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Porous silicon oxide–PLGA composite microspheres for sustained ocular delivery of daunorubicin

Kaihui Nan [a,b], Feiyan Ma [a], Huiyuan Hou [a], William R. Freeman [a], Michael J. Sailor [c], Lingyun Cheng [a,*]

[a] Department of Ophthalmology, Jacobs Retina Center/Shiley Eye Center, University of California, San Diego, La Jolla, CA, USA
[b] Eye Hospital, Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China
[c] Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA, USA

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ABSTRACT

A water-soluble anthracycline antibiotic drug (daunorubicin, DNR) was loaded into oxidized porous silicon ($pSiO_2$) microparticles and then encapsulated with a layer of polymer (poly lactide-co-glycolide, PLGA) to investigate their synergistic effects in control of DNR release. Similarly fabricated PLGA–DNR microspheres without $pSiO_2$, and $pSiO_2$ microparticles without PLGA were used as control particles. The composite microparticles synthesized by a solid-in-oil-in-water emulsion method have mean diameters of 52.33 ± 16.37 μm for PLGA–$pSiO_2$_21/40–DNR and the mean diameter of 49.31 ± 8.87 μm for PLGA–$pSiO_2$_6/20–DNR. The mean size, 26.00 ± 8 μm, of PLGA–DNR was significantly smaller, compared with the other two ($P < 0.0001$). Optical microscopy revealed that PLGA–$pSiO_2$–DNR microspheres contained multiple $pSiO_2$ particles. In vitro release experiments determined that control PLGA–DNR microspheres completely released DNR within 38 days and control $pSiO_2$–DNR microparticles (with no PLGA coating) released DNR within 14 days, while the PLGA–$pSiO_2$–DNR microspheres released DNR for 74 days. Temporal release profiles of DNR from PLGA–$pSiO_2$ composite particles indicated that both PLGA and $pSiO_2$ contribute to the sustained release of the payload. The PLGA–$pSiO_2$ composite displayed a more constant rate of DNR release than the $pSiO_2$ control formulation, and displayed a significantly slower release of DNR than either the PLGA or $pSiO_2$ formulations. We conclude that this system may be useful in managing unwanted ocular proliferation when formulated with antiproliferation compounds such as DNR.

1. Introduction

Proliferative vitreoretinopathy (PVR) is the most frequent cause of failure of retinal reattachment surgery [1]. Previous studies have shown that daunorubicin (DNR) is effective in inhibiting PVR formation [2], and also has been shown to be effective for the treatment of experimental PVR [3–5]. However, DNR has a short half-life in the vitreous and also a narrow therapeutic concentration range, which would require too frequent injections to allow intravitreal DNR to be a practical therapeutic [6,7]. A drug appropriate for the control of PVR needs to inhibit cell proliferation effectively and maintain a therapeutic level in the targeting tissue for a minimum 2 months, which is the median time for PVR development [8]. Porous silicon (pSi) is a nanostructured material with a surface area of 400–800 $m^2\ g^{-1}$ that is commonly produced from bulk single crystal silicon by electrochemical anodization in hydrofluoric acid [9]. An oxidized form of pSi that retains the porous nanostructure and displays a lower reactivity with redox-active drugs [10] can be prepared by thermal oxidation of pSi. From a biological and biomedical perspective, pSi and $pSiO_2$ are attractive materials as they are both biocompatible and biodegradable, meaning that they are able to undergo complete degradation in the body to produce silicic acid ($Si(OH)_4$), a nontoxic soluble form of silicon [11]. It has been established that $Si(OH)_4$ is readily cleared from intraocular fluid [12]. Furthermore, surface chemistries such as silanol condensation and hydrosilylation are available for this material that allow adjustment of degradation rate in biological systems [13–15]. It has been shown that therapeutic payloads can be loaded into the pores of pSi or $pSiO_2$ by adsorption or surface grafting [10,14,16,17]. These properties, in addition to the very large internal surface area [18], render pSi a versatile drug delivery platform [19]. In previous works, we reported the possibility of using pSi and $pSiO_2$ microparticles as an intraocular drug delivery system.

* Corresponding author. Address: Department of Ophthalmology, Jacobs Retina Center at Shiley Eye Center, University of California, San Diego, 9415 Campus Point Drive, La Jolla, CA 92093-0946, USA. Tel.: +1 858 534 3780; fax: +1 858 534 7985.
E-mail address: cheng@eyecenter.ucsd.edu (L. Cheng).

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