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Characterization and functional validation of a multilayer biomimetic ungual model for transungual permeation

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ABSTRACT

Introduction: Low transungual permeability constitutes one of the main challenges in the topical treatment of nail disorders, limiting the efficacy of pharmaceutical formulations and contributing to high rates of clinical failure. Diseases such as onychomycosis, with high prevalence and a significant impact on quality of life, exemplify this problem. To study and develop strategies that enable overcoming this natural barrier of the human nail, it is essential to have experimental models that accurately reproduce it. However, the stratified organisation of the nail plate, associated with a keratin-rich matrix and a reduced lipid fraction, hinders such reproduction in conventional models, justifying the need to develop and validate more representative biomimetic approaches.
Objectives: The present work aimed to characterise and functionally validate a multilayer biomimetic ungual model based on a nanofibrous structure with lipid deposition, assessing its selective capacity in the transungual permeation of compounds with different physicochemical properties.
Methodology: The multilayer nanofibrous structure was produced by sequential electrospinning, combining synthetic polymers and keratin extracted from human hair in order to mimic the dorsal, intermediate, and ventral regions of the nail plate. To reproduce the nail lipid fraction, a biomimetic lipid layer was applied. Functional evaluation was carried out through *in vitro* permeation assays using Franz diffusion cells, employing caffeine (hydrophilic compound) and terbinafine (lipophilic compound) as model molecules, enabling the determination of permeation flux and permeability coefficients.

Contributions: Conceptualization: DF, ML and CML; Formal Analysis: DF and ML; Funding acquisition: AR, ML and CML; Investigation: DF and DS; Methodology: DS, AR, ML and CML; Resources: AR, ML and CML; Supervision: ML and CML; Validation: DF and ML; Visualization: DF and ML; Writing – original draft: DF; Writing – review & editing: ML and CML.

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Results: The results revealed distinct permeation profiles dependent on compound characteristics. A significant reduction in caffeine flux was observed across the multilayer biomimetic ungual model. In contrast, terbinafine exhibited higher permeation through the biomimetic model, suggesting greater affinity for the incorporated lipid fraction. The results appear to reproduce the physiological behaviour of the human nail, supporting the selective capacity of the model for transungual transport of different molecules.
Conclusion: It is concluded that the developed multilayer biomimetic ungual model constitutes a promising *in vitro* experimental platform with strong potential as a representative model for transungual permeation studies. However, the need for further validation is acknowledged, and future studies involving a broader range of compounds will allow the consolidation of its applicability.