Annals of Pharmacology and Pharmaceutics

Short Communication
Published: 16 Feb, 2017

Transdermal Drug Delivery and Lipid Lamellar Structure in Stratum Corneum

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Short Communication

Transdermal drug delivery has many advantages, such as drugs can escape from first-pass effect of liver, non-invasive administration and so on. Moreover, maintenance of prolonged plasma concentration of drugs is considered to be possible. Side effect caused by the rapid increase in plasma concentration is possibly prevented by transdermal administration of drugs. Breaking of administration is easy and frequent administration is needless. Those properties of transdermal drug delivery contribute increase in adherence and QOL.

Skin, administration site of transdermal delivery system, has barrier function to prevent invasion of exogenous materials and dehydration. However, in transdermal drug delivery, we have to overcome the barrier function of skin adequately. Incorporation of skin permeation enhancers, such as *l*-menthol, in formulation is considered to be the promising method for effective transdermal delivery system [1-7]. However, the promoting mechanism of those compounds was not fully clarified in molecular level.

Skin surface is covered by stratum corneum, illustrated as "brick-mortal model", which is considered to the key biological tissue as physical barrier properties of skin. In those model, "brick" corresponds to corneocyte and "mortal" means intercellular lipids. Intercellular lipids form regular structure, so called long (13 nm) and short (6 nm) lamellar structure and orthorhombic/hexagonal lattice. Lipid lamellar was investigated mainly using differential scanning calorimetry and Fourier transformed infrared spectroscopy. However, the signals obtained were sometimes complicated and precise analysis was difficult using those data. Stratum corneum is composed of not only lipids but also proteins. We have employed synchrotron X-ray diffraction complementary to clarify the nanostructure in stratum corneum.

Using those methodologies, we found that lipid lamellar structure in intercellular space in stratum corneum partially become liquid crystal by the administration of skin permeation enhancer drugs, *l*-menthol [8]. Recently, we have demonstrated the *l*-menthol-lipid interaction in several reports [9-12].

l-Menthol increases drug partitioning on the surface of skin, diffusion of drugs in the skin, and lipid fluidity in the stratum corneum and alters the rigidly arranged lipid structure of intercellular lipids. However, *l*-menthol is a solid at room temperature, and it is difficult to determine the effects of *l*-menthol alone. Thus, we vaporized *l*-menthol in order to avoid the effects of solvents [13]. The vaporized *l*-menthol was applied to the stratum corneum or lipid models comprising composed of ceramide [EOS], ceramide [NS], cholesterol and palmitic acid. Synchrotron X-ray diffraction, differential scanning calorimetry, and attenuated total reflection Fourier transform infrared spectroscopy analyses revealed that the lipid models were composed of hexagonal packing and orthorhombic packing structures of different lamellar periods. Taken together, our results revealed that *l*-menthol strongly affected the lipid model composed of ceramide [EOS]. Therefore, *l*-menthol facilitated the permeation of drugs through the skin by liquid crystallization of the longer lamellar structure. Importantly, these simple lipid models are useful for investigating nanostructure of the intercellular lipids in the stratum corneum.

Attenuated total reflection Fourier-transform infrared spectroscopy is a powerful tool for evaluating the functional group interaction of intercellular lipids in the stratum corneum. However, as the large amide I and amide II absorption bands are mainly derived from keratin, which constitutes about 90% of the stratum corneum, it is difficult to investigate the amide bonding interactions of intercellular lipids. Thus, extracted lipids from the stratum corneum was used to investigate the amide bonding derived from lipid interaction [14]. Synchrotron X-ray diffraction studies showed

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Received Date: *24 Dec 2016*
Accepted Date: *14 Feb 2017*
Published Date: *16 Feb 2017*

Citation:
Obata Y. Transdermal Drug Delivery and Lipid Lamellar Structure in Stratum Corneum. Ann Pharmacol Pharm. 2017; 2(5): 1028.

that the thermal profiles of stratum corneum lipids and extracted lipids showed similar behavior. The amide absorptions increased with increasing temperature, similar to the observations for the formation of high-temperature hexagonal structures by synchrotron X-ray diffraction. Furthermore, these characteristic changes were disturbed by *l*-menthol, which fluidizes the polar and hydrophobic regions of intercellular lipids in the stratum corneum. The extracted lipids were useful as an appropriate model of stratum corneum lipid organization for investigation of amide bonding interactions in stratum corneum lipids without interference from keratin.

As a next, we focused on nerolidol and levulinic acid and investigated their influence on stratum corneum lipid structures [15]. Nerolidol, a sesquiterpene, has been reported to enhance the permeation of various drugs. Levulinic acid is reported to enhance the permeability of buprenorphine. Synchrotron X-ray diffraction and attenuated total reflectance Fourier transform infrared spectroscopy measurements revealed that nerolidol disturbs the rigidly arranged lipid structure and increases lipid fluidity. Levulinic acid had a smaller effect on stratum corneum lipid structures, but did increase lipid fluidity when co-administered with nerolidol or heat. We found that nerolidol has an effect on stratum corneum lipids similar to that of *l*-menthol, and levulinic acid had an effect similar to that of oleic acid.

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