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QbD-optimized curcumin-lignin nanoparticle spray for targeted wound infection therapy against *Escherichia coli* and *Mycobacterium smegmatis*

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ABSTRACT

Chronic wounds infected with multidrug-resistant bacteria pose a significant therapeutic challenge, requiring biocompatible and effective interventions. This study presents a novel lignin-based nanoparticle spray for the localized delivery of curcumin, a natural anti-inflammatory and antimicrobial compound. Lignin, a sustainable polyphenolic biopolymer with inherent antioxidant and antimicrobial activities, was used both as a carrier and functional agent. Curcumin-loaded lignin nanoparticles (CLLNPs) were synthesized using a dialysis-based solvent displacement method and optimized through a Quality by Design approach. These nanoparticles were incorporated into a Eudragit-L100-based film-forming spray for targeted skin application. The optimized CLLNPs exhibited a mean particle size of 119.2 ± 2.1 nm, PDI of 0.167, zeta potential of −21.5 mV, and high encapsulation efficiency (97.58 ± 0.67%). The spray dried quickly within 60 s, showed good film uniformity, mechanical stability, and a skin-compatible pH of 6.21. *In vitro* release followed Higuchi kinetics, with 88.76% curcumin released within 6 h. *Ex vivo* skin permeation studies demonstrated enhanced drug penetration (165.62 µg/cm^2/h), and CLSM confirmed uniform, deep nanoparticle penetration into skin layers. The formulation exhibited strong antibacterial activity against both Gram-negative *Escherichia coli* and Gram-positive *Mycobacterium smegmatis*, along with potent antioxidant activity (91.85% DPPH scavenging at 500 µg/mL). Together, these findings highlight the potential of lignin-based nanocarriers to offer a synergistic, sustainable, and patient-friendly approach to wound healing and infection control, aligning with the goals of personalized medicine.

Abbreviation: ANOVA: Analysis of Variance; BLNP/BLNP: Blank Lignin Nanoparticles; CLLNP: Curcumin-Loaded Lignin Nanoparticles; CMA: Critical Material Attributes; CPPs: Critical Process Parameters;

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