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Light activated liposomes: Functionality and prospects in ocular drug delivery

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ABSTRACT

Ocular drug delivery, especially to the retina and choroid, is a major challenge in drug development. Liposome technology may be useful in ophthalmology in enabling new routes of delivery, prolongation of drug action and intracellular drug delivery, but drug release from the liposomes should be controlled. For that purpose, light activation may be an approach to release drug at specified time and site in the eye. Technical advances have been made in the field of light activated drug release, particularly indocyanine green loaded liposomes are a promising approach with safe materials and effective light triggered release of small and large molecules. This review discusses the liposomal drug delivery with light activated systems in the context of ophthalmic drug delivery challenges.

1. Introduction

Ocular drug delivery, particularly to the retina, is a difficult challenge [1,2], because the eye is well protected from the surroundings by various barriers and defense mechanisms. Development of efficient drug delivery systems is vital for effective retinal therapy. Several ocular diseases, such as age-related macular degeneration, diabetic macular edema, proliferative vitreoretinopathy, posterior uveitis, cytomegalovirus infection and glaucoma, are affecting the posterior parts of the eye. In addition, there are numerous rare genetic diseases that lead to degeneration of the retina and blindness. Therefore, development of efficient drug delivery to the posterior eye segment is important.

Liposomes have been investigated in ophthalmic drug delivery since 1980's. The earliest applications were liposomes for topical drug delivery in eye drops and intravitreal injections for prolonged action [3,4]. These pioneering experiments showed some promising results, but yet no significant progress towards clinical applications have been achieved. The liposomal eye drops were rapidly eliminated from the ocular surface and no substantial increase in ocular drug bioavailability was reached [3]. Although, in the case of intravitreal injection, liposomal drugs retain in the vitreous longer than free drug in solution, the retention times should be even longer for clinical significance [4]. Finally, microwave based triggered drug release from intravenous thermosensitive liposomes was shown, but no selectivity was built to the liposomes in comparison with the cell membranes that also have lipid bilayers that are sensitive to the microwave heating [5].

In principle, ocular tissues are accessible to light and, therefore, the light activated liposomal drug delivery may have some interesting applications in ophthalmology. In this short review, we are updating the current status and prospects of liposomal drug delivery to the eye, particularly in the case of light activated liposomes.

2. Challenge of ocular drug delivery

The eye can be divided into two main parts: anterior and posterior segments. The anterior segment includes roughly one-third of the eye consisting of cornea, conjunctiva, pupil, aqueous humor, iris, lens and ciliary body. The posterior segment consists of vitreous humor, retina, choroid, sclera and optic nerve making up the remaining two-thirds in the back of the eye. Fig. 1 illustrates the ocular anatomy and the routes of ocular drug delivery. Particularly, drug delivery to the posterior tissues, such as retina, is a major challenge. Currently, topical drug delivery

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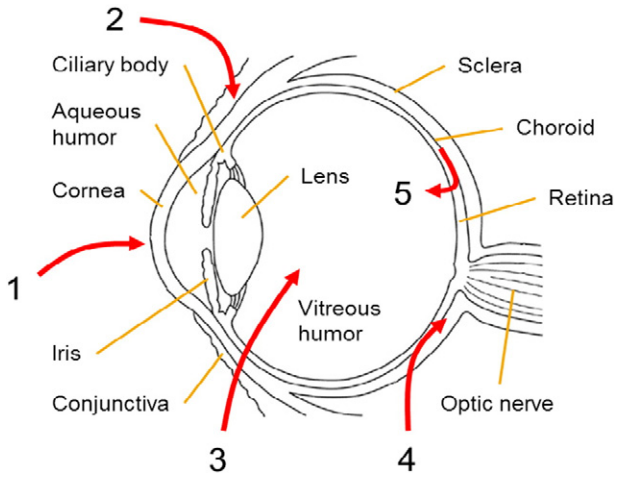

Fig. 1. Schematic presentation of the ocular tissues and routes of drug administration. Topical delivery (1), sub-conjunctival injection (2), intravitreal injection (3), suprachoroidal administration (4), and systemic delivery (5).

is used to treat anterior part of the eye, but the treatment of posterior eye tissues requires intravitreal injections.

Eye drops are used to deliver small molecular drugs that have adequate lipophilicity for trans-corneal permeation to the inner eye, whereas protein drugs do not permeate across the cornea (Fig. 1, arrow 1) [6,7]. Even in the case of small molecules, only the anterior segment can be treated with topical eye drops and bioavailability in the anterior chamber is typically <5%, often below 1% [6,8]. Several barriers (eye drop drainage, corneal epithelium, systemic absorption through conjunctiva) severely limit ocular drug bioavailability [9,10]. Trans-corneal route delivers the drug to the aqueous humor where drug is eliminated via aqueous humor turnover and blood flow of anterior uvea [1, 6]. The elimination factors and the barrier of the lens limit drug distribution to the posterior chamber, and drug concentrations in the retina and vitreous are negligible after topical eye drop administration [6,8].

Topical administration results also in non-corneal drug delivery across the conjunctiva and sclera (Fig. 1). This route is has some potential in posterior eye segment drug delivery, because the elimination factors in the anterior chamber and the physical barrier of the lens are circumvented [11,12]. Interestingly, this approach may show some benefits also in the delivery to biologicals [12]. The same route is partly utilized in the case of sub-conjunctival injection (Fig. 1, arrow 2). Injected solution retains longer in the eye than the instilled eye drop, and increased bioavailability is achieved in the anterior chamber [6]. Dissolved drug escapes from the sub-conjunctival space rapidly to blood and lymphatic flow and the retinal bioavailability is only in the range of 0.1% of the dose [13]. Higher bioavailability can be achieved with suprachoroidal injection with microneedle, but this method is not yet in clinical use (Fig. 1, arrow 4). Improved drug delivery methods are needed to increase topical and sub-conjunctival drug delivery to the eye, particularly to the retina.

Blood-ocular barrier protects the eye from the xenobiotics in the systemic blood circulation. This barrier consists of blood-aqueous barrier in the anterior uvea and a blood-retina barrier in the posterior segment of the eye that limit drug access from the systemic circulation to the inner eye and drug elimination from the eye to the systemic blood circulation [10]. The blood-retina barrier is further divided into two parts: the retinal capillaries and the RPE that have tight intercellular junctions and form a strong barrier against drug permeation. On the other hand, the choroidal blood flow is intense and the vessels have fenestrated leaky walls (pore size of about 80 nm) [14]. Generally, lipophilic molecules permeate the blood-retina barrier more readily than hydrophilic compounds and protein binding in plasma is a crucial parameter in ocular drug distribution from plasma [15]. Systemic drugs may cause adverse effects and this approach may be feasible only in the delivery of relatively safe compounds with wide therapeutic index in the systemic circulation, unless targeted retinal drug delivery from blood circulation could be achieved.

Intravitreal injections (Fig. 1, arrow 3) are widely used to deliver anti-VEGF medications (antibodies, soluble receptors) to the eye, particularly in the treatment of exudative age-related macular degeneration. These injections should be given monthly, but in clinical practise the compliance is sub-optimal and the injection intervals are much longer resulting in decreased efficacy of treatment [16]. Intravitreal injections of drug solutions are not a suitable approach for the delivery of small molecules, because their half-lives in the vitreous are too short (only a few hours as compared to one week in the case of antibodies) necessitating frequent injections [17,18]. Again, improved delivery methods are needed.

3. General features of liposomes

Liposomes can be prepared with various methods and the resulting formulation properties can be adjusted with the processing parameters and liposome composition. Therefore, liposomal drug delivery properties should not be generalized, but instead the properties can be adjusted for each particular purpose.

Liposome size ranges from the theoretical minimum of about 30 nm to several microns. Even though liposome formation is based on the principles of molecular self-assembly, the size can be adjusted with processing parameters [19–21]. Large multi-lamellar liposome-drug formulations are formed by sonication (size range from hundreds of nanometers to micron). Extrusion through polycarbonate membranes above the phase transition temperature of the lipids can be used to control the size and size homogeneity of liposomes over wide size range to narrow and defined sizes [20]. Importantly, this approach results in low polydispersity of the liposome batches. Liposome size has important implications in the ocular disposition and elimination, because various ocular tissues have distinct and different free volumes available for diffusion.

Surface charge of the liposomes is determined by the lipid composition. Inclusion of lipids with cationic head groups results in positive zeta potential values, and anionic lipids can be used to produce negatively charged liposomes [22–24]. The surface charges may be masked with polyethylene glycol (PEG) conjugation and other stealth coatings [25], and the surface can be further modified with targeting ligands for cell recognition and cell penetration enhancing compounds [26]. Surface charges of the liposomes affect their interactions with ocular tissues and cells, thereby either facilitating or preventing the drug delivery process [27–30]. Mostly ocular environment has neutral pH and the tissues and cell surfaces have negative net charge.

The stability of lipid bilayer and its phase transition is usually controlled with the selection of the lipid composition. Longer alkyl chains and saturated phospholipids result in rigid bilayers with low permeability, whereas the double bonds in the alkyl chains and short chains lead to permeable fluid like bilayers [31]. Drug release from the liposomes depends on the external conditions (e.g. temperature, pH, liposome interactions with environment), lipid bilayer tightness and phase status (gel or fluid phase) and drug properties (ability of the drug to partition and diffuse in the bilayer). Generally, small and lipophilic compounds can pass through the liposomal bilayers faster than larger molecules that need disruption in the ordered bilayer for their escape from the liposome [31]. Charged compounds have notably reduced release from the liposomes compared to neutral molecules of the same size [32].

Efficacy of liposomal drug treatment depends on the drug loading capacity of the liposomes and drug release from them. Therefore, the loading should be maximized and the release should be adequate and reproducible. However, drug release in vivo from the liposomes is a complex phenomenon, because the liposomes may be subjected to changing environmental conditions after their administration. For