Green-Synthesized Silica Nanoparticle-Based Thermosensitive Hydrogel for Targeted Delivery of Tranilast in Triple-Negative Breast Cancer

Shraddha Ram
School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, India

Amol A. Tagalpallewar
School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, India

Akshay Baheti *
School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, India

Abstract

Triple-negative breast cancer (TNBC) remains a challenge to oncologists all over the world due to its receptor-negative phenotype, remarkable molecular heterogeneity, and high resistance to traditional systemic therapies. The current study reports the rational design, systematic optimization and in-depth biological testing of a new composite drug-delivery platform of green-synthesized silica nanoparticles (SiNPs) encapsulated within a PDLLA-PEG-PDLLA (poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide)) triblock thermosensitive hydrogel to locally to TNBC tumor cells. Silica nanoparticles were synthesized through plant-mediated green sol-gel approach using aqueous Ocimum sanctum leaf extract as the capping and reducing agent, tetraethyl orthosilicate (TEOS) as the silicon source. The parameters of the formulation were optimized systematically in terms of Box-Behnken design (BBD) statistical model. The optimal TRL-SiNP formulation (TEOS: 6 mM, stirring speed: 1000 rpm, O. sanctum extract: 10 mM) has a particle size of 90.4 +/-3.93 nm, entrapment efficiency of 81.5 +/-2.77, and zeta potential of -28.3 +/-1.5 The nanoparticles that were loaded with drug were then introduced into a thermo responsive hydrogel matrix that could be subjected to sol-to-gel transition at physiological temperature (37oC) and could be injected and delivered locally. The in-depth physicochemical characterization was conducted using UV-Vis spectroscopy, X-ray diffractometry (XRD), fourier-transform infrared spectroscopy (FTIR), transmission electron microscopy (TEM), scanning electron microscopy (SEM), dynamic light scattering (DLS), and zeta potential. The in vitro release of the drugs showed a sustained, biphasic release profile over 14 days. ICH-compliant formulation stability was validated in accelerated stability studies up to 180 days. The biological screening of MDA-MB-231 TNBC cells showed that TRL-SiNP-HG induced an IC50 of 70.13 ug/mL, apoptosis of 85.3 ± 1.2 by PI uptake assay - better than carboplatin (80.8 ± 1.4). All these results make TRL-SiNP-HG an environmentally friendly, biocompatible, and therapeutically superior platform to be used in the local treatment of TNBC.

Keywords

Apoptosis, green nanotechnology, Tranilast, Silica Nanoparticles, TNBC, Thermo-responsive polymer.

Abbreviations

ANOVA: Analysis of Variance, BBD: Box-Behnken Design, DMSO: Dimethyl Sulfoxide, DoE: Design of Experiments, DLS: Dynamic Light Scattering, EE: Entrapment Efficiency, EPR: Enhanced Permeability and Retention , HG: Hydrogel, FTIR: Fourier Transform Infrared Spectroscopy, IC_{50}: Half Maximal Inhibitory Concentration, PBS: Phosphate Buffered Saline, PDI: Polydispersity Index, PDLLA: Poly(D,L-Lactide), PDLLA-PEG-PDLLA: Poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide), PI: Propidium Iodide PLEL: PDLLA-PEG-PDLLA, ROS: Reactive Oxygen Species, SD: Standard Deviation, SEM: Scanning Electron Microscopy, SiNPs: Silica Nanoparticles, TEM: Transmission Electron Microscopy, TEOS: Tetraethyl Orthosilicate, TNBC: Triple-Negative Breast Cancer, TRL: Tranilast, TRL-SiNP-HG: Tranilast-loaded Silica Nanoparticle in Hydrogel, UV-Vis: Ultraviolet-Visible Spectroscopy, XRD: X-ray Diffraction.