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Quercetin conjugated poly(β-amino esters) nanogels for the treatment of cellular oxidative stress

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ABSTRACT

PβAE polymers have emerged as highly promising candidates for biomedical and drug delivery applications owing to their tunable, degradable and pH sensitive properties. These polymeric systems can serve as prodrug carriers for the delivery of bioactive compounds which suffer from poor aqueous solubility, low bioavailability and are biologically unstable, such as the antioxidant, quercetin. Using acrylate functionalized quercetin, it is possible to incorporate the polyphenol into the backbone of the polymer matrix, permitting slow release of the intact molecule which is perfectly timed with the polymer degradation. While formulating these quercetin conjugated PβAE matrix into nanocarriers would allow for multiple delivery routes (oral, intravenous, inhalation etc.), well known oil-water nano-emulsion formulation methods are not amenable to the crosslinked hydrolytically sensitive nanoparticle/nanogel. In this work, a single-phase reaction–precipitation method was developed to formulate quercetin conjugated PβAE nanogels (QNG) via reaction of acrylated quercetin (4–5 acrylate groups) with a secondary diamine under dilute conditions using acetonitrile as the reaction medium, resulting in a self-stabilized suspension. The proposed approach permits the post synthesis modification of the spherical nanogels with a PEGylated coating, enhancing their aqueous stability and stealth characteristics. Nanogel size was controlled by varying feed reactant concentrations, achieving drug loadings of 25–38 wt%. Uniform release of quercetin over 45–48 h was observed upon PβAE ester hydrolysis under physiological conditions with its retained antioxidant activity over the extended times.

Statement of Significance

Here we present the first demonstration of using poly(beta amino ester) chemistry to form nanogels composed of a bioactive polyphenol for the control of cellular oxidative stress. Previous nanogel and nanoparticle approaches, which use a water phase, are not readily amenable to PBAE chemistry due to their hydrolytic sensitivity. Here we demonstrate a simple approach to control particle size, modify surface chemistry and achieve highly regulated controlled release of active antioxidants, which can protect cells against external oxidative stress signals. This work has importance in the area of controlling material biocompatibility through augmenting the antioxidant status of cells.

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1. Introduction

Oxidative stress is a pathophysiological condition, where endogenous antioxidants are unable to counteract the production of oxidants, leading to cellular dysfunction. This overproduction of the reactive oxygen and nitrogen species (ROS/RNS) (e.g., hydroxyl radicals, singlet oxygen, hydrogen peroxide, peroxyl radicals) can be caused by both endogenous sources and exogenous sources. Examples of endogenous routes include ROS generating enzymes such as nitric oxide synthase, xanthine oxidase, amplified mitochondrial metabolism especially in aging cells resulting in mitochondrial dysfunction, damaged membrane and hence leakage of ROS into intracellular environment [1–4]. Some of the exogenous

Abbreviations: ABTS, 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonate); DCF-DA, dichlorofluorocein-diacetate; DEGDA, diethylene glycol diacrylate; DLS, dynamic light scattering; DMSO, dimethyl sulfoxide; EBM, endothelial basal medium; HCl, hydrogen chloride; HPLC, high pressure liquid chromatography; HUVEC, Human Umbilical Vein Endothelial Cell; IgG, imunnoglobin G (antibody); NNDA, N,N′ dimethyl 1,3-propane diamine; PBAE, poly(β-amino esters); PBS, phosphate buffer saline; PEG, polyethylene glycol; PEGDA, polyethylene glycol diacrylate; PEGME5000, polyethylene glycol methylether, Mn ~ 5000; PEGMEMA4000, polyethylene glycol methylether methacrylate, Mn ~ 4000; PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic acid); QMA, quercetin multiacrylate; QNG (x), quercetin conjugated PBAE nanogels (feed QMA concentration); RNS, reactive nitrogen species; ROS, reactive oxygen species; SLN, solid lipid nanoparticles; TCA, trichloroacetic acid; TEAC, trolox equivalent antioxidant capacity; THF, tetrahydrofuran; TNF-α, tumor necrosis factor-α.

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