ALA-Loaded Microneedles for Photodynamic Therapy – from Fabrication to *In Vivo* Application

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Dissolving microneedles (DMNs) have emerged as a promising modality for intradermal and transdermal drug delivery, eliciting considerable scientific interest across diverse pharmaceutical compounds and polymer matrices tailored to specific therapeutic contexts. Addressing a key challenge in topical photodynamic therapy (PDT) for non-melanoma skin cancer, which often faces limitations in cream permeation, DMNs offer a potential solution by enhancing the permeation of prodrugs, thereby facilitating the distribution of photosensitizers within lesions.

Building upon our prior work published in 2021, wherein we observed an augmentation in protoporphyrin IX (PpIX) distribution using DMNs loaded with 5% aminolevulinic acid (ALA), we further explored DMNs containing 10% ALA with 20% Gantrez AN-139. However, the higher concentration of ALA posed challenges to the dry process and stability of the DMNs, impacting *in vivo* dissolution kinetics. To address these challenges, we devised a novel manufacturing protocol to ensure mechanical resistance and insertion capability, demonstrating promising performance and paving the way for pilot preclinical studies. Following refinement, these optimized DMNs were tested in a human xenograft tumor model induced in mice to evaluate PpIX distribution, quantified using fluorescence techniques. Subsequently, PDT protocols with DMNs were compared with cream to assess their efficacy. Preliminary findings indicate that DMNs have significantly enhanced treatment responses. This model of DMNs has also been investigated as a light guiding during PDT. Furthermore, while DMNs hold great promise in drug delivery, ensuring their safety and efficacy in clinical settings requires effective decontamination protocols. Our study investigated ozone's efficacy in decontaminating ALA-loaded DMNs. Results indicated ozone's effectiveness in decontaminating *E. coli* and *S. aureus* while preserving the mechanical properties of the polymer. Furthermore, MALDI-TOF analysis revealed no drug degradation. This ensures DMNs remain contaminant-free, bolstering their efficacy in clinical applications. Our approach enhances the safety and reliability of DMN-based drug delivery. It paves the way for broader adoption in medical practice, marking a significant step to moving forward to clinical trials.