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ΦΑΡΜΑΚΕΥΤΙΚΗ, 38, ΙΙ, 2026 | 97-111 ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

PHARMAKEFTIKI, 38, II, 2026 | 97-111 RESEARCH ARTICLE

Liposomal Drugs in Ophthalmotherapy: Development and Clinical Translation

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https://doi.org/10.60988/p.v38i2.149

KEYWORDS: drug delivery systems; liposomes; emulsion; bioavailability; ophthalmology; eye drops

ARTICLE INFO:
Received: September 1, 2025
Revised: November 24, 2025
Accepted: March 12, 2026
Available on line: May 19, 2026

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ABSTRACT

The success of ophthalmotherapy depends significantly on the physicochemical affinity or antagonism of the eye structures and the drug. The pronounced hydrophobicity of the corneal epithelium promotes the delivery of lipophilic drugs to the eye and limits the penetration of hydrophilic systems. The translation of active pharmaceutical ingredients incorporated into drug delivery systems can be a targeted approach to the optimization of the ophthalmotherapy. Liposomal systems have an uncontested status among known drug delivery systems due to a complex of sought-after characteristics of liposomal nanoparticles.

The aim of this article is to review the knowledge accumulated to date on the use of liposomal forms in ophthalmological clinical practice as well as perspective composition under development. An analysis of the market of liposomal ophthalmic drugs, well-established in clinical practice, has been conducted. In particular, the liposomal form of verteporphyrin, vitamins A and E, the bioflavonoid quercetin, as well as drugs based on "empty" liposomes were discussed. In addition, data on promising liposomal ophthalmic drugs that are under development are provided.

The results of current clinical and experimental studies reflect the advantages of the effectiveness of action, safety and targeting of ocular transport of liposomal forms of drugs of variable nature in the prevention and treatment of a wide range of common ophthalmological pathologies. Optimized pharmacotoxicological profile and verification of ophthalmological quality of liposomal preparations in combination with a favorable pharmacoeconomic basis substantiate the irreplaceable role of the liposomal factor in modern ophthalmotherapy technologies.

1.Introduction

The result of ophthalmotherapy as an alternative or accompaniment to invasive treatment is determined by a sequential algorithm which includes the stages of adsorption, bioavailability, administration and maintenance of effective concentration of the drug in the target structures of the anterior and posterior segments of the eye. The implementation of such an algorithm is a priori determined by the method of drug administration: the creation of intraocular therapeutic concentration of the drug is complicated by systemic losses and the hemato-ocular barrier with injected or oral administration, and by frequent formation and significant clearance of tears with local administration.

The success of ophthalmotherapy may also depend on the physicochemical affinity or antagonism of the eye structures and the drug. Thus, the pronounced hydrophobicity of the corneal epithelium promotes the delivery of lipophilic drugs to the eye and limits the penetration of hydrophilic systems.

The translation of active pharmaceutical ingredients (APIs) incorporated into transport systems (drug delivery systems or DDSs) can be a targeted approach to the optimization of the ophthalmotherapy. DDSs can improve the balance between efficiency and safety of API due to increased bioavailability and targeting of action, as well as expand the methods of clinical use of the drug, including the personalized medicine.

Liposomal systems have an uncontested status among known DDSs due to a complex of sought-after characteristics of liposomal nanoparticles, such as non-toxicity, safe biodegradation, controlled stability, adjustable nanosize and universal structure that provides affinity for both hydrophilic and lipophilic APIs[1-4]. According to the liposome size and the structure of the phospholipid bilayer, liposomal drugs are classified into: small unilamellar vesicles (SUV) – single-layer particles with sizes in the range of 20 nm to 100 nm, large unilamellar vesicles (LUV) – single-layer particles with sizes in the range of 100 nm to 500 nm; multilamellar vesicles (MVL), consisting of several bilayers with sizes in the range of 10 μm to 60 μm. The amount of encapsulated API is determined by the number of bilayers and the size of the liposomes[5, 6].

At the turn of the 21st century, innovations in liposomal DDSs provided the basis for the development of more than 100 drugs for oncology, cardiology, nephrology, pulmonology, vaccine prophylaxis, antibacterial and antifungal therapy (Fig. 1).

The aim of this review is to summarize and analyze current achievements in the development and clinical use of liposomal ophthalmic drugs. Ophthalmology was a "belated branch" of the liposomal DDS genealogical tree. This factor still determines the gap between the significant amount of promising results of preclinical studies of liposomal drugs and the limited number of commercial liposomal drugs for ophthalmology. To reduce this gap, it is important to evaluate the influence of liposomal DDS on various aspects of pharmacotherapeutic efficacy and safety of liposomal drugs used in the clinic or developed for the interests of ophthalmology.

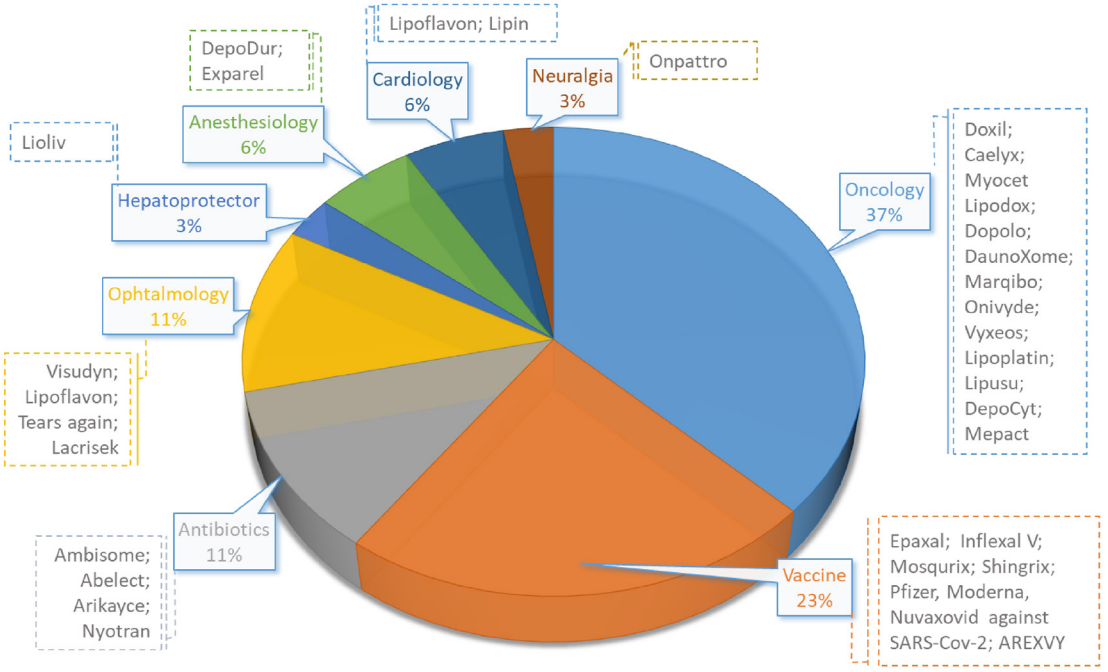

Figure 1: *Distribution of liposomal drugs on the market by medical application:*

The aim of this article is to review the knowledge accumulated to date on the use of liposomal forms in ophthalmological clinical practice as well as perspective composition under development.

2. Materials and Methods

To search for sources of information for the study, open access electronic resources of scientific periodicals were used: scientific databases Google Scholar, PubMed, Clarivate, Web of Science, Scopus, etc.; electronic repositories of higher education institutions and scientific institutions, where dissertation abstracts, scientific publications and other scientific works are stored, including the results of own previous research. Research methods were used: information search, theoretical analysis and systematization of data from scientific sources, logical analysis.

3. Results and Discussion

Registered Liposomal Drugs for Ophthalmology

"Visudyn" is one of the first licensed ophthalmic liposomal agents (Table 1) used in the treatment of classic subfoveal choroidal neovascularization caused by age-related retinal degeneration or pathological myopia[7]. Verteporphyrin (the API of "Visudyn") was encapsulated in liposomes based on dimyristyl phosphatidylcholine. Verteporphyrin possesses a chemotherapeutic effect due to its specific ability to generate reactive oxygen radicals during photosensitization, causing the destruction and occlusion of vessels in the neovascularization zone. The targeted effect of photodynamic therapy with "Visudyn" is based on the selective capture and

Table 1 – Registered liposomal ophthalmic drugs

Name of the drug, dosage form	**Manufacturer / developer of the drug**	**Composition of the API and lipids; liposome size**	**Therapeutic effect**
“TEARS AGAIN”, eye spray	OPTIMA Pharmaceutical GmbH, Germany	Soy phosphatidylcholine, vitamin A, vitamin E; 150 nm	Treatment of dry eye syndrome
“Lipoflavon”, lyophilizate for the preparation of eye drops	PJSC "PHARMSTANDART-BIOLIK", Ukraine; State Institution "Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine"	Egg phosphatidylcholine, quercetin; 130-160 nm	Treatment of diabetic retinopathy, cataracts, uveitis, dry eye syndrome, age-related macular degeneration, and keratitis
“Visudyn”, lyophilizate for the preparation of solution for infusion	Novartis Pharma S.A.S., France	Verteporphyrin, dimyristoyl phosphatidylcholine, egg phosphatidylglycerol, 140 нм	Photodynamic therapy for the treatment of eye diseases affecting blood vessels, such as the wet form of age-related macular degeneration, pathological myopathy and ocular histoplasmosis
“LipoLat”, lyophilizate for the preparation of solution for subconjunctival injection	Singapore Eye Research Institute	Latanoprost, egg phosphatidylcholine; 91-127 nm	Treatment of ocular hypertension (glaucoma). Pharmacological efficiency and duration of action of the liposomal form were studied on the glaucoma model in rabbits with different methods of administration of the drug

Liposomal latanoprost, lyophilizate for the preparation of solution for subconjunctival adminiastration	State Institution "Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine"; NanoMedTech LLC, Ukraine	Latanoprost, egg phosphatidylcholine, dipalmitoyl phosphatidylglycerol, cholesterol; 112-148 nm	Treatment of ocular hypertension (glaucoma). Pharmacological efficiency and duration of action of the liposomal form were studied on the glaucoma model in rabbits with different methods of administration of the drug
Liposomal cytochrome C, lyophilizate for the preparation of emulsion for eye drop	State Institution "Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine"; NanoMedTech LLC, Ukraine	Cytochrome C, egg phosphatidylcholine, dipalmitoyl phosphatidylglycerol; 100-120 nm.	Treatment of cataract. In rabbits cataract models, the prevention of its development, reduction of lens damage to the initial stages, normalization of enzyme activity and the content of lipid peroxidation products in the lens (85–95% of the norm) was shown. The liposomal formulation was more effective than the free form of cytochrome C.

retention of verteporphyrin by rapidly proliferating cells[8, 9] and involves local laser irradiation of the ocular location. In this case, the stable liposomal form of the drug ensures the transport of the API to the neovascularization zone after infusion, and the affinity of the phospholipid membrane of liposomes to lipoprotein fragments of plasma and endothelium enhances the targeted effect. The administration of the liposomal drug with subsequent laser activation at a wavelength of 689 nm leads to selective occlusion of the vessels of the choroidal neovascularization zone, but keeps large normal vessels of the eye shell open [10, 11].

"Lacrisek" is eye drops based on the vitamins A and E encapsulated in phospholipid liposomes. The liposomal form promotes not only the penetration of lipophilic vitamins into the eye tissues, but also creates a barrier on the surface of the eye that reproduces the lipid layer. This way, "Lacrisek" provides functional support for the lipid component of the eyelids and stabilizes the lipid layer of the tear film, which is crucial for the protective function of the tear fluid and the control of its evaporation[12].

"TEARS AGAIN" is a gel dosage form which contains the phospholipid itself (natural phosphatidylcholine) as a main API. The liposomal organization of phosphatidylcholine emulsion determines the possibility of rapid migration of the lipid compo-

nent into the eye after aerosol spraying of the gel[12, 13]. "TEARS AGAIN" was designed to compensate for the stability and thickness of the damaged lipid layer of the tear film. The drug normalizes the temperature of the eyelids in patients with dry eye syndrome complicated by hypersecretory dry keratoconjunctivitis. It should be noted that the phenomenon of polyfunctional pharmacological activity of so-called "empty" liposomes were previously demonstrated and used in the phosphatidylcholine-based drug "Lipin", which is widely used in obstetrics, nephrology and pulmonology[14].

"Lipoflavon" is an indicative case of liposomal drugs for ophthalmotherapy. It is produced in lyophilized form for preparing a preservative-free eye drops[15, 16]. "Lipoflavon" was created according to the DDS narrative as a transport system for the quercetin (natural flavonoid) by incorporating it into a matrix of phosphatidylcholine liposomes. The powerful antioxidant effect of quercetin (cited as a "universal antioxidant") determines a wide spectrum of its pharmacological activities, including anti-inflammatory, immunomodulatory, antitumor effect, etc.[17, 18]. The antioxidant activity of liposomal forms of quercetin and other polyphenols was confirmed[19, 20]. Experimental studies predicted the prospects of using of quercetin and some other polyphenols for the treatment of eye diseases[21-24]. However, the effect of free quercetin in the clinical ophthalmotherapy was not achieved due to the extremely low bioavailability of this API (no more than 5%). On the other hand, the liposomal form can provide a multiple increase in the bioavailability of quercetin and combine its specific antioxidant effect with the regenerating effect of phospholipid on cell membranes[25, 26]. These factors determined the polyfunctional use of "Lipoflavon" in ophthalmotherapy. With 20 years of clinical use, the effectiveness of "Lipoflavon" instillations was shown for keratitis of various etiologies, traumatic corneal erosion, in the postoperative period in patients with corneal syndrome after excimer laser vision correction and cataract extraction with intraocular lens implantation. The effect of the drug is manifested in a significant acceleration of regression of inflammatory processes and convalescence of patients, a reduction of the recovery period. The use of "Lipofavon" in complex treatment regimens for diabetic non-proliferative retinopathy (for example, with immunofan) and primary open-angle glaucoma (for example, with cycloferon) can reduce the manifestations of the inflammatory reaction, improve visual function and normalize systemic and local immunity, the violation of which accompanies the development of the pathological process [27-31].

The combination of pronounced anti-inflammatory effect, immunocorrective action and positive dynamics of re-epithelialization processes substantiated the use of "Lipoflavon" also for the treatment of uveitis, chorioretinal burns and dry eye syndrome, including etiologically associated with herpetic keratitis or trauma of the eye surface[32, 33]. The results of clinical studies of "Lipoflavon" showed that its inclusion in the complex treatment of patients with herpetic keratitis and dry eye syndrome significantly reduced the severity of clinical symptoms that allowed to reduce the duration of treatment. The use of "Lipoflavon" in combination with traditional therapy allowed to significantly increase the effectiveness of therapy due to the reduction of the time of corneal epithelialization and resorption of infiltrates by 30.8% and 29.5%, respectively, compared with the control group of patients who had a traditional treatment without liposomal quercetin. A significant reduction in swelling of the cornea, epitheliopathy of the cornea and conjunctiva by almost 25% was also demonstrated. The use of "Lipoflavon" had a positive effect on the quantitative and qualitative indicators of tear production, in particular the Schirmer II test indicators increased by 29.7%, the tear film breakup time increased by 14.5%, the degree of folding decreased by 66%, and the height of the tear meniscus increased by 38.8%, respectively, compared to the group of patients who did not receive liposomal quercetin in the complex treatment [32].

The use of "Lipoflavon" in combined therapy of diabetic retinopathy in a clinical reduced proinflammatory cytokines (IL-1 and TNF-γ) by 17% and 14.5%, respectively, while the only traditional therapy reduced them by 9.5% and 4.9%, respectively ($p<0.001$). The use of "Lipoflavon" in the treatment

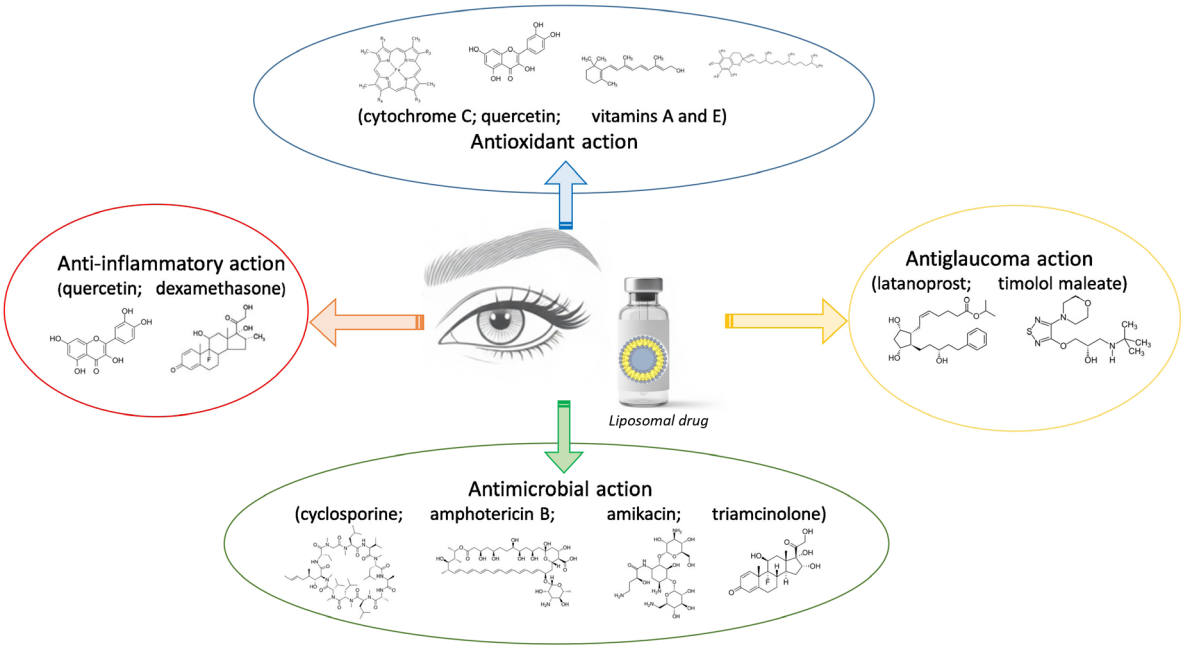

Figure 2: *Application of liposomes for ocular drug delivery*

of patients with diabetic retinopathy increased functional activity of the visual analyzer (sensitivity and lability) on indicators of threshold of electric sensitivity on phosphene by 16.2% and critical frequency of disappearance of flickerings on phosphene by 26.6%, and, as a result, improved visual functions on the average on 0,2 units (against 0,1 at traditional therapy) that testifies about more efficacy of the new modified method of treatment of patients with diabetic retinopathy[34].

In the context of expanding the clinical translation and ensuring the targeted effect of "Lipoflavon", the efficacy and safety of its variable periocular administration (subconjunctival, parabulbar, sub-tenon) in combination with clinical confirmation of the absence of systemic toxicity (using the example of "Lipoflavon-cardio", which is an injectable licensed drug with similar composition) were verified[35].

Liposomal Drugs for Ophthalmology under Development

An array of preclinical studies is represented by the development of liposomal drugs with sought after APIs of various natures for ophthalmotherapy of common eye diseases[36-40]. This section provides a summary of experimental studies of significant drugs in liposomal form and their ophthalmotherapeutic potential (Fig. 2).

For many years, in Ukraine, researchers of State Institution "Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine" (Kyiv), State Institution "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (Odesa), "Biolik" enterprise (Kharkiv), LLC "NanoNedTech" (Kyiv), etc. participated in the development of a number of liposomal forms of drugs

(quercetin, cytochrome C, latanoprost) and their preclinical and clinical studies. The current edition of the State Pharmacopoeia of Ukraine contains a Monograph on Liposomal forms[41].

Ukrainian researchers are constantly studying the pharmacological and clinical efficacy of the liposomal form of quercetin ("Lipoflavon") to expand its medical indications[35]. For example, a positive effect of liposomal quercetin on reparative osteogenesis was shown[42]. Radioprotective activity of liposomal form of quercetin in acute radiation syndrome was established[43]. Regarding ophthalmotherapy, the effects of "Lipoflavon" on metabolic processes in stage II acid corneal burns in models of keratitis and keratoconjunctivitis were studied[44, 45]. Furthermore, the antiinflammatory activity of "Lipoflavon" was demonstrated in models of exudative inflammation in mice, induced by subplantar administration of various phlogogenic agents[46]. The results showed that "Lipoflavon" in the quercetin dose range of 3.8–15.2 mg/kg statistically significantly inhibited carrageenan–induced swelling by 37.09-63.43 %. The antiexudative effect of "Lipoflavon" was demonstrated in a model of experimental inflammation caused by another phlogogenic agent – histamine. The inflammation in the group treated with "Lipoflavon" was reduced by 27.61-32.73 %. And also in the model of serotonin swelling, the positive dynamics of the antiinflammatory effect of the liposomal form of quercetin was in the range from 17.95 to 32.00%. The antiexudative activity of "Lipoflavon" exceeded diclofenac sodium in the model of exudative carrageenan swelling and was on the same level as the reference drug in other models[46].

In experimental ophthalmotherapy of abnormal intraocular pressure (IOP) and glaucoma, the advantages of liposomal agents containing synthetic prostaglandins were shown[47]. Among the latter, latanoprost, the active component of well-known eye drops for reducing IOP ("Xalatan" and its generics), is most in demand. The short-term hypotensive effect of this eye drops is due to weak penetration of latanoprost through the corneal epithelium that requires permanent daily instillations, leading to low patient compliance and violation of the treatment protocol[48, 49].

For liposomal forms with established in vitro gradual release of latanoprost, a prolonged hypotensive effect on IOP, competitive with instillations of commercial drop preparations of latanoprost, was predicted. The antihypertensive and antiglaucoma effect of latanoprost encapsulated in liposomes of different lipid composition was declared by a number of research[40, 47, 49-51], however, their effect on the manifestations of optic neuropathy was not discussed, and the hypotensive effect was established only in laboratory animals with normal IOP, which may not correlate with the activity in pathophysiologically formed ocular hypertension.

For liposomal latanoprost based on egg phosphatidylcholine ("LipoLat"), the advantages of the antihypertensive effect of the injectable liposomal form were demonstrated for the first time. In preclinical studies, the hypotensive effect of a single subconjunctival injection of "LipoLat" was manifested in a decrease in IOP by 10-12 mmHg and was maintained for up to 3 months with optimal ophthalmic safety, but the medical technology for using "LipoLat" in a clinical trial was not validated. At the same time, to achieve a similar effect (a decrease in IOP by 10 mmHg) with non-liposomal latanoprost eye drops, long-term daily use is necessary. Moreover, the use of free latanoprost in the form of daily instillations leads to a number of side effects[55].

An original composition of latanoprost in liposomes based on a mixture of egg phosphatidylcholine with dipalmitoylphosphatidylcholine and cholesterol was proposed and standardized for use in ophthalmology including such indicators as liposome size, API encapsulation, osmolality and pH[52, 53]. Long-term daily instillations for 10 weeks of liposomal latanoprost demonstrated a pronounced hypotensive effect in animals with an ocular hypertension model and reduced intraocular pressure by an average of 30.5% ($p<0.001$). Whereas, a single subconjunctival injection of liposomal latanoprost effectively reduced intraocular pressure in animals with an ocular hypertension model by an average of 36.7% ($p<0.001$) for 10 weeks. Thus, subconjunctival injections of liposomal latanoprost have pros-

pects for use in the treatment of patients with high IOP to improve pharmacoefficacy and compliance in the treatment of patients with ocular hypertension and glaucoma, it can provide a competitive clinical result and high compliance in comparison with daily instillations of the drug[54]. The prolonged antihypertensive activity is accompanied by an antiglaucoma effect of the liposomal drug, reflecting a pronounced neuroprotective effect, which is evident in maintaining the uniformity and density of neurons in the ganglion layer and the number of neurons in the bipolar cell layer, as well as a decrease in the content of specific biochemical markers of neurotoxicity in the retina. Ophthalmic safety of instillation and subconjunctival administration of the proposed latanoprost liposomal composition in combination with the absence of toxicity with intravenous administration allows to predict the absence of a systemic toxic effect[55].

Latanoprost-encapsulated liposomes based on dioleoylphosphatidylcholine, dipalmitoylphosphatidylcholine and cholesterol, which were also combined with hyaluronic acid and contained osmoprotectors (betaine, leucine), were proposed by a group of researchers from Spain[56, 57]. This combination enhanced the hypotensive properties of the developed drug in the glaucoma treatment. With a single administration of drops of a complex liposomal latanoprost and hyaluronic acid into the eyes of rabbits, the effect persisted 24 hours longer compared to the commercial drug of free latanoprost, and the relative bioavailability was almost three times higher.

The ability of a liposomal incorporated timolol maleate to regulate IOP was demonstrated, and the modification of the liposome surface with chitosan increased the hypotensive activity of the liposomal composition due to its improved permeability. The chitosan-modified liposomal form of timolol maleate was capable of prolonging the process of continuous release of API by two times, that determined its more significant effect on reducing abnormal IOP[48, 58, 59].

Experimental studies of cytochrome C incorporated liposomal systems are of interest for ophthalmotherapy[60, 61]. The aqueous solutions of cytochrome C are used in a number of synonymous drugs for the prevention of cataract development due to the ability of the protein to accelerate metabolic processes in tissues, improve oxygen utilization and reduce the effects of hypoxia and toxic effects. Liposomal encapsulation allows to increase the bioavailability of cytochrome C and slows down its rapid metabolic inactivation (half-life period of about 4 minutes)[62-64]. The proposed methods for obtaining liposomal forms of cytochrome C include different lipid compositions that improve the level of anti-cataract activity compared to "free" cytochrome C[65, 66]. The use of the liposomal form of cytochrome C after modeling a penetrating wound of the optical zone of the cornea helps to accelerate regenerative processes, reduces the severity of clinical manifestations of eye tissue damage and eliminates residual effects during the healing process. When varying the lipid composition of liposomes with cytochrome C, positively charged lipids showed advantages in the level of anti-cataract activity, which may be associated with the interaction of cationic liposomes with the negatively charged surface of the cornea. Modification of the liposomal membrane with polyethylene glycol (PEG) creates conditions for effective deposition and targeted delivery of cytochrome C[61]. However, the patterns between anti-cataract activity and parameters and in vivo stability of liposomes have not been established for the above-described liposomal systems of cytochrome C, that requires expansion of preclinical studies.

An original standardized composition of cytochrome C in liposomes based on phosphatidylcholine and DPPG was reported[67-70]. The advantages of the pharmacotherapeutic activity of this composition in comparison with other liposomal and aqueous forms of cytochrome C are shown in models of penetrating wound of the optical zone of the cornea (model 1) and cataract induced by chronic polychromatic irradiation (model 2), the clinical signs of which correspond to severe human nuclear cataract. The proposed liposomal composition of cytochrome C has a significant anti-cataract effect in accordance with the specificity of the eye pathology model. In model 1, the effect of the composition is manifested

in promoting corneal regeneration, reducing the fibrin clot, accelerating the epithelialization process and compact scar formation, reducing clinical manifestations of eye tissue damage and having an anti-inflammatory effect. Long-term instillation of the composition in the eye with a light cataract (model 2) prevents and stops the development of pathology, that reduces the degree of lens damage to the initial stages in the absence of manifestations of cataract with severe irreversible stages, and also practically normalizes enzyme activity and the content of lipid peroxidation products in the lens without irritating the eye tissue. According to the results of the studies [67-70], the use of liposomal cytochrome C eye drops was more effective than the use of an aqueous solution of free cytochrome C (reference group) in terms of inflammation and regeneration processes. Thus, in the liposomal form group, the content of malondialdehyde and diene conjugates were decreased by 21.8% and 22.5%, respectively, and in the group of free cytochrome C – by 16.7 and 15.7%, respectively. Catalase enzyme activity in the liposomal form group was 19.6% higher than in the control group (sodium chloride solution), while in the reference group this indicator was 15% higher. The enzyme activity of the acidic phosphatase in both groups (liposomal and free cytochrome C) was decreased by 20.1 and 13.2%, respectively, and the enzyme activity of lactate dehydrogenase was decreased by 13 and 9.9%, respectively. Clinical observations confirm the results of the evaluation of biochemical data, liposomal cytochrome C normalizes enzymatic disorders in the lens, has a protective effect on the antioxidant system and slows down the processes of lens opacification, thereby demonstrating a high anti-cataract preventive and therapeutic effect. The results of a preclinical study of the liposomal form of cytochrome C in combination with verification of its composition and stability allowed to recommend it for clinical trials and use[67-70].

Liposomal systems have a potential for pharmacotherapy of another severe ophthalmological pathology – age-related macular degeneration (AMD). Liposomes are capable of providing effective transport of specific antioxidants to the posterior segment of the eye, which neutralize the effects of oxidative stress as the main factor in the development and progression of AMD. In this case, the use of above-described drug "Lipoflavon" was proposed for the prevention and treatment of AMD[31], which is justified by the high antioxidant activity of quercetin and the possibility of its targeted delivery to the corpus luteum region as part of the liposomal transport form of "Lipoflavon". The encapsulation of berberine hydrochloride and chrysophanol in liposomes coated with the polyamidoamine dendrimer PAMAM G3.0 increased the stability of this antioxidant and antiangiogenic agents[47]. Modified liposomes significantly increase the bioavailability of encapsulated antioxidants in AMD and exhibit a protective effect on the retinal pigment epithelium of humans and laboratory animals after photooxidative damage without a side effect on the structure of the eye surface.

The development of ophthalmological drugs containing dexamethasone is focused on the use of the ambivalence of the liposome structure, which determines the possibility of incorporating both hydrophobic dexamethasone and its hydrophilic derivative, dexamethasone phosphate. The study of biocompatibility and distribution of the liposomal form of dexamethasone in intravitreal administration showed the liposomes penetration through all the retinal layers[71]. The intravitreal administration of the liposomal form of infliximab in experimental autoimmune uveoretinitis prolongs the persistence of the drug in the vitreous body with satisfactory safety, that indicates a possible therapeutic potential [39].

An antibacterial liposomal system containing ceftazidime (the semi-synthetic β-lactam antibiotic) in a matrix of variable lipid composition based on DPPC, DPPG and cholesterol was proposed[72]. The liposomal dosage form for topical use in ophthalmology ensures the stability of ceftazidime, which degrades in an aqueous medium, and increases its activity against gram-negative bacteria (*Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus vulgaris, Enterobacter*, etc.).

4. Conclusions

The results of current clinical and experimental

studies reflect the advantages of the effectiveness of action, safety and targeting of ocular transport of liposomal forms of drugs of variable nature in the prevention and treatment of a wide range of common ophthalmological pathologies. Optimized pharmacotoxicological profile and verification of ophthalmological quality of liposomal preparations in combination with a favorable pharmacoeconomic basis substantiate the irreplaceable role of the liposomal factor in modern ophthalmotherapy technologies.

Perspectives for further research. Further technological, pharmacological, and clinical studies of liposomal drug delivery systems will expand the arsenal of ophthalmic drugs and increase the effectiveness of eye disease treatment. In our opinion, the use of combined liposomal drugs containing two or more APIs is a promising approach. The synergistic effect of different APIs will increase the effectiveness of therapy. Another important line of research is the study of already known liposomal compositions for new medical indications which will expand the range of applications for liposomal drugs.

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