Review Article

Liposomes as ocular drug delivery platforms: A review

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Abstract: Topically applied drugs need to overcome physiological, anatomical and dynamic barriers in the ocular milieu for effective ocular penetration. There exists an urgency to develop novel approaches for the treatment of ophthalmic complications such as glaucoma, uveitis, retinitis, age related macular degeneration, diabetic retinopathy, retinitis pigmentosa. Efflux protein pumps present in the ocular tissues restrict the ocular absorption. Novel drug delivery strategies and approaches could improve ocular bioavailability of drugs which would be beneficial for the intervention of disorders. At present, the intravitreal route is widely used for posterior ophthalmic delivery. Over the past few years, liposomal systems were being exploited and targeted for posterior ocular delivery due to their unique structural framework to entrap lipophilic/hydrophilic drugs. The present review discusses about the recent advances the niche of liposomal ocular delivery.
Keywords: ocular delivery, bioavailability of drugs, diabetic retinopathy, retinitis pigmentosa

INTRODUCTION

Delivery of drugs/drug candidates to the ocular posterior segment is highly challenging task. However, treatment of the sight threatening posterior ocular diseases requires overcoming the limitations. The design and development of novel topical delivery systems such as polymeric gels, colloidal systems, and cyclodextrins has been shown to be effective in the treatment of ocular complications [1, 2]. However, drug delivery to ocular posterior segment through topical application still remains a challenge, only 1-5% or less of a topically instilled dose was delivered into inner ocular tissues [3, 4]. Oral or systemic delivery of therapeutic entities is not effective because of blood-aqueous and retinal barriers, limiting the ocular entry of drugs from the systemic circulation [5, 6]. Intravenous administration is effective to maintain the drug concentrations at high doses but pose adverse effects and systemic toxicity. Currently, intravitreal injection (i.e., direct injection of a drug into the vitreous body) is reported to be the most promising method for posterior ocular delivery. However, this method of administration is too invasive technique and may lead to retinal detachment, cataract, endophthalmitis and increased intraocular pressure [7, 8]. It is reported that sclera is significantly more permeable than cornea [9, 10]. Subconjunctival injection, administration of drug into the region between the conjunctiva and the sclera (subconjunctival space), is reported for back-of-the eye delivery through the trans-scleral route. The subconjunctivally injected drugs have direct contact with the sclera, so that the trans-scleral transport of drugs may be quite higher. Moreover, subconjunctival injection has the ability to circumvent the conjunctival absorption, which is considered to be a barrier in terms of permeability. Consequently, periocular and intravitreal routes of administration serve as viable option for the delivery of drugs to posterior tissues [11-13]. Depending upon the ophthalmic disease state, complexity and origin delivery systems may vary from simple topical solutions to advanced formulations, such as intraocular implants, intravitreal injections [14, 15]. Even though the tight cellular junctions and various barriers of eye that restrict the diffusion and transport of drugs, administration of therapeutic agents through various novel ophthalmic drug delivery systems have to be developed. As such, many novel strategies have been designed to circumvent these ocular barriers [16-18]. This review presents summary of current literature and the recent advances/developments related to liposomal platforms.

Colloidal formulations

Liposomes, nano/micro particulate formulations and various delivery platforms constitute colloidal formulations. Tailored release at the targeted site, reduced frequency of administration, ability to overcome blood–ocular barriers, and reduced efflux rate are some of advantages offered by liposomes [19, 20]. Localization of drugs, superior bioavailability and other pharmacokinetic properties are the factors with respect

to colloidal formulations which make them as viable alternative to the conventional dosage forms.

Liposome as colloidal delivery systems

Liposomal colloidal carriers are microscopic vesicular systems made up of aqueous core compartments enclosed by phospholipid bilayers of natural or synthetic origin. The lipid layers are comprised mainly of amphiphilic phospholipids with characteristic structure comprising hydrophilic head and a lipophilic tail. Liposomes are structurally categorized on the basis of lipid bilayers such as small unilamellar vesicles (SUVs) or multilamellar vesicles (MLVs). A single lipid bilayer enclosing an aqueous compartment is referred to as unilamellar lipid vesicle; according to their size they are known as small uni-lamellar vesicles (SUV) or large unilamellar vesicles (LUV). Multilamellar vesicles (MLV) are to be referred when vesicular system is composed of various phospholipid bilayers [21]. Lipophilic and hydrophilic molecules can be encapsulated by the liposomal formulations. Hydrophilic drugs could be entrapped in the aqueous core compartment, while hydrophobic drugs will get trapped into the lipid bilayers. Loading capacity of charged drug molecules can be further prominently improved by using cationic or anionic lipids for the preparation of liposomes formulations [22, 23]. Timolol maleate loaded chitosan coated liposomes were prepared by Tan *et al* to enhance the ocular permeation, precorneal residence time and bioavailability. Significant mucin adhesion and 3.18-fold increase in corneal permeation was observed with liposome in comparison to commercial eye drops. Gamma scintigraphic and ocular irritation study showed prolonged precorneal residence of liposome compared to eye drops and did not exert irritation. Furthermore, pharmacodynamics results from liposomes demonstrated the significant IOP lowering effect in comparison to marketed eye drops [24]. Liposomal formulations can be administered as topical solutions, subconjunctival/intravitreal injections and through systemic route depending up on the desired need. Nucleic acids (siRNA and pDNA) were delivered to the posterior segment of the eye for treatment of age-related macular degeneration (AMD) using noninvasive ophthalmic liposomes by Takashima *et al*. These liposomes demonstrated high pDNA encapsulation efficiency with good cellular uptake ability in human retinal pigment epithelial cells (ARPE-19 cells). Further modification of ligand improves interaction onto the RPE cells which could improve gene delivery [25]. Submicron-sized liposomes (ssLips) for the delivery to the ocular posterior segment by Hironaka *et al*. The ssLip based on l-alpha-distearoyl phosphatidylcholine (DSPC ssLip) showed higher fluorescence emission in the retina than that based on egg phosphatidylcholine (EPC ssLip). ssLip delivered via the non-corneal pathway after administration was confirmed by eye imaging. The liposomes tested in ocular cells showed little cytotoxicity. These results demonstrate that ssLip can be used to deliver drugs to the posterior segment of the eye [26, 27]. Ion-exchange carrier nanocomposite based on montmorillonite (Mt) intercalated with betaxolol hydrochloride (BH) was encapsulated in liposomes by Huang *et al*. Immortalized human corneal epithelial cell cytotoxicity, in vivo rabbit eye-irritation tests, and chorioallantoic membrane–trypan blue staining all revealed no irritation on ocular tissues. The results showed that liposomes maintained significant concentration in tear fluid for prolonged period than the solution. In vivo precorneal retention studies indicated liposomes prolonged ocular retention significantly than the BH solution. Pharmacodynamic studies of liposomes demonstrated IOP lowering effect when compared to topical eye drops [28]. Ganciclovir (GCV) was injected intravitreally for the treatment of cytomegalovirus retinitis by Manuel Diaz. Kinetics of GCV entrapped in liposome were compared with the intravitreal injection of free GCV and the results suggest that no retinal toxicity was exerted from GCV liposomes and maintained therapeutic levels up to 14 days [29, 30]. Novel ocular proniosomal gels of lomefloxacin HCl were formulated by Khalil *et al* for the management of bacterial conjunctivitis. Optimized formulation appeared as spherical shaped vesicles with high entrapment efficiency (>80%), good vesicle size (187 nm) and was released in controlled manner over 12 hours. Stability and ocular irritation tests demonstrated formulation was stable over 3 months and did not exert irritation to eyes. Antibacterial efficacy of the proniosomal gel was significantly higher compared to the commercially available LXN eye drops [31]. Amikacin encapsulated liposomes prepared by reverse phase evaporation method were injected into vitreous body to treat bacterial endophthalmitis. Intravitreal kinetics of the liposomes was compared with amikacin in PBS by fluorescence polarization immunoassay. Results suggest that the liposome-encapsulated amikacin prolonged half-life of the drug in vitreous and pharmacokinetic characteristics [32]. Ketorolac tromethamine ocular liposomes were prepared with a closed vesicular multi-lamellar structure. Poloxamer *in situ* gel was used to disperse liposomes with aim for tailored drug release for prolonged ocular application. The results demonstrated the superior ocular retention and patient compliance in comparison to conventional eye drops [33, 34]. Bevacizumab loaded liposomes prepared by dehydration-rehydration method were targeted for delivery to vitreous humor to treat ocular complications. The free drug concentration in aqueous humor and vitreous samples at days 3, 7, 14, 28, and 42 after the injection was determined by enzyme-linked immunosorbent assay. Mean concentration of free bevacizumab in the eyes that received liposomal bevacizumab compared with the eyes injected with soluble bevacizumab was 1 and 5 times higher at days

28 and 42, respectively [35]. Effect of liposomal encapsulation on the pharmacokinetics of gentamicin, after injection in rabbits. Intravitreal injection of 100 mg liposome-encapsulated gentamicin or 100 mg gentamicin in 0.1 mL of phosphate-buffered saline was administered to each rabbit. The peak free drug concentration in the vitreous was significantly greater for liposome-encapsulated gentamicin than for gentamicin at 24, 72, 120, and 192 hours respectively. The areas under the drug concentration-time curve for the total drug and for the free drug in the case of liposome-encapsulated gentamicin were two fold and 1.5-fold higher, respectively, than those for gentamicin [36]. Liposomal formulation of foscarnet was formulated for the treatment of Cytomegalovirus retinitis. Foscarnet inhibits replication of herpes viruses, including CMV. Liposomes were prepared by reverse-phase evaporation method and pharmacokinetic parameters in vitreous humor were evaluated. Results suggested that liposomal formulation achieved significant therapeutic levels in retina for 72 hours reaching the vitreous humor [37]. Pharmacokinetics governing the distribution and elimination of intravitreally injected vancomycin in normal and infected rabbit eyes. The half-lives were 69 hours in normal vitreous and 14.53 hours in infected vitreous. Therapeutic drug levels were present in the vitreous 84 hours post-injection in all eyes; they were detected from 2 to 48 hours in normal vitreous but at lower levels in the infected ones [38, 39]. Zhang *et al*. utilized cytochrome-C (Cyt-C) loaded cationic liposomes prepared by thin layer evaporation technique for the treatment of selenite-induced cataract in rats. Cyt-C loaded freeze-dried liposomes were stable for one year at 4°C. Furthermore, these liposomes exhibited remarkable efficacy (28% decrease in lens opacity) in minimizing the cataract formation [40]. In one study Kawakami attempted to deliver O-palmitoyl prodrug of tilisolol-encapsulated liposome to improve the retention time of tilisolol in the precorneal area and vitreous body. The liposomes were administered topically, as well as intravitreally to the rabbit eye. Following topical administration, very low retention of O-palmitoyl tilisolol in the tear fluid was observed even when it was applied as liposomal formulation. The researchers significantly increased the retention property of liposomes by adding 2% of carmellose sodium which acted as a reservoir for liposomes. In case of intravitreal administration, o-palmitoyl tilisolol-encapsulated liposomes achieved higher drug concentration in the vitreous body compared to free tilisolol [41]. Liposome formulation used as artificial tears by Romani *et al*. Liposome particles were uniformly distributed across whole porcine corneal epithelium immediately after 5 min of exposure. Liposomes increased protein expression and nuclear translocation of progesterone receptor in comparison to controls. Liposomes significantly reduced the cell proliferation rate after the exposure. Liposome formulation supplied lipids to tear film and could be loaded with anti-inflammatory agents that can be delivered into the cells and activate specific drug receptors which may be effective in the treatment of inflammatory ocular diseases [42]. In a study tacrolimus encapsulated liposomes were formulated and subsequently evaluated for efficacy and safety following intravitreal injection in rats. Significant changes in the retinal function were not observed in the liposome-treated rats. Histo-pathological examination revealed reduced inflammatory response in comparison to free drug. Liposomes were able to maintain the vitreous concentration more than 50ng/mL for 2 weeks after single administration. Investigators concluded that tacrolimus-loaded liposomes were more effective in the treatment of uveoretinitis [43]. Fluconazole-encapsulated liposomes was prepared and attempted to deliver to vitreous body of rabbit eyes. Entrapment of fluconazole in liposome significantly reduced clearance of free fluconazole after intravitreal injection with higher fluconazole concentration in the vitreous. The liposomes showed longer half-life (23.40h) in comparison to free fluconazole (3.08h) [44].

CONCLUSION

Ocular posterior segment drug delivery present formidable impediments for topically applied drugs. Topical route is not yet promising and needs to be addressed with viable formulation matrices to target ocular posterior tissues. Ocular efflux transporters need to be effectively targeted to explore novel opportunities for posterior ocular drug delivery. Novel technologies integrating multi-disciplinary fields of basic, clinical, applied sciences and nanotechnology are to be designed and developed to provide efficient and effective ophthalmic products.

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