Influence of the water content of the skin and the microemulsion structure on the penetration mechanism

M. Sakuragi[A], E. Nakamura[A], S. Shinoda[A]

[A]*Sojo Univ.*

The outermost layer of the skin, the stratum corneum (SC), is known as a skin barrier. The SC is composed of corneocytes and intercellular lipid layers. It has been reported that the periodicity and regularity of SC lamellar structures change depending on the SC water contents. The water content of the SC can affect the skin penetration mechanism of a drug carrier since the carrier crosses the intercellular lipid lamellar in the SC. However, the interaction mechanism between the drug carrier and intercellular lipids remains unknown when the drug carrier is applied to the SC with different water contents.

In our previous study, we investigated the SC penetration mechanism of water in oil-type microemulsions (W/O MEs) depending on the SC water contents. MEs were prepared by two non-ionic surfactants, Tween-80 and Span-20 (Tween-80 / Span-20 = 1 / 2 (wt/wt)), D_2O as an inner phase, and isopropyl myristate (IPM) as an oil phase. According to our SANS analysis, MEs formed a spherical structure with a radius of inner phase of 4 nm. Subsequently, we observed the inner D_2O phase of MEs after applying to the SC by SANS. In addition, the water phases of the SC lamellar were replaced to D_2O to observe the lamellar structure when applying MEs containing H_2O. Results showed that the inner water of MEs was released to the SC when applied to the dry SC. Conversely, when MEs are applied to hydrated SC, the MEs absorb the water from the SC into their inner phases (no. 22404 for JRR-3 and 2022C0003 for J-PARC, *RSC Adv.* 13, 17742, 2023). In this study, we investigated the structural changes of the cylindrical MEs and MEs adding a skin penetration enhancer.

The cylindrical W/O MEs were prepared with Tween80/Span20 = 2/1 (wt/wt). For cylindrical MEs, the ratio of a cylinder to a sphere significantly decreased immediately after applying to the dry or hydrated SC (Fig.1). After that, the cross-sectional diameters of cylindrical MEs and spherical MEs decreased for dry SC and increased for hydrated SC. As a result, the skin permeation of spherical MEs was superior to that of cylindrical MEs, likely because the cylindrical MEs disintegrated immediately after application to the SC, releasing the drug prematurely and preventing it from reaching deeper layers of the skin.

To further enhance the skin permeation of MEs, a hydrophobic deep eutectic solvent (DES) as a skin penetration enhancer was added to the oil phase of MEs. Upon adding DES, MEs did not disperse stably at the compositions of Tween 80/Span 20 = 1/2 and 2/1 but it dispersed stably at Tween 80/Span 20 = 9/1. SANS analysis showed that the MEs form a sphere with an inner diameter of 4.2 nm. When applied to hydrated SC, the ME size gradually increased, similar to conventional W/O spherical ME, indicating that it penetrates while incorporating water from the SC. On the other hand, when applied to dry SC, the ME size with DES added did not change. MEs can stably permeate the skin without releasing the water in its inner phase into the SC, as DES's components incorporate into the ME's surfactant. This fact suggests that MEs can penetrate the dry SC while retaining the encapsulated drug within the MEs. We plan to investigate the structural changes in SC lamellar during ME application.

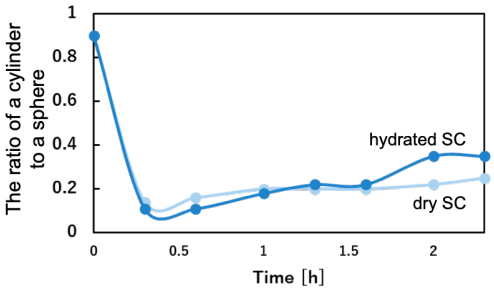

Fig. 1 The ratio changes of a cylinder to a sphere of MEs when applying to the SC.