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"Development of a Model Mimicking Lipid Matrix in the Stratum Corneum for Simulating Percutaneous Absorption"

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1. Introduction

The global cosmetics industry is rapidly expanding, with its market size reaching approximately USD 340 billion as of 2024 and a projected CAGR exceeding 5% by 2027 [1]. Developing skincare products capable of efficiently delivering active compounds across the skin barrier is critical to this growth. However, traditional evaluations using human tissue or reconstructed human skin models are limited by accessibility issues, inter-individual variability, and low reproducibility [2-6]. Animal-derived models face ethical and regulatory restrictions [2-4], while reconstructed human skin models exhibit long fabrication times and batch-to-batch variability, compounded by ethnic differences in epidermal stratification and gene expression [5-7]. These limitations hinder their widespread adoption as standardized platforms for high-throughput screening.

To overcome these challenges, we developed a stratum corneum (SC) lipid membrane model which replicates the nano- and microstructural features of native SC. The SC, composed of corneocytes embedded within a continuous intercellular lipid matrix forming a "bricks-and-mortar" structure, serves as the principal barrier regulating trans-epidermal water loss and penetration of exogeneous substances [8-9]. Given that most substances permeate through the lipid matrix rather than passing through corneocytes, accurately replicating the SC lipid structure is critical for developing reliable human skin substitutes. Our fabricated SC lipid membrane achieves high inter-batch reproducibility, structural fidelity, and physicochemical relevance by mimicking the lateral lipid packing structures of native SC. Although liposomes, colloidal vesicles composed of phospholipid bilayers capable of encapsulating both hydrophilic and lipophilic compounds [10], are well recognized for their ability to enhance skin penetration, the mechanisms underlying their interaction with stratum corneum (SC) lipids remain poorly understood. In this study, we utilized the fabricated SC lipid membrane model to investigate these mechanisms and provide deeper insights into liposome–SC lipid interactions.

2. Materials and Methods

2.1 Fabrication of the SC Lipid Membrane Model

A SC lipid membrane model was fabricated by depositing a lipid mixture composed of ceramide, free fatty acid, cholesterol, and cholesterol sulfate onto a porous polycarbonate membrane. After deposition, the membranes were annealed under controlled conditions to promote the formation of lateral lipid packing structures.

2.2 Characterization of Lipid Membrane Model

The morphological structure of the fabricated SC lipid membrane was characterized by field-emission scanning electron microscopy (FE-SEM; Regulus 8220, Hitachi, Japan). Samples were prepared by cryo-sectioning after embedding in optimal cutting temperature (OCT) compound and freezing in liquid nitrogen. Thin sections were sputter-coated with platinum and imaged to confirm the uniformity and thickness of the lipid layer.

The lateral lipid packing structure was analyzed by attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectroscopy using a Spectrum 3 spectrometer (PerkinElmer, USA) equipped with a MIRacle ATR ZnSe crystal. Spectra were collected in the range relevant to methylene stretching and scissoring vibrations, providing information about the ordering and reproducibility of lipid packing across independent batches.

2.3 Percutaneous Absorption Experiment

For skin permeation studies, lecithin- and cholesterol-based liposomes containing niacinamide (NIA) were provided by COSMAX (Seongnam, Republic of Korea). Liposomal NIA formulations and aqueous NIA solutions were applied to the SC lipid membrane mounted in Franz diffusion cells. Both solutions were prepared to contain 5% NIA. The cumulative amount of permeated NIA was quantified by high-performance liquid chromatography (HPLC).

3. Results

3.1 Fabrication of the SC lipid membrane model

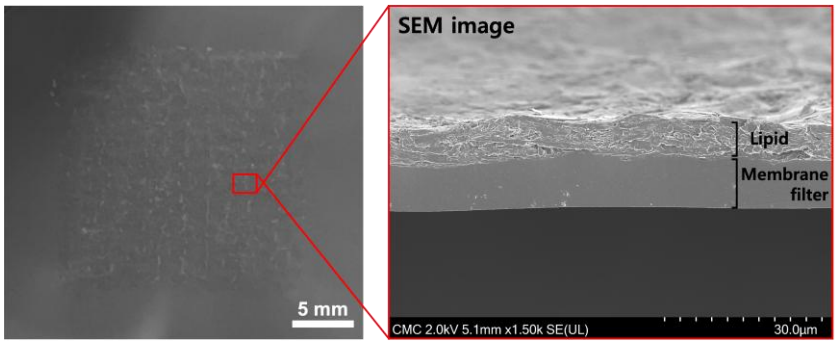

Figure 1. Macroscopic and SEM image of frabricated SC lipid membrane model.

We developed a SC lipid membrane model that mimics the nano- and microstructure of native stratum corneum (SC). The lipid solution was uniformly sprayed onto a polycarbonate track-etched membrane with 10 nm pores, followed by annealing at 90°C to induce lateral packing structures comparable to native SC. A nitrogen-stream-based spraying system was

used to minimize lipid oxidation and achieve uniform coverage across the porous substrate [11]. The fabricated model formed a homogeneous lipid layer, providing a reliable platform for permeation studies (Figure 1).

3.2 Characterization of lipid packing of the SC lipid membrane model

The lipid packing of the SC lipid membrane model was evaluated by preparing five independent healthy orthorhombic (OR) models. ATR-FTIR spectroscopy was employed to analyze the methylene stretching and scissoring bands, which reflect the lateral lipid packing structures. All models exhibited highly consistent spectral profiles, indicating minimal batch-to-batch variability (Figure 2). These results confirm that the fabricated SC lipid membrane provides excellent reproducibility, ensuring reliable outcomes for skin permeation studies.

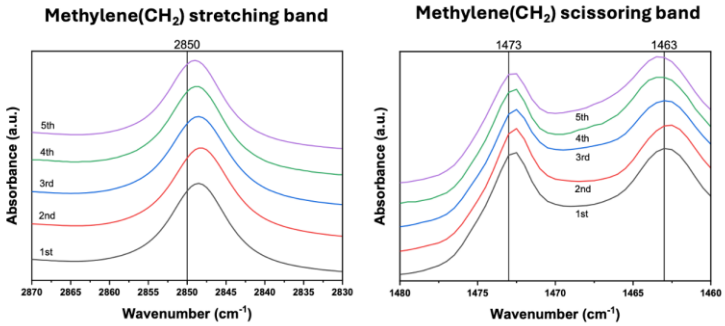

Figure 2. Methylene stretching (left) and scissoring (right) bands of SC lipid membrane models which were independently fabricated.

3.3 Investigation of liposomal skin permeation using the SC lipid membrane model

The permeability of liposomes was evaluated using the SC lipid membrane model by comparing the cumulative skin penetration of niacinamide (NIA) encapsulated in liposomes with that of an aqueous NIA solution. Both formulations contained 5% (w/v) NIA and were applied under identical conditions. After 24 hours, the cumulative amount of NIA that permeated through the SC lipid membrane was approximately 20-fold higher with the liposomal formulation than with the aqueous solution (Figure 3). These results demonstrate the superior capability of liposomes to enhance transdermal delivery of hydrophilic active ingredients.

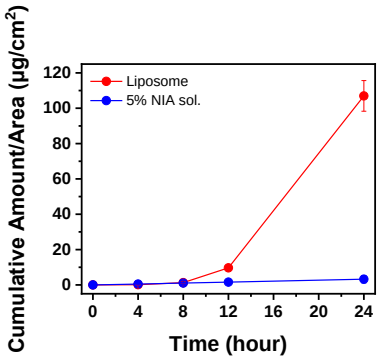

Figure 3. Permeability of liposome and NIA solution across the SC lipid membrane model.

4. Discussion

The SC lipid membrane model developed in this study successfully recapitulated the structural features of native stratum corneum, as demonstrated by uniform lipid deposition and the formation of a lateral packing structure comparable to human SC. The model exhibited excellent reproducibility across independent batches, with minimal variation in lipid packing structure confirmed by ATR-FTIR analysis. Utilizing this model, the cumulative permeation of niacinamide encapsulated in liposomes was found to be approximately 20-fold higher than that of the aqueous niacinamide solution, highlighting the effectiveness of liposomes in enhancing percutaneous absorption of hydrophilic actives. These findings suggest that the fabricated SC lipid membrane provides a robust and consistent platform for studying percutaneous absorption mechanisms and optimizing liposomal delivery systems.

5. Conclusion

The SC lipid membrane model developed herein offers a reproducible and physiologically relevant platform for studying percutaneous absorption. By utilizing this model to investigate the mechanisms of liposomal skin permeation, we envision that advanced liposomal delivery systems would be rationally designed and optimized for applications in the dermocosmetic and pharmaceutical industries.

6. References

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