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Research Article

OH-Rich Interfacial Nanoarchitectonics for the Reconciliation of Structural Stability and Functional Accessibility in Curcumin Nanotherapeutics

Goen Lee,[I] Woo Hyuk Jung,[I] Tae Kyung Won,* and Dong June Ahn*

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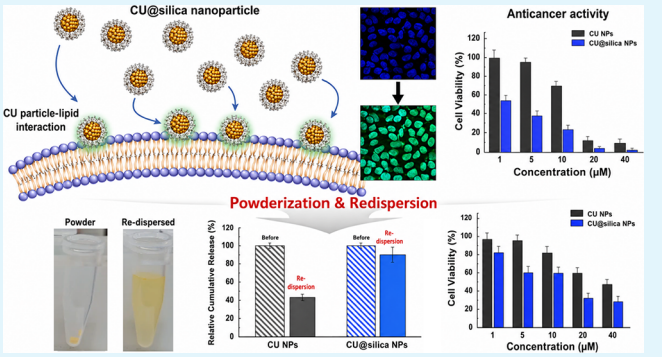
ABSTRACT: Curcumin offers significant therapeutic potential but is hindered by poor aqueous stability and limited cellular accessibility. Here, we present a curcumin nanotherapeutic platform featuring OH-rich, silanol-rich porous silica nanointerfaces (CU@silica NPs) that successfully decouple structural stabilization from molecular mobility. By employing poly(allylamine hydrochloride) (PAH)-assisted assembly and rapid tetramethyl orthosilicate (TMOS) hydrolysis, we engineered a mesostructured silica shell with a high density of surface silanol groups, creating diffusion pathways that preserve curcumin mobility while protecting it from degradation. This permeable nanointerface enables lipid-triggered fluorescence activation, allowing activation-responsive monitoring of drug delivery. The OH-rich silica interface further ensures exceptional redispersibility and functional preservation even after repeated powderization cycles, a critical requirement for long-term storage and transport. Supported by molecular dynamics simulations and in vitro evaluations, CU@silica NPs demonstrate accelerated cellular uptake and a five-fold improvement in anticancer efficacy compared with CU NPs. These findings establish silica nano-interface engineering as a robust strategy for developing storage-stable, stimuli-responsive, and image-guided nanomedicines for hydrophobic drugs.



KEYWORDS: *OH-rich silica nanointerfaces, curcumin nanotherapeutics, activation-responsive fluorescence, molecular mobility, colloidal stability and redispersibility*

1. INTRODUCTION

Recently, curcumin (diferuloylmethane, CU) has attracted considerable attention due to its cost-effectiveness and safety.[1,2] Curcumin primarily exists in the keto-enol tautomeric form and has been utilized in the medical industry for its diverse properties, including anticancer, antiviral, antioxidant, and anti-inflammatory effects.[3−8] In addition to these biological effects, curcumin has been successfully employed as a probe for studying liposome properties and detection applications. However, a major challenge associated with curcumin is its low solubility in water, which limits its availability in biological systems.[9−11] Although increasing the pH of the solvent can improve the solubility of curcumin,[12] it is known to hydrolyze rapidly in alkaline conditions. The low bioavailability of curcumin results in low activity, poor absorption, high metabolic rates in vivo, and rapid elimination from the system,[13] posing a significant hurdle in translating curcumin's chemo preventive and therapeutic potential from the laboratory to clinical settings.

To overcome these limitations, numerous nanotechnology-based formulations have been explored, including liposomes and phospholipid complexes,[14,15] polymer nanoparticles,[16,17] gold nanoparticles,[18] multiple cyclodextrin inclusion complexes,[19] and encapsulation methods such as surfactant micelles and mesoporous silica carriers.[16,20−22] While these approaches partially alleviate solubility limitations, many conventional encapsulation strategies rely on dense matrices or tightly packed cores, which can restrict molecular mobility, diminish curcumin's photophysical response, and complicate re-dispersion after drying. Thus, a platform that simultaneously ensures structural stability, molecular accessibility, and fluorescence responsiveness remains highly desirable. Silica nanoparticles offer several advantages, including hydrophilicity, tunable porosity, biocompatibility, and facile surface modification.[23−27] In particular, as the density and distribution of surface silanol groups are known to critically modulate the surface hydration structure and interfacial molecular interactions, a

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