

Effect of cosmetic ingredients as functional agents: synergistic action of electroporation and sonophoresis in clinical efficacy

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Background: This study examined the effects of electroporation (EP) and sonophoresis (SP) on the skin permeation of various ingredients and the resulting changes in skin properties.

Methods: Twenty participants used whitening and hyaluronic ampoules as adjunctive cosmetics. The intervention group used an EP with an SP device for application while the control group used their hands, both groups over a 4-week period. The outcomes measured included skin elasticity, gloss, pores, tone, and soothing. In addition, this study determined the absorption amount, absorption rate, and skin permeation of the cosmetic ampoules 30 minutes after applying the cosmetics in a clinical test.

Results: Significant improvements in skin hydration, elasticity, tone, and pigmentation were observed in the intervention group. In particular, the most pronounced effects were observed immediately after use. In addition, application with EP and SP led to a more than 200% increase in the absorption amount, absorption depth, and absorption speed of cosmetics compared to hand application.

Conclusion: These findings suggest that simultaneous EP and SP significantly enhance skin permeability and cosmetic absorption, improving skin properties.

Key words: Electroporation; Ultrasonic waves; Drug delivery systems

INTRODUCTION

Skin penetration for drug delivery involves navigating a series of complex barriers to achieve the desired therapeutic effects, either at the site of application or systemically. The three main layers of the skin are the epidermis (the outermost layer), the dermis (the middle layer), and the subcutaneous tissue (the innermost layer). The epidermis can be subdivided into five layers, from the deepest to the outermost: the basal layer, the spinous layer,

the granular layer, the stratum lucidum, and the stratum corneum [1].

The stratum corneum acts as the surface layer of the epidermis. This lipophilic layer, composed of ceramides, cholesterol, and free fatty acids, is the outermost barrier to foreign substances and makes it difficult for drugs to penetrate the skin [2]. Despite this challenge, advancements in delivery strategies have significantly improved the efficacy of transdermal drug delivery [3].

In drug delivery, molecular and physicochemical fac-

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tors influence skin penetration, with molecules smaller than 500 Da typically exhibiting better permeability. Although the stratum corneum is only 10–20 μm thick, only small lipophilic drugs can penetrate the skin, typically at very low concentrations. In contrast, most large hydrophilic macromolecules, such as peptides and proteins, cannot permeate passively. Nano-carriers can encapsulate both lipophilic and hydrophilic drugs, enhancing their delivery across the skin barrier [4].

Therefore, augmentation techniques are required to facilitate the transport of these molecules through the stratum corneum. In this study, we focused on two physical augmentation methods: ultrasound (sonophoresis, SP) and electrical pulses (electroporation, EP). Both methods increase permeability by creating an aqueous path through the stratum corneum. This study aimed to investigate the effects of EP and SP on skin permeation of cosmetic functional agents and its effects on skin properties.

METHODS

Ethics statement: The study protocol was approved by the Institutional Review Board of the P&K Skin Research Center (P2402-5839) and was fully explained to all participants, who provided written informed consent before participation.

Study design

This double-blind, randomized, parallel, placebo-controlled study was conducted at the P&K Skin Research Center (Seoul, Korea) between January 2024 and February 2024. The clinical study involved 20 individuals, and all participants completed the study. Female aged 20 to 55 who met the inclusion criteria were enrolled in this study. The participants rested for 30 minutes in an environment maintained at 20°C to 24°C and 40% to 60% humidity to allow their skin surface to adapt to the measurement conditions before the experiment. During this period, they refrained from drinking water. For objective measurements, the same researcher consistently measured a single parameter, ensuring that each measurement was performed on the same area. For each participant, four drops of cosmetic functional agents (CNP Derma+ Answer Mela Spot Brightening; LG Household & Health Care) was first applied on one of their cheeks and spread by the EP and SP device (Skin Booster BBS1; LG Household & Health Care Ltd.) or by hand, for a minute and 30

seconds. Then, the 4 drops of other cosmetic functional agents (Toxnfill Hyaluron Boosting) was applied to the same cheek, and spread either with the device or by hand. The EP and SP device was set to an intensity level of 6 in the combined mode. The test was conducted over 4 weeks, twice weekly, for a total of eight sessions.

Measurement of skin hydration and skin elasticity

Skin hydration was measured using the Epsilon E100 (Biox Systems Ltd.) on the cheek before and after using the cosmetic. The measurement parameter was the ϵ -value, where higher values indicate effective skin hydration. Inner skin elasticity was measured using a 4 mm probe of the Cutometer MPA580 (Courage + Khazaka electronic GmbH) on the cheek before and after applying the cosmetic. The measurement parameter was the R^2 value, with higher values indicating better maintenance of inner skin elasticity.

Measurement of skin tone and skin pigmentation

Skin tone was measured using a VISIA-CR (Canfield Imaging Systems) on the cheek before and after applying the cosmetic. The cheek areas in the captured image (standard 2 mode) were analyzed using Image-Pro Plus software (Media Cybernetics). Skin pigmentation measurements were performed using the Antera 3D CS (Miravex) to assess the cheek before and after the application of the cosmetic. The captured image (Melanin mode) was analyzed using a scale of 0.7.

Raman spectroscopy

Skin absorption rate (skin absorption amount, rate, and depth) were measured using a 3D Raman microscope system Nanofinder30 (TOKYO Instruments). 3D Raman scanning was performed with the participant's right cheek fixed to the equipment before and 30 minutes after use. Skin absorption rate was evaluated in 10 stages by dividing the z-axis of the 2D image into 10 equal parts at 5 μm intervals. Skin absorption depth was calculated by multiplying the change in absorption before and 30 minutes after product use by 5 μm , while skin absorption rate was calculated by dividing the skin absorption depth by the product use time (0.5 hour). The absorption amount was assessed by converting the color intensity of the 3D image into data to evaluate the degree of absorption within the skin. The clinical data of each study subject were initially expressed as 2D images using imaging software. The amount and depth of skin absorption were derived from 2D images. The skin absorption rate was calculated by integrating application time as a variable input. Multi-

ple 2D images obtained from the test were automatically merged into 3D images using Raman spectroscopy software to provide a columnar 3D representation within the visible light spectrum of electromagnetic wavelengths (380–740 nm).

Skin safety

Skin safety (defined as erythema = redness) was measured using a VISIA-CR on the cheek before and after using the cosmetic. The cheek area in the captured image (standard 2 mode) was analyzed using Image-Pro Plus. The skin redness (a^*) value was the analysis parameter.

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 16 (SPSS Inc.). Statistical significance was set at $p < 0.05$ with a 95% confidence level. All statistical values were rounded to three decimal places. For data from more than three repeated measurements, repeated measures ANOVA was used as a parametric method after a normality test, followed by Bonferroni post-hoc analysis. The Friedman test, a non-parametric method, was used with pairwise comparisons conducted via the Wilcoxon signed-rank test (post-hoc Bonferroni correction).

RESULTS

Clinical test of cosmetic efficacy

All 20 participants who completed this clinical study were female with an average age of 42.13 years. The selected participants had no medical or medication history that could have affected the study.

Objective evaluation of the skin moisture revealed significantly improved values immediately after use, as well as at 3 days (72 hours), 2 weeks, and 4 weeks, in the area where the cosmetic was applied (Fig. 1A). While both groups showed improvement immediately after use, a significant difference in skin moisture between the intervention and control groups was observed at 3 days, 2 weeks, and 4 weeks, favoring the intervention group. Compared to the baseline, the intervention group had significant improvement in skin elasticity (4 mm) immediately after use, as well as at 3 days (72 hours), 2 weeks, and 4 weeks (Fig. 1B). The comparison between the intervention and control groups revealed significant differences in the functional ampoule usage area: immediately after use, 3 days (72 hours) after 1 use, 2 weeks after use, and 4 weeks after use.

The intervention group demonstrated significant improvements in skin tone values immediately after use, as well as at 3 days (12 hours) after 1 use, 1 week, and 4 weeks, compared to baseline values (Fig. 2A). Regarding skin pigmentation (Fig. 2B), the intervention group showed significant improvement at 3 days (72 hours), two weeks, and four weeks compared to the baseline. This finding was consistent with the improvement in the melanin values.

Measurement of skin absorption

The effect of the product containing hyaluronic acid (HA) on skin absorption characteristics was analyzed using Raman spectroscopy. The results were obtained based on three specified parameters: skin absorption amount (A.U.), skin absorption rate ($\mu\text{m}/\text{h}$), and skin absorption depth (μm). As shown in Fig. 3, the intervention group

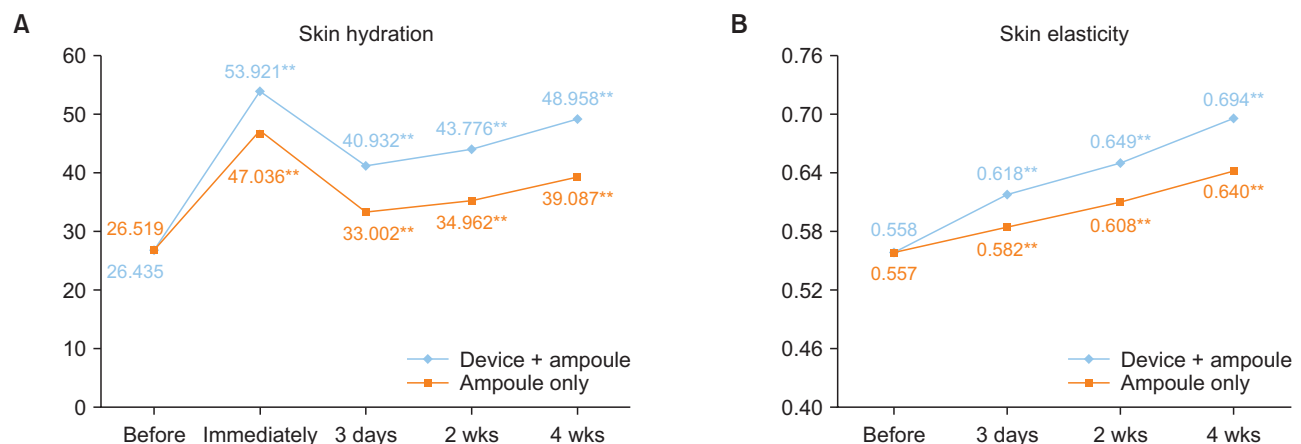


Fig. 1. Measurement results of skin hydration (A) and elasticity (B). Values were measured immediately after use, as well as at 3 days (72 hours), 2 weeks, and 4 weeks, compared to baseline (before use). ** $p < 0.05$ by repeated measures ANOVA with Bonferroni post hoc correction.

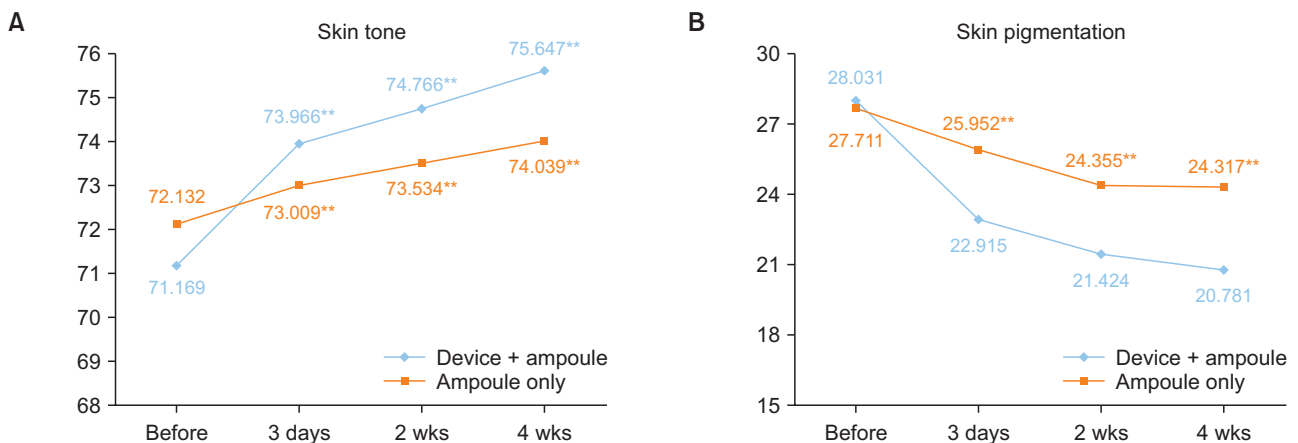


Fig. 2. Measurement results of skin tone (A) and pigmentation (B). Values were measured immediately after use, as well as at 3 days (72 hours), 2 weeks, and 4 weeks, compared to baseline. ** $p < 0.05$ by repeated measures ANOVA with Bonferroni post hoc correction.

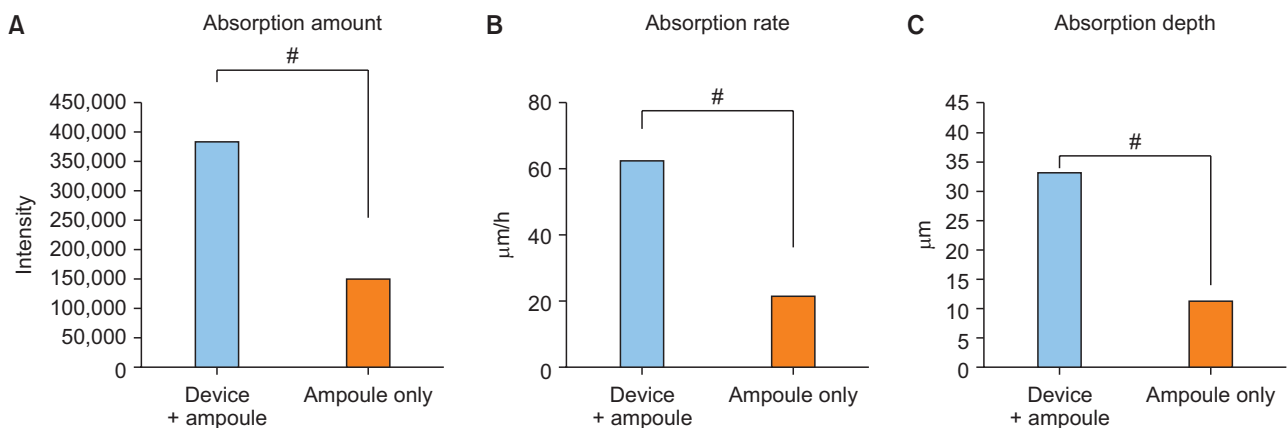


Fig. 3. Measurement of skin rate (skin absorption amount [A], rate [B], and depth [C]) using a 3D Raman Microscopy System. The three-dimensional distribution (x, y, z plane) was visualized in the visible light spectrum $\lambda = 380\text{--}740\text{ nm}$, comparing the control and test groups. # $p < 0.05$ by Wilcoxon signed rank test.

demonstrated significantly greater improvements than did the control group (HA applied by hand) in efficacy. Overall, these results confirmed that, compared to using the ampoule alone, the facial (cheek) skin absorption amount increased by 256.66%, skin absorption rate increased by 230.78%, skin absorption depth by 293.33%.

Skin safety

Additionally, the intervention group showed no adverse reactions, and the device was confirmed to be safe (Fig. 4).

DISCUSSION

Enhanced techniques for skin drug delivery aim to overcome the formidable barrier posed by the stratum corneum, the outermost layer of the skin, to facilitate

effective therapeutic drug penetration. Below is an overview of the various strategies that have been explored to enhance drug delivery through the skin.

Chemical enhancers function by temporarily altering the lipid structure within the stratum corneum, thereby enhancing permeability. These include solvents, such as ethanol and isopropanol, which disrupt lipid organization, thereby facilitating drug penetration [5]. Surfactants, such as sodium lauryl sulfate, and fatty acids, such as oleic acid, increase the fluidity of lipids, enabling improved diffusion of drugs [3]. Terpenes, including natural compounds such as menthol and limonene, are also effective in modulating the stratum corneum lipid arrangement to enhance permeability [6]. Nanocarriers, a formulation-based strategy, include liposomes, ethosomes, and nanoparticles. These systems encapsulate

(Mean $\pm$ SD)			
Classification		Skin redness (a* value)	
		Device + ampoule	Ampoule
Before use		13.987 $\pm$ 2.048	14.695 $\pm$ 2.562
30 min after use		14.120 $\pm$ 2.142	14.436 $\pm$ 2.429
Within group	p-value	Before use-30 min after use	0.474
Between groups	p-value	Before use-30 min after use	0.172

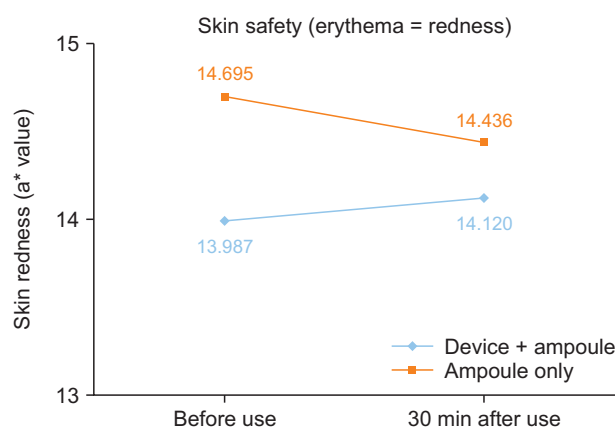


Fig. 4. Color analysis of the zones by image processing of VISIA photographs; a* red-green component. Measurement of skin safety was performed using the VISIA-CR (Canfield Imaging Systems) to measure the cheek before and after using the test product.

drugs, improving their stability and penetration. They can cross the stratum corneum, enabling both local and systemic delivery. Hydrogels and adhesive patches enhance adhesiveness to the skin, improving drug release and absorption by maintaining a moist environment at the application site [7]. Lipid nanosystems, due to their easy scalability and stability, provide promising platforms for enhancing skin permeation [8]. Enzyme inhibitors slow down the degradation of stratum corneum enzymes, preserving its integrity while enhancing drug penetration. This helps prolong the drug's effectiveness in the skin [9].

Physical techniques provide a more direct method for enhancing penetration by creating temporary pathways through the skin barrier [10]. Microneedles create micro-scale perforations in the skin, allowing drugs to bypass the stratum corneum with minimal discomfort. Innovations such as gelatin methacryloyl microneedles have provided biodegradable options for sustained drug release. Iontophoresis utilizes a low electrical current to propel charged drug molecules through the skin, thereby effectively increasing the rate of transdermal drug delivery. SP uses ultrasound waves that temporarily disrupt the stratum corneum to facilitate deeper drug penetration. EP allows brief electrical pulses to form transient

pores in the skin, thereby providing a direct route for drug molecules. Thermal methods, such as localized heating, enhance drug permeability by increasing the stratum corneum lipid fluidity [11-14].

The combination of chemical and physical methods, along with advanced formulation technologies, holds great promise for overcoming skin impermeability and optimizing transdermal drug delivery systems. However, each method comes with inherent considerations, such as potential skin irritation, formulation complexity, and individual variability. Therefore, careful selection is essential based on the specific drug, target site, and therapeutic outcome. Researchers continue to innovate hybrid strategies that combine the benefits of different enhancement techniques to improve the efficacy and safety of transdermal drug delivery.

In this study, we performed depth profiling of skin hydration using noninvasive in vivo confocal Raman spectroscopy and identified changes in skin hydration levels at specific depths below the skin surface. A combination of physical and electrical enhancement methods, namely EP and SP, was used to improve the rate and range of drug delivery through the skin.

The combined method was significantly more effective than the drug-alone method in enhancing human skin permeation. This was evidenced by enhanced skin permeation of HA. SP is an augmentation technology that can noninvasively deliver multiple therapeutics by temporarily increasing skin permeability. Our findings confirm its synergistic effect with EP treatment, which creates a new aqueous pathway to promote enhanced macromolecular transport through permeable skin. Thus, the combination of EP and SP presents a promising alternative strategy for transdermal drug delivery without causing structural changes or skin damage. EP effectiveness depends on the applied electric field, while SP enhances penetration through low-frequency energy in aqueous media. Their simultaneous application expands drug delivery pathways via EP and SP. The primary mechanism involves enhanced convection, accelerating active ingredient absorption, and inducing dynamic structural changes in the skin. Cavitation bubbles induce the generation of fluid velocities in the porous medium, which affect transdermal transport and induce convective transport through the skin, hair follicles, and sweat ducts, resulting in extensive and efficient drug absorption.

We want to highlight that our analysis with Raman spectroscopy has several limitations: the Raman effect is very weak, making low-concentration measurements challenging; fluorescence can obscure the Raman band

by emitting lower-energy light; uneven sample surfaces may affect accuracy; and poor repeatability hinders reliable quantitative measurements. In addition, although the current experimental design confirmed the skin absorption of HA and collagen formation at the cellular level, its delivery to the dermal layer remains to be verified. Longitudinal studies are required to assess the long-term safety, skin barrier function, and potential systemic effects of repeated EP and SP applications.

Taken together, EP with SP provide an effective, targeted, and uniform method for delivering both low- and high-molecular-weight substances into deeper skin layers. This noninvasive method represents a modern and sophisticated approach in cosmetology for treating and improving aesthetic concerns.

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AUTHOR CONTRIBUTIONS

Conceptualization: TRK, KHY. Data curation: TRK, SMK. Formal analysis: TRK. Funding acquisition: HJK. Investigation: TRK. Methodology: TRK. Project administration: JL. Software: JK. Validation: KHY. Visualization: JK. Writing—original draft: TRK. Writing—review & editing: all authors.

CONFLICT OF INTEREST

Kwang Ho Yoo is the Editor-in-Chief of the journal but was not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

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DATA AVAILABILITY

Contact the corresponding author for data availability.

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SUPPLEMENTARY MATERIALS

None.

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