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Original Research Paper

Novel approaches for posterior segment ocular drug delivery with folate-modified liposomal formulation

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The leading causes of vision impairment and blindness are posterior segment-related diseases including age-related macular degeneration, diabetic macular edema and endophthalmitis. Recently, pharmaceutical approaches to these diseases have used steroids and oligonucleotides. These drugs are usually administered via invasive injection because noninvasive delivery method such as eye drop administration of drugs is not available. However, repeated injections are associated with potential risks of complications. Moreover, patients may not comply with such regimens. Thus, there is a pressing need for noninvasive delivery systems targeting the posterior segment of the eye. In previous studies, we have reported the potential of liposomal eye drop formulation composed of submicron-sized liposomes (ssLip) as a novel system for delivering drugs to the posterior segment of the eye, including the retina [1,2]. In a series of our studies using ssLips containing a fluorescence marker, coumarin-6, the die was shown to be delivered into the retina after eyedrop administration in mice, rabbits, and monkeys [2]. The purpose of this study was to improve the drug delivery efficiency to the retina by folate-modification of liposomes. We designed folate-modified ssLip (FA-modified ssLip) to aim at selective targeting of the folic acid receptor, which is expressed on retinal pigment epithelia cells. This active targeting may lead to increase in the delivery efficiency of the liposomal systems.

The ssLip containing coumarin-6 was prepared using hydration method, and the folate ligand was inserted into preformed liposomes by the post insertion technique [3]. A single dose of 3 μL of the liposomal formulation was dropped onto the left eye of mice. The mice were then sacrificed 15, 30, 60, 120, 180, 240 min after the administration of the liposomal formulation. Frozen section of the enucleated eyes was prepared with a cryostat. Images were obtained using an epifluorescence microscope and were analyzed using Image J software. Fig. 1 shows the typical epifluorescence microscopic images of the retina 0, 30, 120 min after eyedrop administration. To estimate the delivery efficiency to the retina, the magnitude of fluorescence emission in the inner

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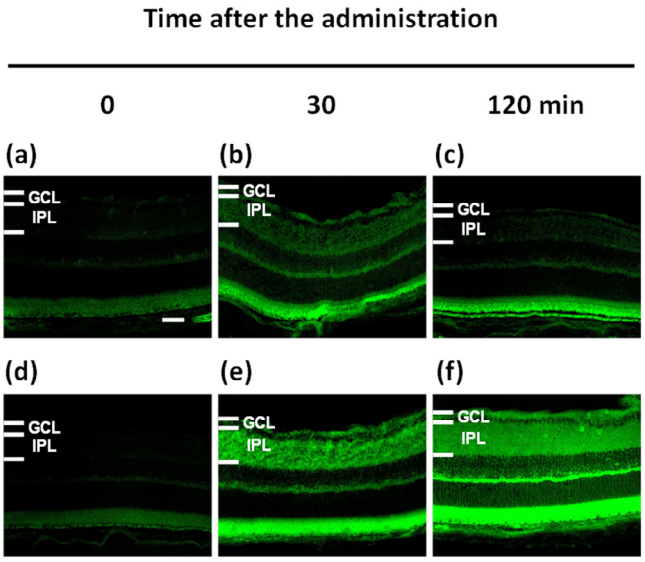

Fig. 1 – Epifluorescence microscopic images of the retina after definite intervals of eyedrop administration. (a–c) Unmodified ssLip, (d–f) FA-modified ssLip.

plexiform layer (IPL) of the retina was quantified using Image J software. The fluorescence intensity of unmodified ssLip showed the maximal value at 15–30 min, thereafter pronounced decrease was observed up to 120 min. On the other hand, FA-modified ssLip showed the higher intensity whole range of the period after the administration compared to that of unmodified ssLip. Besides, the liposomes tested in ocular cells showed little cytotoxicity. The FA-modification of liposomes may advance the delivery efficiency of compounds to the retina.

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