International Journal of Pharmaceutics 498 (2016) 1–11

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Laser-triggered intraocular implant to induce photodynamic therapy for posterior capsule opacification prevention

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ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form 16 September 2015
Accepted 3 October 2015
Available online 8 October 2015

Keywords:
Laser-triggered
Intraocular implant
Indocyanine green
Photodynamic therapy
Posterior capsule opacification

ABSTRACT

Posterior capsule opacification (PCO) is one of the main reasons for loss of vision again after cataract surgery. In this study, intraocular lenses were modified with indocyanine green (ICG) and sealed up with PLGA to form long-term intraocular implants (ICG-IOL). When triggered by laser, ICG-IOL would induce photodynamic therapy (PDT). *In-vitro* cell viability assay and scratch wound healing assay demonstrated that ICG-IOL could effectively inhibit HLEpiC proliferation and migration without causing damage to the cells far away from it. Laser attenuation test indicated that ICG-IOL could be applied *in vivo*. *In-vivo* pharmacodynamics and safety study showed that ICG-IOL could significantly prevent the occurrence of PCO and was safe for intraocular normal tissue. All these results suggested that ICG-IOL would be a very promising candidate for PCO prevention.

1. Introduction

Posterior capsule opacification (PCO) is also known as secondary cataract, which always occurs as a long term complication after cataract surgery. It is caused by the rapid proliferation and migration of the human lens epithelial cells (HLEpiC) left during the cataract surgery. The cells approach the central optical axis and cause visual axis obscuration, resulting in progressive loss of vision again (Awasthi et al., 2009; Wormstone, 2002; Wormstone et al., 2009). According to observation in clinical practice, the incidence of PCO 1 to 5 years after surgery ranges from 12% to 67% for adults while it is nearly 100% for children (Findl et al., 2010; Jorge et al., 2014; Lloyd et al., 2007; Pandey et al., 2004; Schaumberg et al., 1998; Sundelin and Sjöstrand, 1999). Thanks to the advances of surgical tools, procedures, skills and appropriate IOL designs, the incidence of PCO has gradually decreased. However, once PCO occurs, an expensive treatment—Neodymium-doped Yttrium Aluminium Garnet (Nd:YAG) laser capsulotomy must be used to treat the complication. This procedure may also lead to rhegmatogenous retinal detachment or even cystoid macular edema (Javitt et al., 1992). What is worse, it is somewhat difficult to treat dense capsular opacification after operation for congenital cataract by Nd:YAG laser in infancy (Awasthi et al., 2009; Fan et al., 2006). Thus, it is urgent to develop a pharmaceutical method for preventing PCO.

Many chemical drugs have been proved to have strong inhibitory effects on HLEpiC's proliferation, such as Genipin, dexamethasone, lithium, mitomycin C, 5-FU, diclofenac and docetaxel (Dong et al., 2013; Inan et al., 2006; Kim et al., 2007; Kitano et al., 2006; Malecaze et al., 2006; Stump et al., 2006; Wang et al., 2007; Wong et al., 2004). Some of these drugs were irrigated into the capsular bag for a few minutes after phacoemulsification and some were developed into sustained release intraocular preparations to prevent the occurrence of PCO. But using "effective" drugs also means that we have to face their toxicity. Serious toxicity of these drugs to other intraocular structures has become their biggest limitation (the upper half of Fig. 1).

In order to eliminate the side effects of cytotoxic drug, we introduced photodynamic therapy (PDT) for PCO prevention. PDT is a potential treatment for some skin diseases and cancers. It combines non-toxic dyes or photosensitizers (PS) with harmless visible light to transform oxygen ($^3O_2$) into singlet oxygen ($^1O_2$), which can kill or induce apoptosis in cells (Castano et al., 2004). The most attractive feature of PDT is the concept of dual selectivity. By increasing the selective accumulation of PS to lesions and delivering the light in a spatially confined and focused manner, the collateral damage to other tissues will be minimized (the lower half of Fig. 1). PDT has been approved for treatment of some ophthalmic diseases. For example, Verteporfin was the first PS that was approved by the FDA for the treatment of age-related macular

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http://dx.doi.org/10.1016/j.ijpharm.2015.10.006
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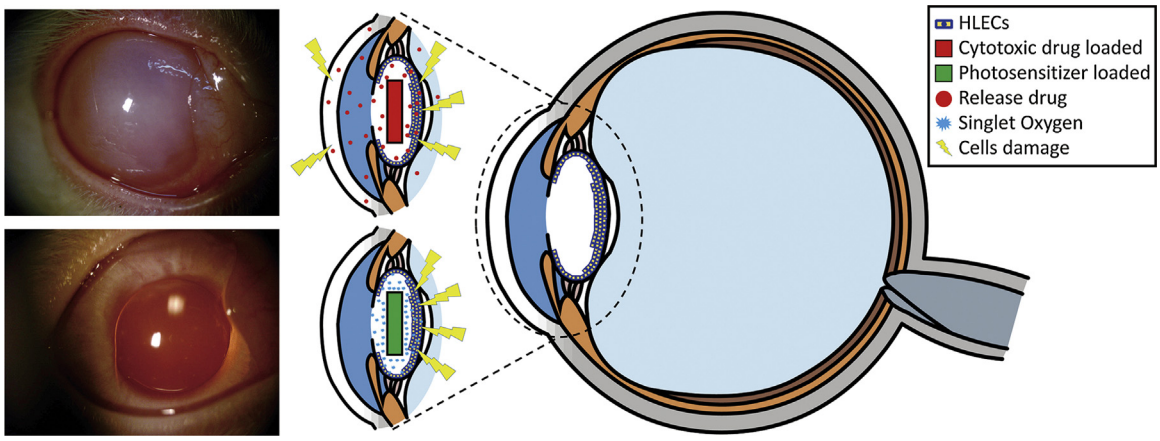

Fig. 1. Safety contrast between using photosensitizers and using cytotoxic drugs for PCO prevention.

degeneration (AMD) in 2000 and now it is one of the most common therapies (Sharma et al., 2001).

In this study, commercially available IOLs were modified with indocyanine green (ICG) through electrostatic attraction and sealed up with a biodegradable polymer poly(lactic-co-glycolic acid) (PLGA) to form intraocular implants ICG-IOL. The preparation was expected to retain ICG on it for a month and gradually turn clear and transparent within another month (Fig. 2).

Indocyanine Green (ICG) was selected as a model photosensitizer in this study. It is a non-toxic, water-soluble dye that has been widely used in ophthalmology. Indocyanine green angiography (ICGA) can be used to diagnose various diseases of retina and choroid (Roider et al., 2000; Yannuzzi et al., 2000). Intraocular ICG administration is always performed during macular hole surgery and anterior continuous curvilinear capsulorhexis to stain the internal limiting membrane (ILM) and posterior capsule respectively (Weinberger et al., 2001). Some research reported the photodynamic actions of ICG on LECs, HepG2, Hele and V79Chinese hamster fibroblasts *in vitro* (El-Daly et al., 2013; Melendez et al., 2005; Skřivanová et al., 2006), which indicated that ICG would be a promising candidate for the eradication of cells.

PLGA was utilized to control the residence time of ICG. Polymers are always necessary for long-term implants and sustained release systems. However, intraocular environment is somewhat different from blood environment. Intraocular substance is mainly discharged via aqueous humor circulation. Since the amount of aqueous humor is small and its circulation rate is slow, introducing too many materials or using non-degradable polymers may cause

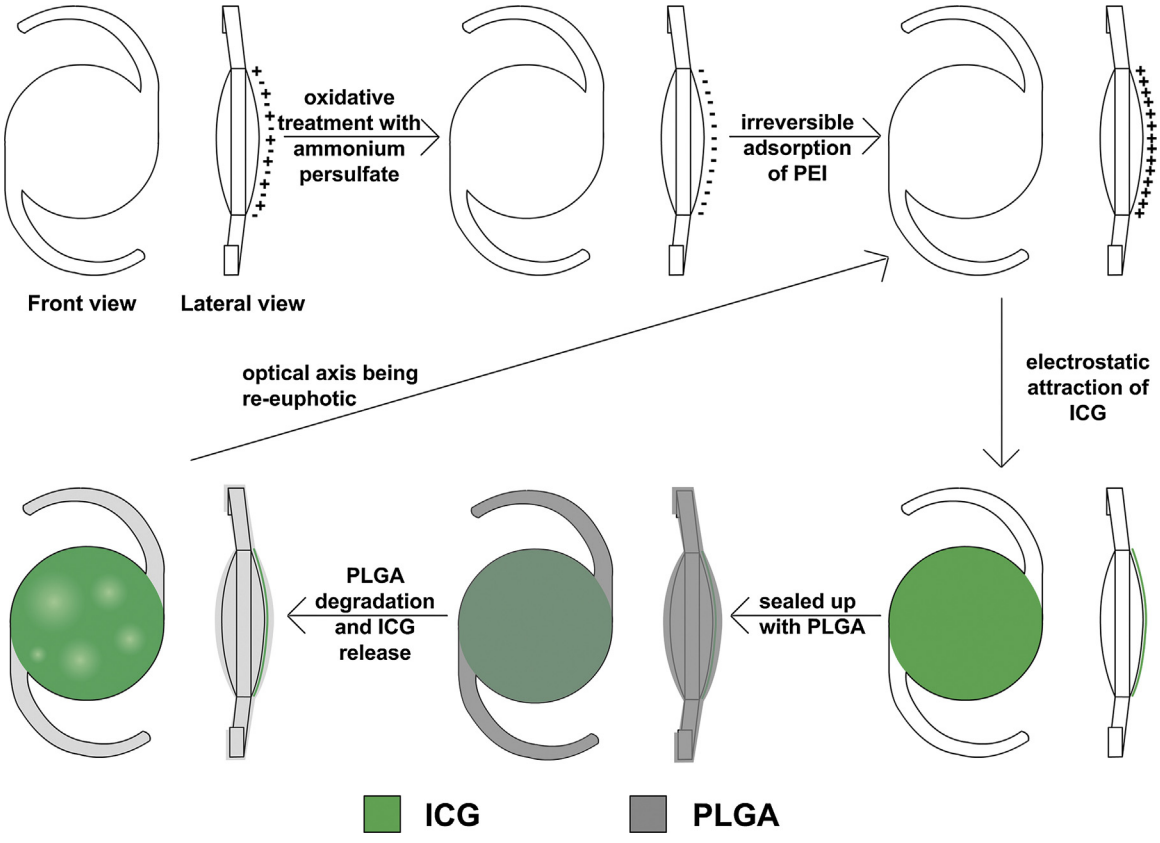

Fig. 2. Illustration of the preparation of ICG-IOL and its changes after implantation.