The Synthesis of New Pseudoceramides using Alkylketene Dimer and Their Physical Properties

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Abstract: As cosmetic raw materials, novel pseudoceramides have been synthesized and their physical properties have been investigated. The pseudoceramides, PC-4 (N-(2,3-dihydroxypropyl)-2-myristyl/palmitoyl-3-oxoetaramide/arachidamide), and PC-5 (N-(1,3-dihydroxyisopropyl)-2-myristyl/palmitoyl-3-oxoetaramide/arachidamide), were synthesized according to the reaction between alkylketene dimer (AKD) and alkanolamines. The reduced types of new pseudoceramides, PC-4R (N-(2,3-dihydroxypropyl)-2-myristyl/palmitoyl-3-hydroxyetaramide/arachidamide) and PC-5R (N-(1,3-dihydroxyisopropyl)-2-myristyl/palmitoyl-3-hydroxyetaramide/arachidamide) were prepared by the reduction of PC-4 and PC-5, respectively. An effective and economical synthetic pathway with high purity and high yield enabled the industrial production of these pseudoceramides. It was confirmed that there were several kinds of hydrogen bonding in them by the FT-IR study. X-ray diffraction (XRD) method and cross-polarized microscopy results make us confirm their intrinsic characteristics of lamellar structure formations. This intrinsic power to form the lamellar structure made it possible to form a pseudo-stratum corneum lipid emulsion, which shows the multi-lamellar structure.

Keywords: pseudoceramide, lamellar, alkylketene dimer, alkanolamine, stratum corneum, emulsion

1. Introduction

The outermost layer of the skin plays a very important role in human living. They prevent transepidermal water loss and the penetration of the harmful compounds from environment, and resist mechanical influence to some extent [1]. The ceramides are the most prominent lipids found in stratum corneum (SC). They have important functions in formation and retention of SC. The structure of SC was proposed to illustrate as a “Brick & Mortar” Model by Elias in 1981 [2,3]. The corneneocytes are filled with keratin and embedded in the intercellular lipids, which form lamellar structures. According to the Elias model, the brick represented corneneocytes and the mortar represented intercellular lipids. Three-dimensional structure of SC is the basis of the skin barrier function.

Skin damage caused by detergents, which remove the SC lipids, will result in increase of transepidermal water loss (TEWL), and deteriorate the barrier function. Moreover, a damaged skin barrier leads to increase skin sensitivity and potential irritation such as atopic dermatitis or psoriasis [4]. It has been found those topical applications of ceramide or pseudoceramide containing compositions are effective in relieving atopic eczema [5,6]. They also have been found to exhibit therapeutic properties such as wound or ulcer healing through the promotion of cell restoration and growth. For these reasons, many extensive efforts have been made by lots of cosmetic and pharmaceutical companies to access natural ceramide [7-9] or pseudoceramide [10]. Natural ceramides existing in the nature are classified into six types, and the basic structure of these natural ceramides has two or more hydroxyl groups, at least
two alkyl groups and one amide bond [11]. In order to synthesize appropriate pseudoceramides, it is preferable that the structure of natural ceramides should be examined first, and then pseudoceramides having similar structure to natural ceramides should be synthesized. Although several pseudoceramides have been reported, they show disadvantage in preparation because of lengthy synthetic steps [12]. Recently, we synthesized four kinds of the new pseudoceramides (PC-4, PC-5, PC-4R, and PC-5R) by the reaction of alkanolamine and alkylketene dimer (AKD). The new pseudoceramides were designed to have the properties similar to the natural ceramides and to mimic the behavior of them. They could be effectively prepared by one or two step reaction(s) and showed ability to form the lamellar structure.

2. Experimental

2.1. The Preparation of Samples for the Study

AKD (Nippon Yushi), 3-amino-1,2-propanediol (Aldrich), 2-amino-1,3-propanediol (Aldrich), NaBH₄ (Janssen), toluene (Duksan), methanol (Tedia), and petroleum ether (Duksan) were used for the synthesis of pseudoceramides. Stearic acid (Junsei), cholesterol (Junsei), Tween 80 (ICI), stearyl alcohol (Henkel), liquid paraffin (Seojin Chemical), POE (8) C₆₆₋₂₀ Guebet alcohol (Henkel), and glycerin (Duksan) were used as the component for pseudo-SC lipids emulsion.

2.2. The Preparation of Emulsion

The oil phase which was composed of pseudo-SC layer components (pseudoceramide, stearic acid, cholesterol), emulsifiers (Tween 80, stearyl alcohol, POE (8) C₆₆₋₂₀ Guebet alcohol) and oil (liquid paraffin) was melted in about 80 °C and mixed homogeneously. Then the water phase was added into the oil phase slowly with vigorous stirring, and it was cooled to room temperature.

2.3. The Characterization of Lipids

The phase transition behavior of the pseudoceramides was determined by differential scanning calorimetry (DSC) (Perkin Elmer, PL-700). The structures and the states of lipids were identified by XRD (Philips, PW 1830 Generator) and Cu-Kα radiation was used in the XRD measurement. In addition, NMR (Varian, Jemini 200) spectra, FT-IR (Mattson, Mattson 7000) spectra, and melting points (Fisher) were measured for the characterization of the synthesized pseudoceramides.

2.4. The Observation of Optical Texture by a Cross-polarized Light Microscopy

A cross-polarized light microscopy (Nikon) was used for the observation of the cross-microscopic optical texture in the meta-stable state of the pseudoceramides. A thermo-regulator (cooling rate : 2 °C/min) as a combined system to the microscope was used to control the temperature in order to catch the meta-stable state of the samples.

2.5. The Synthesis

N-(2,3-dihydroxypropyl)-2-myristyl/palmitoyl-3-oxostearamide/arachidamide (PC-4): 3-tetradecyl/hexadecyl-4-pentadec/ heptadec-1-enylxetane-2-one (AKD) (15 g, 31.5 mmol) and 3-amino-1,2-propanediol (3.16 g, 34.7 mmol, [α]D² = 0) were heated under refluxing toluene (50 mL) for about 24 h. After adding about 200 mL of petroleum ether and cooling this mixture, white solids precipitated. The solid was purified by recrystallization from methanol or ethanol to give PC-4 as a white crystalline powder (yield: 90%).

Rt = 0.29 (CHCl₃ : Methanol : Acetic acid = 95 : 5 : 1).

Melting Point: 84 – 85 °C. IR (cm⁻¹, KBr): 3312, 2918, 2849, 1716, 1636, 1540, 1467. ¹H-NMR (CDCl₃): δ 0.8 – 1.9 (m, alkyl), 2.4 (2H, t, R=CH₂-CON-), 3.4 (1H, t, CO-CH(R)-CON-), 3.4 (2H, q, -CO-CH₂-R), 3.55 (2H, d, -CH(OH)-CH₂OH), 3.65 (1H, m, -CH₂-CH(OH)-CH₂), 6.8 (1H, t, -CONH₂). N-(1,3-dihydroxyisopropyl)-2-myristyl/palmitoyl-3-oxostearamide/arachidamide (PC-5): 3-tetradecyl/hexadecyl-4-pentadec/ heptadec-1-enylxetane-2-one (AKD) (15 g, 31.5 mmol) and 2-amino-1,3-propanediol (3.16 g, 34.7 mmol) were heated under refluxing toluene (50 mL) for about 24 h. After adding about 200 mL of petroleum ether and cooling this mixture, white solids precipitated. The solid was purified by recrystallization from methanol or ethanol to give PC-5 as a white needle-like crystal (yield: 95%).

Rt = 0.24 (CHCl₃ : Methanol : Acetic acid = 95 : 5 : 1).

Melting Point: 87 – 88 °C. IR (cm⁻¹, KBr): 3289, 2917, 2849, 1720, 1633, 1537, 1467. ¹H-NMR (CDCl₃): δ 0.8 – 1.9 (m, alkyl), 2.4 (2H, t, R=CH₂-CON-), 3.4 (1H, t, CO-CH(R)-CON-), 3.8 (4H, d, -CH₂OH), 3.9 (1H, m, -CON-CH₂), 6.9 (1H, d, -CONH₂). N-(2,3-dihydroxypropyl)-2-myristyl/palmitoyl-3-hydroxyxystearamide/arachidamide (PC-4R): PC-4 (5 g, 8.8 mmol) was placed under methanol (20 mL) and the pH was adjusted into 10~12 by NaOH. While stirring and heating the reactant, sodium borohydride (NaBH₄) (0.33 g, 8.8 mmol) was added thereto, and the mixture was refluxed overnight. Upon cooling, off-white solids precipitated. The solid was purified from methanol to give PC-4R as a white needle-like crystal (yield: 70%).

3. Results and Discussion

3.1. The Synthesis of the Pseudoceramides

The pseudoceramides, PC-4 and PC-5, were synthesized by the reaction of 3-tetradecyl/hexadecyl-4-pentadec/1-hexadecyl-1-enclyoxetane-2-one (AKD) with 3-amino-1,2-propandiol and 2-amino-1,3-propandiol, respectively. The AKD could be synthesized from the reaction between one acyl chloride and the other by use of a catalyst, triethylamine [13-15]. Nowadays, AKD is available commercially in several types according to their carbon chain length. The AKD used in this experiment has different carbon number, i.e., C16-C16 dimer, C16-C18 dimer and C18-C18 dimer (the ratio of 16:18 was about 3:7). As a solvent, toluene was used because of its high solubility to AKD. The synthetic scheme of the pseudoceramides, PC-4 and PC-5, from AKD was shown in Figure 1.

The FT-IR spectrum shows the typical amide peak, where any ester bond was not formed (Figure 2). This can be explained by the relative reactivity of amine and alcohol with AKD [16], and it is known that the amino group is much more reactive than the hydroxyl group with the AKD. On contrast, it was reported previously that the reaction between alcohol and AKD was very sluggish without a catalyst.

The structural features of the synthesized pseudoceramides are, that first they have two alkyl groups, and secondly they have the functional groups of one amide bond, two hydroxyl groups and one ketone group at β-position (however the ketone group doesn't exist in natural ceramides). In addition, these functional groups can participate in hydrogen bonds for not only intramolecular interaction but also intermolecular interaction.

The reduced types of pseudoceramides, PC-4R and PC-5R, can be obtained just by reducing PC-4 and PC-5 respectively. The ketone group at β-position of PC-4 and PC-5 can be changed into hydroxyl group by the reducing agent to produce PC-4R and PC-5R. Figure 3 represents the reduction scheme of PC-4 and PC-5 by using NaBH₄.

Methanol was used as a solvent in reduction. The reaction was cooled to room temperature and the
product was crystallized and easily purified. In this case, any additional solvent was not required in the purification process. The PC-4 and PC-5 were synthesized via only one-step reaction from commercial AKD. In addition, from a commercial AKD as a starting material, the reduced pseudoceramides, PC-4R and PC-5R could be synthesized via two-step reactions, which are very simple and effective process of preparing pseudoceramides. The reduction of PC-4 and PC-5 was monitored by FT-IR. Figure 2 shows the FT-IR spectra comparing PC-5 and PC-5R. The synthesis of the pseudoceramides, PC-4 and PC-5 resulted from the ring opening reaction of \( \beta \)-lactone and new bonds formation of \( \beta \)-keto group (1713 cm\(^{-1}\)) and amide bond (1637 cm\(^{-1}\)). And the selective reduction of PC-4 and PC-5 into PC-4R and PC-5R resulted in the disappearance of the ketone peak (1713 cm\(^{-1}\)) and the formation of \( \beta \)-hydroxyl group. The stereochemistry of the products, PC-4, PC-5, PC-4R and PC-5R, was not clarified although they seem diastereomeric mixtures.

3.2. The Physical Properties of the Synthesized Pseudoceramide

The barrier function of ceramides is due to the lamellar structure formation with fatty acid and cholesterol. It was known that the intermolecular hydrogen bonding among head groups of the ceramides play an important role in the formation of stable lamellar structure. In the crystalline state, which was crystallized from organic solvent, the carbonyl group of amide bond takes part in hydrogen bonding with another molecules. However, when the ceramide was dissolved in hydrophobic solvent such as chloroform, the hydrogen bond between the molecules is usually greatly weakened or completely removed. At the crystalline state, the lipid molecule packed regularly. The hydroxyl group of head group can make hydrogen bonding with the amide bond. The strong hydrogen bonding around the amide bond resulted in the shifting to low wave number. When natural ceramide (Ceramide IIIB : Natural ceramide-type 3, Gist-Brocades Co.) was dissolved in chloroform, the wave number of amide within ceramide was 1646 cm\(^{-1}\). On contrast, the wave number of its amide in the crystalline state was 1614 cm\(^{-1}\). This typical wave number shifting may be due to the intermolecular hydrogen bonding among ceramides. The similar phenomena were observed with four kinds of pseudoceramides (PC-4, PC-4R, PC-5, and PC-5R) synthesized. Table 1 shows that the wave number of amide bonds of four kinds of PCs shift in different states, that is, liquid state and crystalline state.

The wave number of the reduced forms at the

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p.(( ^\circ )C)(^1)</th>
<th>Liquid state (in CHCl(_3))</th>
<th>Crystal state (in KBr)</th>
<th>( \Delta \sigma (\text{cm}^{-1}))(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceramide IIIB</td>
<td>102.5</td>
<td>1646</td>
<td>1614</td>
<td>32</td>
</tr>
<tr>
<td>PC-4</td>
<td>87.7</td>
<td>1654</td>
<td>1640</td>
<td>14</td>
</tr>
<tr>
<td>PC-4R</td>
<td>113.3</td>
<td>1645</td>
<td>1634</td>
<td>11</td>
</tr>
<tr>
<td>PC-5</td>
<td>87.5</td>
<td>1663</td>
<td>1646</td>
<td>17</td>
</tr>
<tr>
<td>PC-5R</td>
<td>120.0</td>
<td>1639</td>
<td>1627</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^1\) Determined by DSC

\(^2\) \( \Delta \sigma (\text{cm}^{-1})\) value was the difference of the amide wave number between crystalline state and dissolved state.

![Figure 4: Schematic illustration of the intramolecular hydrogen bonds: (A) intramolecular hydrogen bonding in PC-4 and PC-5, (B) intramolecular hydrogen bonding in PC-4R and PC-5R.](image)

crystalline state showed lower values than that of the non-reduced forms. In addition, the melting points of the reduced forms increased compared to non-reduced forms. It can be supposed that the increased hydroxyl group has hydrogen bonding with the amide group of another molecule. The amide peak’s wave number of PC-4R and PC-5R at crystalline state is lower than that of PC-4 and PC-5 respectively. Moreover, the natural ceramide type 3 has lower wave number than pseudoceramides. Besides, the intermolecular hydrogen bonding, they have high possibility to form intramolecular hydrogen bonding. It was reported that an intramolecular hydrogen bond occurred in the six-member ring very easily [17]. In Table 1, the amide peak’s wave numbers of PC-4R and PC-5R are lower than those of PC-4 and PC-5 in CHCl\(_3\) and KBr respectively. Figure 4 illustrated that the non-reduced forms, PC-4 and PC-5 have only one type of intramolecular hydrogen bond, but the reduced forms, PC-4R and PC-5R can
Figure 5. Phase transition behavior of PC-4 measured by XRD; (A) crystalline state, (B) meta-stable state.

Figure 6. Phase transition behavior of PC-5 measured by XRD; (A) crystalline state, (B) meta-stable state.

Figure 7. Phase transition behavior of PC-4R measured by XRD; (A) crystalline state, (B) meta-stable state.

Figure 8. Phase transition behavior of PC-5R measured by XRD; (A) crystalline state; (B) meta-stable state.

have three kinds of intramolecular hydrogen bond. Therefore, it can be suggested that reduced forms have higher potential of the intramolecular hydrogen bond formation than non-reduced forms.

In Table 1, $\Delta \nu$ (cm$^{-1}$) value was the difference of the amide wave number between crystalline state and dissolved state. In data, the $\Delta \nu$ (cm$^{-1}$) of natural ceramide, 32 (cm$^{-1}$) represented larger value than that of all synthesized pseudoceramides (14, 11, 17, 12 (cm$^{-1}$); PC-4, PC-4R, PC-5, PC-5R, respectively) The hydrogen bonds in the pseudoceramides can be involved in both intramolecular and intermolecular interactions among molecules. However, in natural ceramide the hydroxyl groups are supposed to participate in mainly intermolecular interaction because it doesn’t have any amide group that can interact with hydroxyl group to form intramolecular interaction.

3.3. The Results of XRD and Cross-polarized Microscopy

The aggregation structures of the pseudoceramides were investigated by XRD. Figure 5 (PC-4), Figure 6 (PC-5), Figure 7 (PC-4R) and Figure 8 (PC-5R) represented the phase transition behavior of four kinds of the pseudoceramides by XRD.

It was shown that a strong peak was represented at 2$\theta$ = 20.8 (4.265 Å) in the X-ray diffraction pattern in case of PC-4 (Figure 5), and this indicated that the alkyl chains were packed hexagonal within lamellar planes. On measuring after melting and cooling of PC-4, the peak sizes at 2$\theta$ = 22.5 (3.947 Å) and 2$\theta$ = 18.6 (4.765 Å) decreased but the peak at 2$\theta$ = 20.8 (4.265 Å) became stronger. The XRD pattern shows the intrinsic packing pattern of crystalline and $\alpha$-gel, which means that well-ordered lamellar
structure was developed after melting and cooling. Generally, it was well known that the crystalline state had several complex peaks in XRD chart [18]. However in PC-4, well-packed structure was represented at the crystalline state, which was likely due to the intrinsic characteristics of AKD within PC-4. It has been known that AKD forms hexagonal structure at crystalline state different from other fatty acid derived compounds [14]. The results of XRD were summarized at Table 2.

PC-5 (Figure 6) showed a strong peak at $2\theta = 20.8$ (4.26 Å) in the XRD pattern as PC-4. In comparison with PC-4, the spectrum of PC-5 was less complicated. In addition, the peak at $2\theta = 20.8$ (4.26 Å) in PC-5 was shown to be stronger than that at PC-4 XRD. This means that the PC-5's alky chains to have better ordered hexagonal packing within lamellar plane than the PC-4's alky chains. The XRD pattern results suggested that PC-5 as well as PC-4 had the high intrinsic characteristics into crystalline and α-gel packing pattern. The α-gel optical texture of PC-4 spherulites between cross polars was the extinction cross pattern which referred as "Malthesian cross" (Figure 9).

After melting and cooling with 2 °C/min under a thermoregulator, the Malthesian cross configuration of PC-4 was observed at the temperature below 63.8 °C, the exothermic temperature of PC-4. From both results of XRD and the crystalline features of PC-4 under the cross-polarized microscope, it was demonstrated that PC-4 had an intrinsic power to form lamellar liquid crystalline structure. The α-gel state of PC-5 was also taken with a cross-polarized microscope (Figure 9).

Similar to PC-4 and PC-5, the crystalline state of PC-4R showed the strong peak at $2\theta = 20.6$ and the well ordered spectrum. Figure 7 represents the XRD spectrum of the reduced form, PC-4R. However, the cross-polarized optical texture of PC-4R showed quite different pattern from that of PC-4 and PC-5 (Figure 9). PC-4R showed the needle shape crystalline structure rather than Malthesian cross configuration unlike PC-4 and PC-5. The metastable XRD spectrum of PC-5R showed more complex peak pattern than others (Figure 8). That is, it showed a disturbed pattern (split peak) at the cooling point.

### Table 2. The Results of XRD. The Cu-Kα (λ=1.54) Radiation was Used

<table>
<thead>
<tr>
<th>Sample</th>
<th>XRD main peak (2θ)</th>
<th>d (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC-4</td>
<td>20.8</td>
<td>4.265</td>
</tr>
<tr>
<td>PC-5</td>
<td>20.8</td>
<td>4.265</td>
</tr>
<tr>
<td>PC-4R</td>
<td>20.6</td>
<td>4.306</td>
</tr>
<tr>
<td>PC-5R</td>
<td>20.5</td>
<td>4.327</td>
</tr>
</tbody>
</table>

Figure 9. Cross-polarized light microscopic photography of the metastable state of pseudoceramides (× 400); (A) PC-4, (B) PC-5, (C) PC-4R, (D) PC-5R.

In addition, the cross-polarized optical texture of PC-5R showed similar (but cracked pattern) with that of PC-5. The more studies remained though, probably it was the reason that the intermolecular interactions among head groups might be disturbed from the different patterns of intramolecular interactions. The Bragg distance of PC-4 and PC-5 were 4.265 d (Å). However, in the reduced forms, the Bragg distance of PC-4R and PC-5R increased 4.306 d (Å) and 4.327 d (Å) for each. This explains that the hydroxyl group of the reduced forms must take part in the intramolecular hydrogen bonds (Figure 4), so that these intramolecular hydrogen bonds in the reduced types made them to have a large head volume. Moreover, the large head volume made their regular packing to be difficult. After all, as the Bragg distances increase so also the irregularity of organization in metastable phase increase. The high melting point is not a good physical property for cosmetic formulation. PC-4R and PC-5R showed higher melting point than PC-4 and PC-5. Moreover, they showed unstable lamellar configuration in the metastable state. Finally with these reasons, PC-4 and PC-5 were more effective and recommendable than PC-4R and PC-5R for the cosmetic formulation.

### 3.4. The Formation of Multi-lamellar Structure in Emulsion

The synthesized pseudoceramides were used as an active component of the dermatological external preparations for skin. The main aim to use ceramides or pseudoceramides in cosmetic formulation is to improve the barrier function by the maintenance of SC lipid layer. When a pseudoceramide is used in a

Table 3. The Composition of Pseudo-SC Lipid Emulsion and SC Lipid

<table>
<thead>
<tr>
<th>Components</th>
<th>Pseudo-SC lipid emulsion (wt %)</th>
<th>SC lipid (wt %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC-4</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Natural ceramide</td>
<td>-</td>
<td>50</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>4.5</td>
<td>30</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Cholesterol ester</td>
<td>1.5</td>
<td>5</td>
</tr>
<tr>
<td>Tween 80</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Stearyl alcohol</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Liquid paraffin</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>POE(8) C16-20 Guerbet alcohol</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Glycerin</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Water</td>
<td>62.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 10. Cross-polarized light microscopic photography of a pseudo-SC emulsion containing PC-4 (× 400).

cosmetic product, the improvement of barrier function according to lamellar structure formation on SC is the main advantage that we expect. The importance of the lamellar structure in formulation was described in the previous report [17]. Table 3 represents the composition of pseudo-SC lipid emulsion and SC lipid for the continuous multi-lamella emulsion study.

The main compositions of the pseudo-SC lipid emulsion using PC-4 and the SC lipid using natural ceramide are shown in Table 3. When it was observed with using a cross-polarized microscope, the optical anisotropy of “Malthesian Cross”, which was a typical configuration of a multi-lamellar mesophase texture was observed (Figure 10). This demonstrates that the emulsion has the aggregation structure, which is similar to the human skin lipid lamellar bilayer.

4. Conclusions

According to the reaction of AKD and alkanolamine, four kinds of novel pseudoceramides were synthesized by effective synthetic pathway. The hydrogen bonds among head groups of the pseudoceramides were inhibited by hydrophobic solvent dispersion and the amide peak was shifted to high wave number. It was known that carbonyl group and hydroxyl group(s) in a pseudoceramide were involved in not only intermolecular interaction but also intramolecular interaction in itself, which were demonstrated by the wave number shifting in the FT-IR spectra. In addition, according to XRD and cross-polarized microscopy measurements, the synthesized pseudoceramide have high intrinsic characteristics to form lamellar structure. The intrinsic power to form lamellar structure drove the lipids to form a multi-lamellar emulsion and a pseudo-SC lipid emulsion, which showed an optical anisotropy in the cross-polarized microscope. In the future, the effect of multi-lamellar structure of an emulsion will be observed when it is used as a cosmetic formulation.

References