The Influence of Stratum Corneum Lamellar Structures on Microemulsion Permeation

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The stratum corneum (SC), the outermost layer of the skin, acts as the main barrier against transdermal permeation. This barrier function is mainly governed by the highly ordered lamellar structures of intercellular lipids. Microemulsions (MEs) are useful carriers for transdermal delivery because they can solubilize hydrophilic compounds in the inner aqueous phase while interacting with the hydrophobic lipid environment of the SC. However, how the lamellar state of the SC affects ME adsorption and permeation remains unclear. In this study, we investigated the influence of deep eutectic solvents (DESs)-induced SC lamellar structures on ME behavior using SANS.

DESs with different properties were used as pretreatment agents to change SC environments before ME application. Hydrophobic DESs, including thymol–decanoic acid (TD), menthol–decanoic acid (MD), and geraniol–decanoic acid (GD), can disrupt or extract SC intercellular lipids. In contrast, the hydrophilic DES choline chloride–glycerol:water (9ChG:H_2O) causes relatively mild barrier disruption and modifies the hydration state and lipid organization of the SC. After DES pretreatment, D_2O-loaded MEs were applied to the SC, and the structural behavior of MEs retained in the SC region was monitored by SANS.

Stacked SC sheets were put on a PEEK film, pretreated with DES, rinsed, dried, and then exposed to the ME. In this setup, MEs that were not adsorbed onto the SC moved out of the neutron beam path. Therefore, the obtained scattering profiles mainly reflected MEs adsorbed or retained in the SC region.

For 9ChG:H_2O-pretreated SC, clear SANS profiles derived from spherical ME structures were obtained. The profiles were fitted using a sphere model, indicating that the ME inner phase was retained in the SC region. Time-resolved analysis showed that the apparent radius of the ME gradually decreased from approximately 4.0 nm to 3.5 nm over 180 min (Fig.1). This result suggests that the ME was not simply adsorbed on the SC surface but underwent a gradual structural transition after contact with SC lipids. The hydrophilic DES may have modified the hydration environment and lamellar organization of the SC, allowing the ME to be retained while partially releasing its inner aqueous phase or reorganizing within the intercellular lipid region.

In contrast, no distinct SANS profiles derived from MEs were obtained for TD-, MD-, or GD-pretreated SC. This suggests that MEs were not stably retained in the SC region after hydrophobic DES pretreatment. Hydrophobic DESs likely caused lipid extraction and strong disruption of the SC lamellar structure, resulting in weakened interactions between MEs and SC lipids. Under these conditions, MEs may pass through the disrupted SC or move away from the neutron beam path rather than remaining in the measurable region.

These SANS results indicate that ME behavior strongly depends on the lamellar state of the SC formed by DES pretreatment. Therefore, controlling SC lamellar structures before ME application is an important factor in regulating ME-based transdermal delivery. This study demonstrates that SANS is a powerful method for directly evaluating the relationship between SC lamellar states and ME permeation behavior.

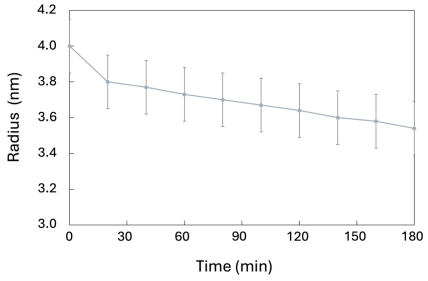

Fig.1 Time course of the inner size of the ME applied to 9ChG:H_2O-treated SC.

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