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Demonstration of the efficacy of the moisturizing and itch-relief cream for sensitive skin that utilizes technology to increase the penetration of water-soluble active ingredients to the skin

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1. Introduction

Sensitive skin dose not have a specific definition, however, it is generally characterized as a condition in which discomfort is caused by stimuli that would normally not cause any irritation [1]. According to the study conducted by Berardesca et al., approximately 70% of individuals perceive themselves as having sensitive skin, and around 50% report experiencing discomfort associated with it [2]. The symptoms include subjective sensory sensations such as itchiness, burning, tingling, tightness, and dryness [3]. Among these, dryness, impaired skin barrier function, and chronic itch are some characteristic features of individuals with sensitive skin, and these factors are known to contribute to the development of atopic dermatitis [4]. The impaired skin barrier and dryness lead to itchiness. While scratching can temporarily relieve from itchiness, this behavior further damages the skin barrier, thereby perpetuating a deleterious cycle. This process is referred to as the "itch-scratch cycle" [5]. Suppressing chronic itch to prevent scratching the skin and protecting the skin barrier function are considered to be essential for the improvement of sensitive skin symptoms. Chronic itch differs from acute itch induced by histamine, and the causative agents and effective treatments for numerous types of chronic itch remain to be unidentified [6].

Previous research has targeted Substance P (SP), a neuropeptide associated with chronic itch, and identified maltotetraose (MTO) as a leading ingredient that inhibits its interaction with the Neurokinin-1 receptor (NK1R) [7]. Since MTO is a type of polysaccharide that contains more hydroxyl groups than common polyhydric alcohols such as glycerin and butylene glycol, it is also known to have a high moisturizing effect [8]. Niacinamide is known for its ability to enhance the skin barrier by regulating the production of intercellular lipids in the stratum corneum or modulating cellular differentiation [9]. If more of these functional ingredients can be deliverd to the skin, it will be possible to reduce itchiness, and improve the skin's moisturizing effect and

barrier function, thereby breaking the cycle of itch and scratching. However, these ingredients are water-soluble, making effective penetration into the lipophilic skin a significant challenge [10]. In general, methods such as iontophoresis, electroporation, ultrasound, microporation, radiofrequency, and microneedles are utilized to enhance penetration of functional ingredients. However, these techniques require specialized equipment, making it challenging for general consumers to implement them at home [11]. Additionally, chemical enhancement methods such as microemulsion and microcapsule technologies are also well-known, but these methods present challenges in formulation and maintaining long-term stability [12, 13].

In this study, we developed a new technology to enhance the penetration of hydrophilic ingredients by controlling the number of moles of hydrophilic groups added to polyglycerol fatty acid esters. This paper demonstrated the efficacy of a cosmetic cream formulation containing MTO and niacinamide developed with this penetrating technology in a clinical trial.

2. Materials and Methods

2.1 Study design of clinical trial

The study was conducted by Ellead Co., Ltd. and involved the selection of 33 participants, comprising females aged between 33 and 64 years. These participants were characterized by having extremely dry skin and itchiness, or previous experience with barrier damage, eczema, or atopic dermatitis. The study was took place from November 27, 2023, to March 08, 2024.

The test sample used was a cream formulation containing 1% MTO and 2.0% niacinamide, designed with penetration enhancing technology. Throughout the study, participants were required to use specified bar soap as daily skin cleansing. The test areas included the legs and forearms. For the forearms, approximately 1 g of cream was applied to the specified area. For the legs, approximately 2 g of cream was applied, twice daily, both in the morning and evening.

A 7-day washout period preceded the initiation of the study to standardize the skin condition of all participants, employing the specified bar soap. During the study period, the specified sites were cleansed exclusively with the same bar soap, and the use of other cosmetic products on these areas was strictly prohibited. Evaluations were meticulously conducted under the supervision of the dermatologist. All assessments were conducted after the participants had acclimated for at least 30 minutes in a controlled environment with a constant temperature range of 20-22°C and relative humidity levels of 45-55%.

2.2 Assessment of moisturizing efficacy

The moisturizing efficacy was assessed using a Corneometer, which measures the stratum corneum water content. The persistence of moisturizing efficacy after a single application of the test cream was assessed on the forearms, with measurements taken at baseline (pre-application), and then at 15 minutes, 24 hours, and 48 hours post-application. During the assessment period until 48 hours, participants were prohibited from washing their forearms.

The moisturizing efficacy of continuous application was assessed on the legs. Measurements were recorded at baseline (pre-application) and after 7, 14, and 28 days of consistent application.

The increase rate in stratum corneum water content (%) was calculated as follows:

- Rate of increase in stratum corneum water content (%)

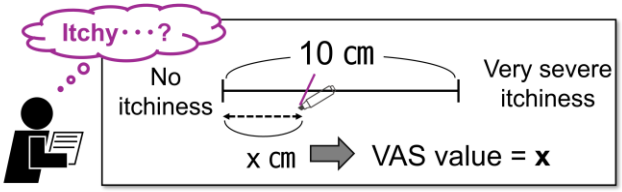
  = {(Measurement after application - Measurement before application) / Measurement before application} × 100

2.3 Assessment of itch-relief efficacy

The itchiness assessment was conducted using the Visual Analog Scale (VAS), which consists of a 10 cm line where 0 cm signifies no itchiness and 10 cm signifies very severe itchiness (Table 1). Participants marked their perceived level of itchiness on this scale, and the length of the mark was used for assessment. After undergoing a 7-day washout period, participants with initial itch scores between 2.5 cm and 7.4 cm were selected under the supervision of a dermatologist.

Table 1. VAS scoring criteria

Score	Degree of itchiness
VAS value =0	No itchiness
	Mild itchiness
	Moderate itchiness
	Severe itchiness
VAS value =10	Very severe itchiness



The persistence of itch-relief efficacy after a single application of the test cream was assessed on the legs, with measurements taken at baseline (pre-application) and at 15 minutes, 24 hours, and 48 hours post-application. During the assessment period until 48 hours, washing of the legs was strictly prohibited.

The itch-relief efficacy of continuous application was assessed on the legs. Measurements were recorded at baseline (pre-application) and after 7, 14, and 28 days of consistent application (Figure 1).

The decrease rate in itch scores was calculated as follows:

- Rate of decrease in itchiness (%)

  = {(Score before application - Score after application) / Score before application} × 100

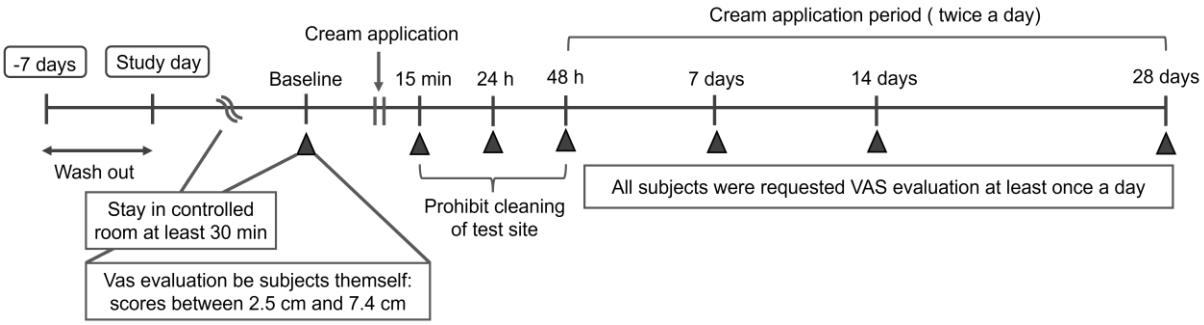


Figure 1. The research protocol of VAS evaluation. Black arrows show the measures of various evaluations depending on time point.

2.4 Assessment of skin barrier function

Skin barrier function was assessed by measuring Transepidermal Water Loss (TEWL) using a Tewameter. The efficacy of continuous application of the test cream on skin barrier function was assessed on the legs, with measurements recorded at baseline (pre-application) and after 14 and 28 days of consistent application.

The decrease rate in TEWL was calculated as follows:

- Rate of decrease in TEWL (%)

= {(Measurement after application - Measurement before application) / Measurement before application} ×100

The skin condition, in terms of the appearance of the skin surface, was visually evaluated by the dermatologist using a Folliscope. The skin condition was evaluated using a 4-point scale (0-3) with 0.5-point intervals. The most severe skin conditions were assigned scores close to 3 points. A decrease in skin dryness indicated an improvement in visual assessment.

The decrease in skin dryness was calculated as follows.

- Rate of decrease in skin dryness (%)

  = {(Score before application - Score after application) / Score before application } × 100

3. Results

3.1 Moisturizing efficacy

3.1.1 Persistence of moisturizing effecacy after a single application

The results demonstrated a statistically significant increase in skin moisture content at 15 minutes, 24 hours, and 48 hours post-application compared to baseline ($p < 0.001$) (Figure 2(a)). These results suggest that the test cream significantly enhances skin moisture levels shortly after application and maintains substantial moisturizing effects over 24 and 48 hours.

3.1.2 Moisturizing effecacy with continuous use

The results demonstrated a statistically significant increase in skin moisture content at 7, 14, and 28 days post-application compared to baseline ($p < 0.001$) (Figure 2(b)). These results suggest that the test cream effectively enhances skin moisture content with continuous use, showing progressive improvements over 7, 14, and 28 days.

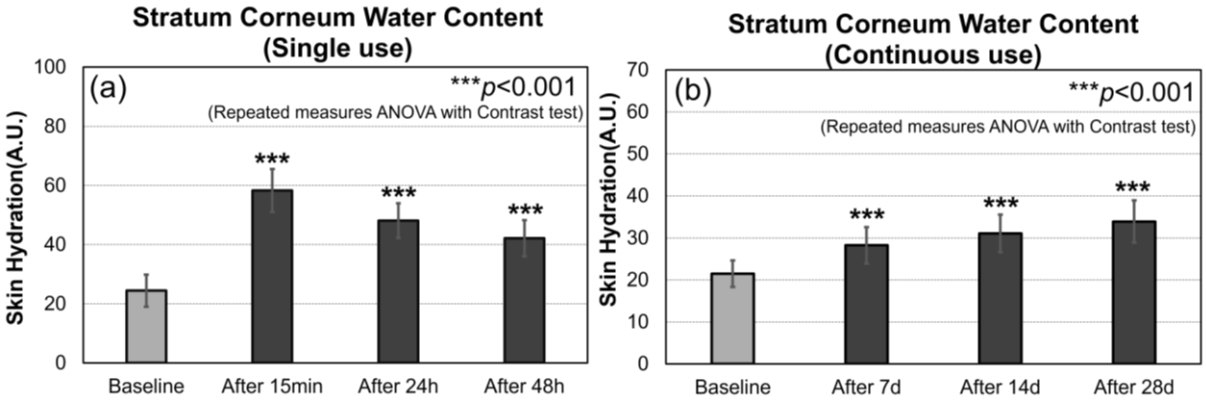


Figure 2. The result of stratum corneum water content measurement for (a) single use; (b) continuous use

3.2 Itch-relief efficacy

3.2.1 Persistence of itch-relief effecacy after a single application

The results demonstrated a statistically significant decrease in itch scores at 15 minutes, 24 hours, and 48 hours post-application compared to baseline ($p < 0.001$) (Figure 3(a)). These results suggest that the test cream immediate temporary relief from itch at 15 minutes post-application and maintains substantial itch-relief effects over 24 and 48 hours.

3.2.2 Itch-relief effecacy with continuous use

The results demonstrated a statistically significant decrease in itch scores at 7, 14, and 28 days post-application compared to the baseline (p < 0.001) (Figure 3(b)). These results suggest that the test cream reduces itchiness with continuous use over the periods of 7, 14, and 28 days.

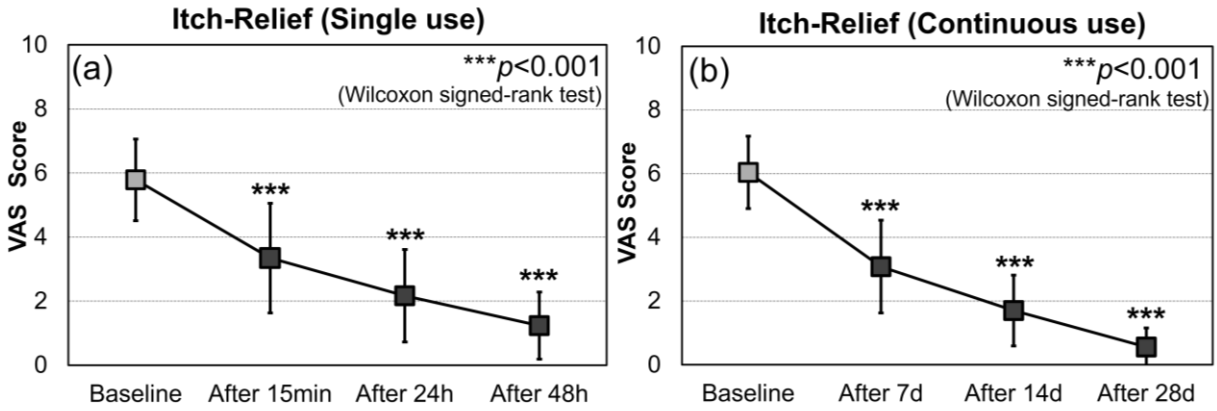


Figure 3. The result of VAS assessment of itch for (a) single use; (b) continuous use

3.3 Skin Barrier Function

The results demonstrated a statistically significant decrease in TEWL at both 14 and 28 days post-application compared to baseline (p < 0.001) (Figure 4). These results suggest that the test cream significantly improves TEWL, enhancing the skin barrier function at both 14 and 28 days post-application.

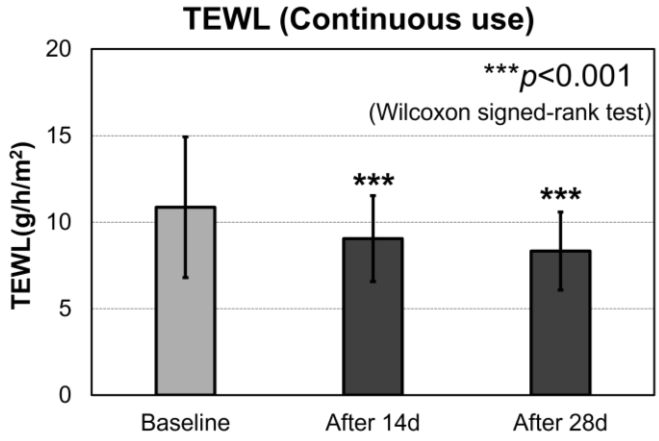


Figure 4. The result of TEWL for continuous use

Furthermore, skin condition assessments were conducted using a Folliscope under the supervision of the dermatologist, which allowed for visual confirmation of the improvement in dryness and skin barrier function (Figure 5). Dermatological evaluations indicated that skin dryness significantly decreased at 7, 14, and 28 days post-application, compared to baseline (p < 0.001) (Figure 6). These results provide substantial evidence that the test cream effectively alleviates skin dryness, demonstrating its efficacy in enhancing skin hydration and skin barrier at 7, 14, and 28 days post-application.

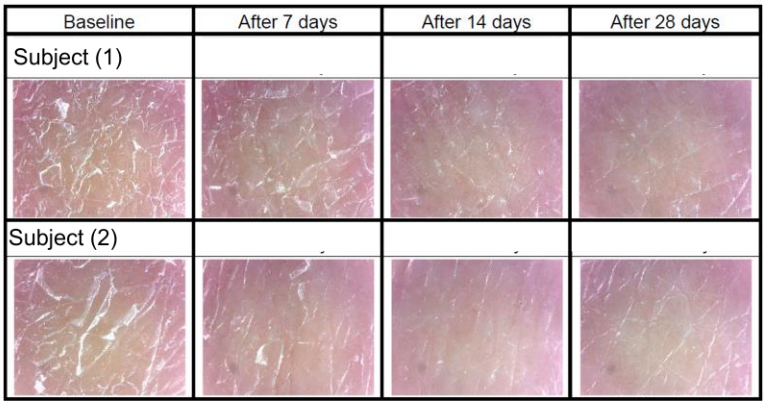


Figure 5. Image data by Folliscope

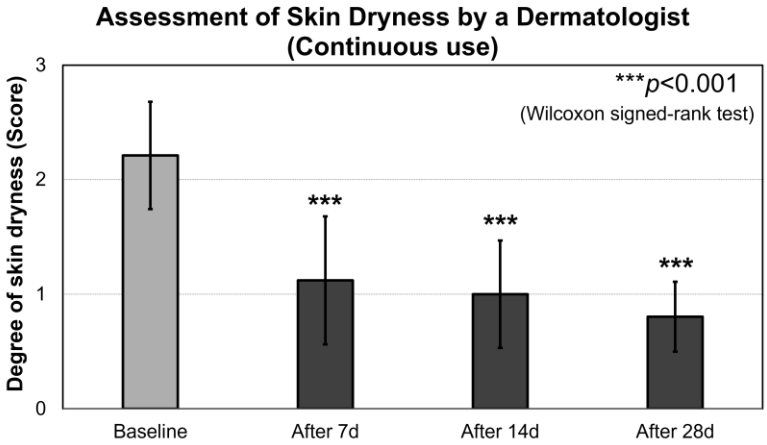


Figure 6. The result of skin dryness assessment for continuous use

4. Discussion

Chronic itch is known to be difficult to treat because the specific underlying causes remain unidentified [14]. MTO is recognized for its high moisturizing properties due to its numerous hydroxyl groups. Furthermore, previous research has revealed that MTO can alleviate chronic itch by binding to the NK1R of SP, which leads to the inhibition of calcium influx [15]. Niacinamide is known to boost ceramide production and improve skin barrier function [16].

In this clinical study, the efficacy of a technology that enhances the penetration of water-soluble active ingredients, which are generally incompatible with lipophilic skin, effectively delivers sufficient amounts of MTO and niacinamide, and suppresses the "itch-scratch cycle" was confirmed in a clinical trial. This new technology improves the penetration of hydrophilic ingredients by controlling the number of moles of the hydrophilic groups in polyglycerol fatty acid esters when formulating cosmetic creams. M. Nanjo et al. studied the stabilization of O/W emulsions using the membrane emulsification method [17]. They reported that when comparing the emulsification states using emulsifiers with the same HLB but different bulkiness of hydrophilic groups, the emulsifiers with bulkier hydrophilic groups resulted in low monodispersity of the emulsified particles, leading to coales-cence of oil droplets and phase separation. We hypothesize that the stability of emulsified particles is influenced by the variable emulsification particle membrane, which is controlled by the number of moles of hydrophilic groups added to polyglycerin fatty acid esters. More specifically, by incorporating polyglycerin fatty acid esters with a suitable number of hydrophilic groups, it is possible to localize the water phase on the skin surface while simultaneously creating an occlusive layer with oil when shearing the

emulsified particles. This configuration is hypothesized to form a cosmetic film structure that reduces evaporation and increased contact frequency between water phase and skin surface, thereby enhancing the penetration of water-soluble active ingredients and contributing to their overall efficacy.

Our clinical study revealed that a single application of the test cream, which is developed by the aforementioned technology, containing water-soluable active ingredients, 1% MTO, 2% niacinamide and polyglycerol fatty acid ester with suitable number of moles of hydrophilic groups led to a statistically significant decrease in skin itchiness and an increase in skin hydration compared to the baseline, with effects persisting for 48 hours. Moreover, continuous application of the test cream not only suppressed itchiness and increased skin hydration but also resulted in a statistically significant decrease in TEWL, demonstrating an enhancement in skin barrier function. This suggests that MTO, which has an anti-itch and moisturizing effect, and niacinamide, which enhances skin barrier function, penetrate the skin in more effective amounts to exert their effects due to the penetrating technology.

5. Conclusion

Through clinical trials have confirmed the efficacy of a cream formulation that enhances the penetration of water-soluble ingredients by controlling the number of moles of hydrophilic groups in polyglycerin fatty acid esters, and the cream contains 1% MTO which can inhibit chronic itch pathways and 2% niacinamide which can improve skin barrier function. A single application of the cream resulted in a statistically significant itch-relief efficacy and improved skin moisture content compared to baseline, with effects persisting for 48 hours. Additionally, continuous use of the cream not only suppressed itchiness and increased moisture content of skin but also significantly decrease TEWL of skin, demonstrating an improvement in skin barrier function. These results indicate that MTO and niacinamide penetrate the skin in more effective amounts and deliver their desired effects. They also suggests that the enhanced penetration of water-soluble ingredients, achieved by controlling the number of moles of the hydrophilic groups in polyglycerol fatty acid esters, significantly contributes to the overall efficacy of the cosmetic cream formulation.

5. Reference

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