of symptoms and the treatment of ocular diseases. They evaluated the preocular retention time of puerarin and scutellarin-loaded cationic lipid nanoparticles using a noninvasive fluorescence imaging system, besides they performed corneal permeation study using excised rabbit corneas [80]. Wang et al. [80] prepared the puerarin and scutellarin-loaded cationic lipid nanoparticles using 1-oleoyl-rac-glycerol, lecithin, cholesterol, Tween 80, pluronic F127, Gelucire® 44/14, and octadecyl quaternized carboxymethyl chitosan. The mean particle size of puerarin and scutellarin-loaded cationic lipid nanoparticles was found to be 181 nm with a polidispesity index of about 0.22 and their zeta potential was 23.8 mV. The particle size and distribution are important parameters for uptake of nanoparticles through the cornea. The positive zeta potential value of the nanoparticles is due to the use of octadecyl quaternized carboxymethyl chitosan. Moreover, the use of F127 as a stabilizer has a beneficial effect on increasing the stability of the nanoparticle dispersion. In corneal permeation study, it was found that compared with puerarin solution and scutellarin solution, puerarin and scutellarin-loaded cationic lipid nanoparticles exhibited a

2.01-fold and 1.23-fold increase in the apparent corneal permeability coefficient, respectively. Therefore, the nanoparticles were more taken up by the rabbit cornea. Due to the high viscosity of puerarin and skutellarin-loaded cationic lipid nanoparticles, an increased retention time on the cornea was observed for nanoparticles. It was found that compared with puerarin solution and scutellarin solution, puerarin and scutellarin-loaded cationic lipid nanoparticles exhibited a 2.33-fold and 2.32-fold increase in the AUC values, respectively [80].

However, for hydrophilic compounds such as epigallocatechin gallate, the lipophilic nature of the corneal epithelium is a hindrance. To overcome this hindrance, positively charged lipid nanoparticles containing epigallocatechin gallate were prepared in the literature [62,83]. Fangueiro et al. [83] prepared cationic lipid nanoparticles containing epigallocatechin gallate using softisan® 100 , glyserol, Lipoid® S75, ascorbic acid, poloxamer 188, and cetyltrimethylammonium bromide/dimethyldioctadecylammonium bromide, by multiple emulsion (w/o/w) technique. The particle size, and zeta potential values of epigallocatechin gallate-loaded cationic lipid nanoparticles containing cetyltrimethylammonium bromide or dimethyldioctadecylammonium bromide were found to be about 149 and 144 nm, and 20.8 and 25.7 mV, respectively. The polidispersity index values of epigallocatechin gallate-loaded cationic lipid nanoparticles were less than 0.25 [83]. They performed e*x vivo* permeation study using isolated rabbit sclera and cornea as a membrane mounted on Franz-type diffusion cell and found that epigallocatechin gallate showed higher permeation than retention in the sclera and cornea when cationic lipid nanoparticles containing cetyltrimethylammonium bromide were used. However, when using cationic lipid nanoparticles containing dimethyl dioctadecyl ammonium bromide, retention in the sclera and cornea was higher than penetration. The results showed that cationic lipid nanoparticles could improve the residence time and bioavailability of epigallocatechin gallate [83].

As a result of the electrostatic interaction between the negatively charged ocular mucosa and the positively charged nanoparticles, the retention time of the compounds such as epigallocatechin gallate on the eye surface and their ocular absorption can be improved [62].

Nanoemulsion and solid lipid nanoparticle formulations for ocular quercetin delivery were prepared by Liu et al [79] to take advantage of the antioxidant capacity of quercetin by providing its physical and chemical stability. The particle size, polydispersity index, zeta potential, and entrapment efficiency % values for quercetin-loaded solid lipid nanoparticles were determined as 143 nm, 0.27, (-)16.57 mV, and 66.56%. On the other hand, the droplet size, polydispersity index, zeta potential, and entrapment efficiency % values for quercetin-containing nanoemulsion formulation were found to be 138.3 nm, 0.25, (-)23.97 mV, and 74.26%. In addition, quercetin-loaded solid lipid nanoparticles showed the lowest cytotoxicity on retinal ganglion and cornea cells. Compared with free quercetin, quercetin-loaded solid lipid nanoparticles effectively protected cornea and retinal ganglion cells from oxidative damage induced by H_2O_2. Besides, scleral and corneal delivery of these formulations was confirmed using *ex vivo* porcine eyes. Quercetin-loaded solid lipid nanoparticles had a higher transcorneal flux for quercetin (158.5 μg/cm^2/day) compared to the quercetin-containing nanoemulsion formulation (130.7 μg/cm^2/day). Solid lipid nanoparticles have been shown to be more suitable for transocular delivery [79].

Surgery for the treatment of cataract, one of the leading causes of blindness globally, is accompanied by some complications, especially intraocular infections. Oxidative stress is one of the important causes of cataract development. Huang et al. [84] stated that nanoformulations may be beneficial for delaying or preventing cataracts, and therefore, they prepared chitosan-coated liposomal formulations containing a combination of lanosterol (It is a tetracyclic triterpenoid compound effective in preventing/reversing protein aggregation in cataracts) and hesperetin by thin film evaporation-active extrusion method. Hesperetin is a bioactive flavanone that is found in some vegetables and fruits (young citrus fruit, tomatoes, apples etc.), being thus easily accessible and isolated at low cost. Active hesperetin can be obtained from hesperidin hydrolysis by the intestinal bacteria. Similar to other flavonoids, it has many biological activities (anti-inflammatory, antioxidant, anti-diabetic, anticancer, estrogenic, neuroprotective, vasoprotective and cardioprotective effects, lipid lowering abilities) beneficial to human health. However, it has poor water solubility due to its hydrophobic nature and does not sufficient stability in the gastrointestinal tract; therefore it has low oral bioavailability [85].

The mean particles size of a combination of lanosterol and hesperetin-loaded chitosan-coated liposomes prepared by Huang et al. [84] was 224 nm with a polydispersity index of 0.25. They found that the coated-liposomes were cytocompatible and showed slow and sustained release of lanosterol and hesperetin from chitosan-coated liposomes. The retention time of the chitosan-coated liposomes in the cornea was more than a week. The authors also investigated the effect of lanosterol and hesperetin-loaded chitosan-coated liposomes in preventing/delaying selenite-induced cataract in rats and reported that the coated liposomes increased the retention time for lanosterol and hesperetin in cornea and allowed the upregulation of antioxidant status and ultimately led to a delay in cataract progression [84].

In another study, for the ophthalmic delivery of baicalin, different vesicular systems such as liposome, penetration enhancer vesicles or transfersomes were prepared by thin film hydration technique using soybean phosphatidylcholine (SPC) with/without cholosterol and/or sorbitol or SPC and labrasol (penetration enhancer) with/without cholosterol and/or sorbitol or SPC and bile salts (such as sodium taurocholate) with/without cholosterol and/or sorbitol. The mean vesicle size and zeta potential values of baicalin-containing vesicular systems were in the range of 667.9- 2712 nm and (-)14.4- (-)31.5 mV, respectively. The EE% values obtained for baicalin-containing vesicular systems were ranged from 25.96 to 99%. They carried out Draize test and found that all baicalin vesicular systems and baicalin control solution had good ocular tolerance and were non-irritant. Besides, the ocular pharmacokinetics parameters for the vesicular systems were studied in rabbits. For this purpose, sterile vesicular formulations or baicalin control solution were dropped into the conjunctival sac, then aqueous humor samples were collected at certain time intervals, and the concentration of baicalin in the samples was analyzed by

HPLC. The author found that the C_{max} values were found to be 4.073 µg/mL for liposomes, 2.313 µg/mL for penetration enhancer vesicles, 1.503 µg/mL for transfersomes, and 2.228 µg/mL for the baicalin control solution. The $AUC_{0-\infty}$ values of penetration enhancer vesicles, transfersomes, or liposome were 5.4, 4.6 and 4.4-fold higher, respectively, compared to the $AUC_{0-\infty}$ value of the baicalin control solution [86].

Liu et al. [14] prepared the solid lipid nanoparticles containing baicalin for ocular administration by emulsification/ultrasonication method using soya phospholipids SL-100, and triglyceride as oil phase, and Poloxamer 188 as surfactant. They found that the solid lipid nanoparticles were spherical and the encapsulation efficiency, particle size, and zeta potential values of these nanoparticles were approximately 62%, 91 nm, and (-)33.5 mV, respectively. Baicalin-loaded solid lipid nanoparticles enhanced the corneal permeability of baicalin. Furthermore, they carried out pharmacokinetic studies in rabbits and found that the bioavailability of baicalin can be significantly increased with the use of solid lipid nanoparticles [14].

2.3. Metallic nanoparticles

Gold is a multifunctional material used in medical applications due to its antioxidative, bacteriostatic and anticorrosive photoacoustic and photothermal properties. Due to the presence of thiol and amine groups, it can be functionalized by allowing conjugation of various compounds such as antibodies or active substances and produced at nanoscale [87]. Spherical gold nanoparticles have large surface-to-volume ratio, excellent biocompatibility, optoelectronic properties, and low toxicity properties regarding their shape and size. The loading of active substances/compounds onto gold nanoparticles can be accomplished via covalent conjugation or non-covalent interactions. Non-covalent interactions (affinity, electrostatic and hydrophobic interactions) are widely used in the fields of delivery and sensing due to reversible nature and their ease of release; covalent conjugation of compounds to gold nanoparticles is utilized in imaging. It has been shown that cell membrane penetration can be regulated by surface ligand arrangement on these nanoparticles. Therapeutics can be delivered to cells via passive or active targeting mechanisms [88].

Li et al. [89] developed poly(catechin) capped-gold nanoparticles containing amfenac to treat dry eye disease. Catechin as a flavonol has an antioxidant effect, while amfenac is a nonsteroidal anti-inflammatory drug. They aimed to use these nanoparticles to simultaneously prevent (to achieve a synergistic effect) the inflammation induced by cyclooxygenase enzymes, and also oxidative stress induced by reactive oxygen species, which are the causes of dry eye disease. As a result of this study, they showed that poly(catechin) capped-gold nanoparticles containing amfenac have both antioxidant and anti-inflammatory effects. In addition, the researchers conducted *in vivo* studies to demonstrate the biocompatibility and the dual effects of the nanoparticles. They showed that the nanoparticles had good tolerability and provided a rapid recovery in the rabbit dry eye model [89].

3. Conclusion

Flavonoids appear to be promising compounds in the prevention/treatment of various ocular diseases. However, most flavonoids are poorly soluble in water and have low bioavailability and stability, limiting their use. *In vitro* and preclinical studies have shown that nano-sized delivery systems improve the water solubility, bioavailability, stability, and consequent *in vivo* activity of flavonoids. However, more studies and especially well-constructed clinical studies are required to examine the effects of flavonoid-containing delivery systems (especially nano-sized systems) on ocular diseases.

Compliance with Ethical Standards

There is no conflict of interest to disclose.

Conflict of Interest

The author(s) declares no known competing financial interests or personal relationships.

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