Fabrication and Characterization of Plant-mediated Zinc Oxide Nanoparticles Loaded into Dissolving Microneedles

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Abstract

Researchers are seeking potential substituents to be used for the treatment of skin cancer instead of the commonly used chemotherapeutic agents given intravenously, which are known for their unavoidable adverse effects. Studies proved that the use of metal oxide nanoparticles that are greenly synthesized was superior for skin cancer treatment. Therefore, the main purpose of this study is to greenly synthesize zinc oxide nanoparticles (ZnO NPs) and load them on non-invasive microneedles (MNs) for the treatment of skin cancer. This study explored an eco-friendly approach to synthesizing ZnO NPs using a volume ratio of 4:1 mixture of *Phoenix dactylifera* (*P. dactylifera*) root hair extract and 0.8M zinc acetate dihydrate. The green-synthesized ZnO NPs had an average size of 24.01 ± 1.70nm, a polydispersity index (PDI) of 0.25 ± 0.02, and a zeta potential of -18.45 ± 1.80mv. To improve the transdermal delivery of ZnO NPs to treat skin cancer, a solution of the greenly-synthesized ZnO NPs was mixed with 10% sodium carboxymethyl cellulose (Na CMC) and incorporated into MNs, forming ZnO NPs-loaded MNs. Additionally, doxorubicin hydrochloride (DOX HCl), a chemotherapeutic agent used to treat various types of cancer, was also loaded into MNs (DOX-loaded MNs) for comparative studies. ZnO NP- and DOX-loaded MNs were evaluated in terms of morphology, mechanical properties, needle insertion, dissolution rate,

ZnO and DOX contents, Fourier transform infrared spectroscopy, *ex vivo* permeation, and stability. Stability studies conducted on ZnO NPs for 1, 2, 4, and 8 weeks showed an increase in average particle size and polydispersity index with a range of 24.01-133.8nm ($p = 0.14$) and 0.25-0.51 ($p = 0.08$) respectively. Meanwhile, zeta potential gradually decreased, attaining -6.55mv, compared to initially reported at -18.45mV ($p < 0.05$). The ZnO NPs- and DOX-loaded MNs showed a pyramidal shape with a square base that possessed the ability to withstand a compression force of 32N for 30sec, pierce the Parafilm M® sheet at a depth of 374-504µm, and dissolve entirely in 30min. The ZnO NPs- and DOX-loaded MNs maintained their stability for up to 2 weeks at room temperature and 4 weeks in the refrigerator. Overall, the findings prove that the greenly synthesized ZnO NPs loaded into MNs could enhance the transdermal delivery of ZnO NPs and DOX through the skin and that the MNs are indeed a successful delivery approach proven by their mechanical properties and *ex vivo* permeation through the skin.

Keywords: Green synthesis, microneedles, nanoparticles, transdermal drug delivery zinc oxide.