

Enhancing collagen synthesis and improving dermal delivery of hyaluronic acid and anti-oxidant ampoule via simultaneous electroporation and low-frequency sonophoresis

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Background: The delivery of desired drugs through the skin can enhance the effectiveness of cosmetic treatments and further enhance skin recovery and collagen regeneration. This study evaluated the potential of a device to achieve noninvasive transdermal drug delivery using simultaneous electroporation (EP) and low-frequency sonophoresis (SP).

Methods: The percutaneous absorption after applying the device that administered EP and SP was evaluated using an ex vivo porcine skin model. Porcine skin tissue was placed on a polyurethane foam dressing impregnated with 3% povidone-iodine (PI). Four drops of ampoule were applied, and the device was applied to the skin for 3 minutes. The reaction between the penetrated whitening agents and 3% PI, indicated by color changes, was analyzed using an Antera 3D camera.

Results: The simultaneous application of EP with SP to skin tissue at a specific ratio for 3 minutes resulted in a significant increase in the area that reacted with iodine after skin penetration. The results showed that exposure to hyaluronic acid ampoule (HAA) increases type I collagen synthesis in human dermal fibroblasts in a concentration- and time-dependent manner. In addition, treatment with HAA combined with the application of EP with SP increased cell proliferation and significantly increased type I collagen levels in human dermal fibroblasts, with device-assisted synthesis showing greater efficiency.

Conclusion: These results suggest that simultaneous EP and SP efficiently deliver large molecules, such as hyaluronic acid, deep into the skin without causing skin damage.

Key words: Electroporation; Ultrasonic waves; Drug delivery systems

INTRODUCTION

Transdermal drug delivery systems (TDDSs) have gained prominence in pharmaceutical research because of their potential to enhance drug bioavailability, improve patient compliance, and boost therapeutic efficacy. This

non-invasive method involves the administration of drugs through the skin, offering unique advantages over traditional delivery routes such as oral or parenteral [1].

Various physical penetration-enhancement approaches have been designed to overcome the barrier posed by the stratum corneum (SC) and promote drug absorption

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through the skin. Popular physical penetration-enhancement techniques include sonophoresis (SP), iontophoresis, magnetophoresis, thermophoresis, electroporation (EP), needleless injection, and microneedling. Iontophoresis involves the application of an electric current to force the charged molecules of a drug into the skin, thereby effectively enhancing drug absorption. Magnetophoresis involves applying a magnetic field to transport drug carriers into the dermis, and has shown promise in assisting targeted drug delivery. Thermophoresis involves controlled heating of the skin to enhance drug absorption, especially for heat-sensitive drug carriers [2-4].

EP causes a transient change in skin structure by the application of an electric field pulse that creates a transient aqueous path in the lipid bilayer membrane [5]. The formation of aqueous pores allows the transdermal permeation of neutral molecules via diffusion; however, diffusion also allows the transport of charged molecules. This rearrangement also provides a local driving force that facilitates the transport of hydrophilic molecules. EP is commonly used to introduce various molecules such as DNA across the single-layer phospholipid bilayer of bacterial cell membranes; however, EP also affects the SC, which consists of multilayer intercellular lipid bilayer membranes [6,7]. This technique is termed a nonthermal phenomenon (the so-called cold technique) because pore formation owing to cell membrane rearrangement occurs without any desirable effects. Electric pulses provide a safe and noninvasive mode of drug delivery using closely spaced electrodes to induce skin permeability and has been demonstrated to effectively deliver low-molecular weight drugs such as doxorubicin, fentanyl, mannitol, and calcein, as well as high-molecular weight substances such as peptides, heparin, and calcitonin [8,9].

SP uses ultrasound to deliver therapeutic compounds through the skin. This technique temporarily increases skin permeability; however, the underlying mechanism is not yet clearly understood. Cavitation may enhance the effect of electric fields on transdermal transport. First, the vibration of cavitation bubbles induces partial structural disruption of the skin lipid bilayer [10]. Second, the vibration of cavitation bubbles may also induce convection across the skin. Low-frequency SP can deliver a wider range of molecules, including small hydrophobic and large hydrophilic compounds, than high-frequency SP [11].

The evaluation of the percutaneous absorption of molecules is a critical step in the evaluation of topical drug delivery systems or formulations. A dosage form intend-

ed to be used in humans should ideally have skin absorption data from clinical studies. However, such studies are generally not feasible during the early development of new pharmaceutical dosage forms. Various animal models have been used as alternatives to human skin to evaluate percutaneous penetration of substances. Porcine skin is histologically similar to human skin and has a similar SC thickness of 21-26 μm . In the present study, a simple skin model was developed to test skin absorption during dermal and percutaneous delivery. Although the significance of the test needs to be further validated, it is expected to be a useful absorption evaluation method that uses iodine-antioxidant reactions.

In summary, various physical penetration-enhancement strategies are available for TDDSs. The combination of various methods can complement the weaknesses of a single method and produce synergistic effects. In this study, we present such a combination of methods for TDDS that will be of great use in aesthetic medicine and therapeutic fields.

METHODS

Ethics statement: This study was a secondary analysis using the National Health and Nutritional Survey data and the data were received in an anonymous format. As such, Institutional Review Board approval was not sought, but the study adhered to the principles of the Helsinki Declaration.

Cell viability

Hunan dermal fibroblasts (Passage 7; Thermo Fisher Scientific) were cultured in a medium containing 10% fetal bovine serum (Gibco) and 1% penicillin-streptomycin (Gibco) in DMEM (Lonza) at 37°C and 5% CO₂. The TOXNFILL Hyaluronic Boosting Ampoule (water, glycerin, propanediol, 1,2-hexanediol, methylpropanediol, sodium hyaluronate [3,100 ppm, molecular weight: 3,000-1.4 million Dalton] xylitylglucoside, xylitol, hydrolyzed hyaluronic acid, glyceryl glucoside, tromethamine, anhydroxylitol, ethylhexylglycerin, allantoin, beta-glucan, tocopherol, magnesium chloride, tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate, hydrogenated lecithin, ceramide NP, sucrose stearate, stearic acid, palmitic acid, cholesterol, glycosphingolipids, carbomer) group was treated with the test product at different concentrations for 48 hours after 24 hours of seeding cells in a 96-well plate. Two combined techniques (EP and low-frequency SP device; EP frequency, 30 $\pm$ 3 kHz and SP



frequency, 355 kHz, BBS1; LG Electronics; Fig. 1) group was seeded with cells in 100 mm dishes, and after 24 hours, the test device was applied according to each mode and time, and cultured for 48 hours. The hyaluronic acid ampoules (HAAs) and device combination group was seeded with cells in 100 mm dishes, and after 24 hours, the test product and optimal conditions of the test device were applied and cultured for 48 hours. After culture, WST substrate solution was added to the medium, and cultured for 2 hours at 37°C. The absorbance (OD) was measured at 450 m using a microplate reader (Varioskan LUX; Thermo Fisher Scientific).

Collagen protein production evaluation

Cultured human dermal fibroblasts (HDFs) were dispensed into 100 ml dishes and applied under the optimal conditions of the test product and test device when more than 80% cultured, and cultured for 48 hours. The cell culture solution was centrifuged at 2,000 g for 10 minutes, and only the supernatant, excluding cell debris, was used for the test. For quantification of collagen-1 protein, the Human Pro-Collagen I Simple Step ELISA Kit (Abcam) was used, and the test was performed according to the manufacturer's instructions. The OD value was measured using a microplate reader (Varioskan LUX), and the measured value was substituted into the regression equation obtained from the standard curve and multiplied by the dilution factor to calculate the protein concentration.



Fig. 1. Combined application of two techniques—electroporation (EP) and low-frequency sonophoresis (SP)—using a BBS1 device (LG Electronics). Simultaneous application of EP with SP physically creates transient new aqueous pathways (pores) in the stratum corneum, which enhance skin permeation. Maximizing absorption of active ingredients is achieved by repeating these treatments at an efficient rate.

Immunofluorescence staining

The cells were attached to 12- μ m cover glass coated with poly-L-lysine. After 24 hours, they were transferred to a 100-mm dish and cultured for 48 hours under the optimal conditions of the test product and test device. Then, the cells were fixed and treated with blocking buffer. Next, the primary antibody that specifically binds to collagen-1 (anti-collagen I antibody, ab34710; Abcam) was added, followed by a fluorescently labeled secondary antibody (goat pAb to Rb IgG-FITC, ab6717; Abcam). Finally, the cells were fixed with a fixative containing blue fluorescent DAPI (VECTASHIELD mounting medium with DAPI; VectorLabs), and images were obtained at 200 $\times$ magnification using a confocal laser-scanning microscope equipped with a fluorescence system (LSM700; Zeiss).

Ex vivo animal skin models

Porcine skin ex vivo (size: 5 $\times$ 5 cm, thickness: >1,000 μ m) was purchased from Cronex. The porcine skin samples were cut using a Zimmer Brown Electro Dermatome (Model 666; Zimmer). Betaform (size: 5 $\times$ 5 cm, thickness: 2 mm; Genewel) is a foam dressing containing povidone-iodine (PI, 3%) that can be used to manage infected wounds while also providing a moist environment. A 3% PI reaction test on the skin penetration of active ingredients was conducted using a device (BBS1) that could apply both EP and SP (Fig. 2A). About four drops of a whitening agent (CNP Derma Answer Mela Spot Brightening Ampoule; LG Household and Healthcare) were applied on the skin, which was then subject to either SP alone (335 kHz for 3 minutes), EP alone (30 kHz for 3 minutes) or both SP and EP. The area of skin that exhibited reaction with iodine after skin penetration was evaluated using an Antera 3D (Miravex) camera.

Statistical analysis

Statistical Analysis Package for Statistical Science (SPSS for Windows, version 16; SPSS Inc.) was used for the evaluations. Significance was set at $p < 0.05$, with the 95% confidence and probability rounded to three decimal places. Continuous variables are summarized as averages and categorical variables are summarized as frequencies with percentages. For data resulting from more than three repeated measurements, repeated-measures ANOVA was used as a parametric method after the normality test, and the post-test was used after pairwise comparison with the Wilcoxon signed rank test (post hoc Bonferroni correction).

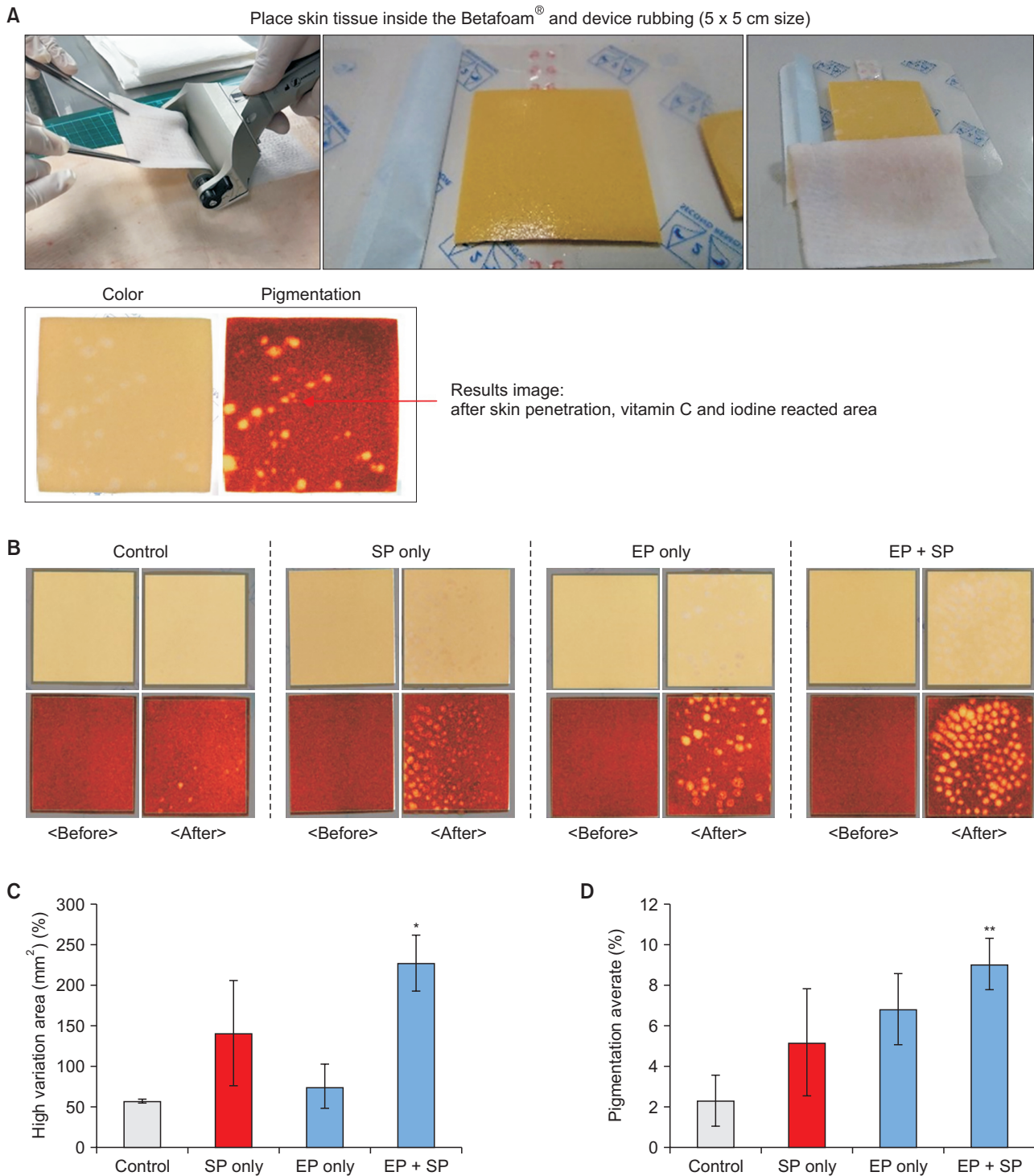


Fig. 2. Penetration and absorption effects on ex vivo porcine skin treated with a functional antioxidant ampoule. (A) After placing porcine skin on Betafoam using an electro dermatome, a functional antioxidant ampoule was applied, and the test device was applied for about 3 minutes under the conditions of electroporation (EP) only, sonophoresis (SP) only, and simultaneous EP plus SP. The area of the reacted and colored part was photographed using Antera 3D (Miravex) equipment to measure the high variation area (mm²) and pigmentation area (%). (B) The 3% povidone-iodine (PI) reaction test for skin penetration of active ingredients was performed using EP and low-frequency SP technology equipment (BBS1, boosting mode, 6 level, 3 minutes; LG Electronics). The images representing the changes are as follows. (C) High variation area represents the actual image of the changed area, and (D) pigmentation area represents the change area in the pigment area. Independent samples ($n = 3$) t-test compared with the non-treated group; * $p < 0.05$, ** $p < 0.01$.

RESULTS

Determination of cell growth and secretion of collagen I

The effects of HAA on HDFs proliferation and collagen synthesis were evaluated. Treatment of HDFs with HAA (0.063%, 0.125%, 0.25%, 0.5%, 1%) for up to 24 hours did not induce cell toxicity. At 72 hours, cell viability increased in a concentration-dependent manner (Fig. 3A, B). The ability of HAA to increase HDFs proliferation was measured at 24 and 72 hours using the WST-1 assay. At 24 hours, HAA induced a dose-dependent increase in HDFs proliferation, with a maximal increase of 1.59-fold

observed with 1% HAA. The expression of type I collagen increased in a dose-dependent manner in HAA using device treated cells (Fig. 3C, D). When EP was applied alone, cell viability increased by 1.27-fold, and when EP and SP were applied simultaneously, cell viability increased by 1.62-fold. In addition, collagen type 1 increased 2.25-fold when EP was applied alone, and 2.87-fold when EP and SP was applied simultaneously. Fig. 3E shows that both intracellular collagen production and extracellular collagen secretion increased after 48 hours of treatment with HAA. Therefore, we confirmed an increase in collagen-1 protein production by HAA in HDFs.

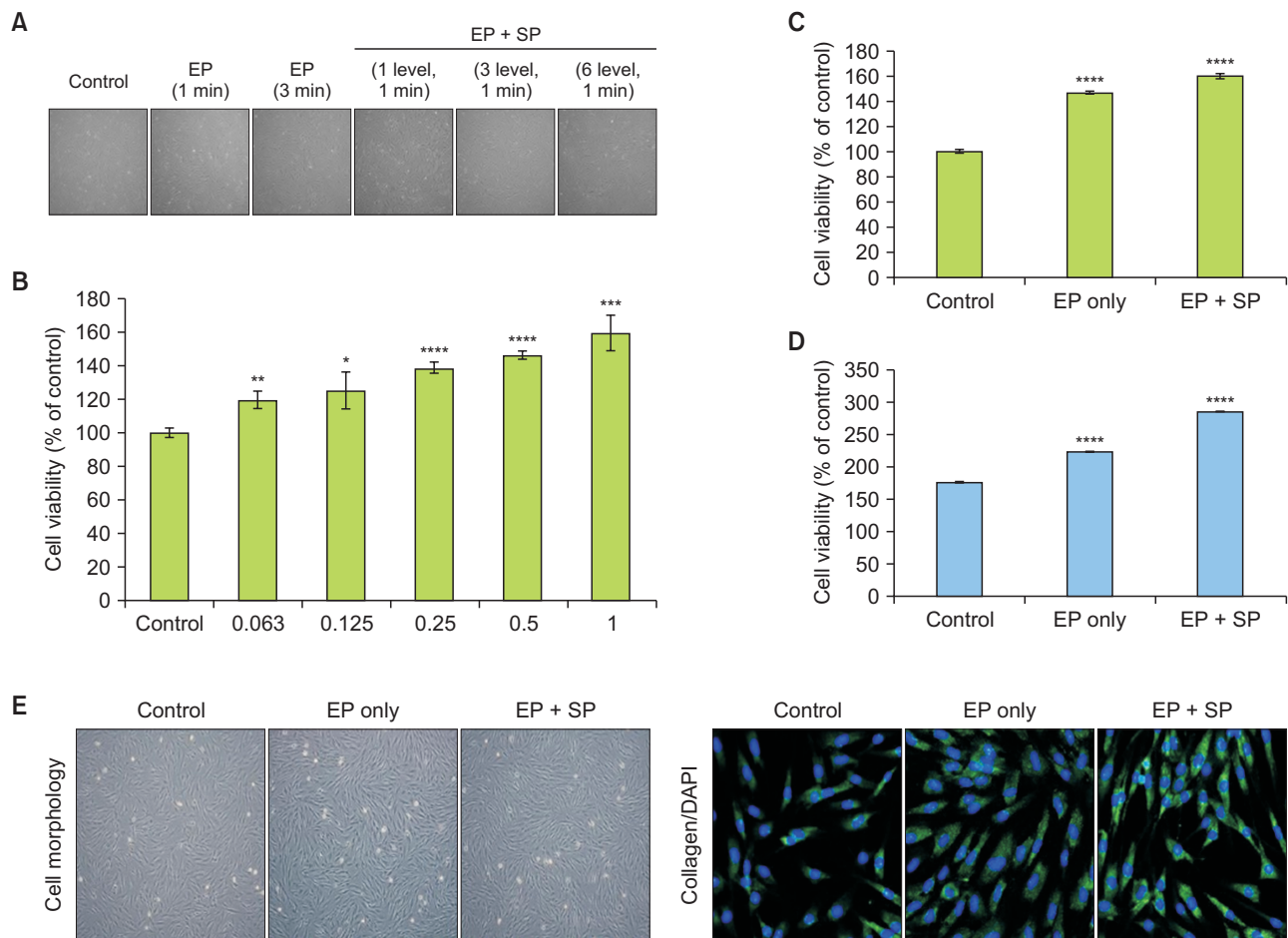


Fig. 3. Cell proliferation and collagen synthesis of human dermal fibroblast (HDFs). (A) After incubation of firming serum at different concentrations (0.063%, 0.125%, 0.25%, 0.5%, and 1%) for 24 hours, the cell viability was determined using the WST-1 assay. Data were normalized using the proliferation rate of the blank control. Proliferation of HDFs treated with various concentrations of hyaluronic acid ampoule (HAA) for 72 hours. (B) Time course of HDF proliferation up to 72 hours. Data are shown as the mean $\pm$ standard deviation of three independent experiments. Effects of HAA in combination with electroporation (EP) or EP plus sonophoresis (SP) on cell viability (C) and collagen synthesis (D) in HDFs. HDFs were treated with medium (control), 1% HAA, 1% HAA + EP only, 1% HAA + EP with SP for 72 hours and the expression of type I collagen was measured using an ELISA kit. (E) Immunocytochemical analysis showing the activation of type I collagen in HAA-treated HDFs. HDFs were fixed and then incubated with a goat anti-rabbit type I collagen antibody. Type I collagen staining was detected with a fluorescein isothiocyanate-conjugated anti-goat IgG antibody using fluorescence microscopy. Magnification, $\times 100$. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, and **** $p < 0.001$ vs. control.

Results of ex vivo animal skin models

In this study, pig skin cut into equal thicknesses was placed on foam dressing containing PI to examine the interaction between the drug to be treated and the device ($n = 3$). Photographs were obtained using an Antera 3D camera and analyzed. Iodine response tests for skin penetration of antioxidant active ingredients were conducted after the skin had been subject to EP and SP. When SP was applied for 3 minutes at 355 kHz and EP was applied for 3 minutes at 30 kHz, changes in absorption were observed compared with when neither was applied. In particular, when EP and SP were applied simultaneously to skin tissue for 3 minutes at a certain ratio, the area that reacted with iodine after skin penetration significantly increased. Considering that the reaction area of the active ingredient penetrated widely depending on the energy ratio, the part that reacted to the area was quantified and displayed. The reaction area increased significantly only when EP and SP were combined (Fig. 2B-D). Therefore, based on these results, this test confirmed that a specific antioxidant ingredient can penetrate the skin more deeply and in greater amounts by the simultaneous use of EP and SP and that quantification is possible.

DISCUSSION

The dual goal of enhancing collagen synthesis and improving the dermal delivery of skincare ingredients aligns with recent advances in dermatological technologies. These techniques are significant because of their potential to offer non-invasive solutions for skin rejuvenation and anti-aging applications, meeting both clinical and cosmetic needs. The combination of EP and SP may provide a synergistic effect, where EP facilitates initial penetration and SP enhances deeper distribution. The integration of EP and low-frequency SP to enhance collagen synthesis and improve the dermal delivery of hyaluronic acid and antioxidant ampoules is a promising area of research with significant implications for dermatology and the cosmetics industry [12,13].

As highlighted in the preliminary response, EP employs electrical pulses to transiently alter the lipid bilayer of the skin, facilitating the penetration of macromolecules, such as hyaluronic acid. The efficacy of this technique in enhancing permeability is supported by its ability to effectively introduce high-molecular weight compounds through the skin [1].

Low-frequency SP uses ultrasonic waves to disrupt the SC, the outer barrier of the skin, thereby augmenting transdermal drug delivery. Studies on the development

of ultrasound-responsive devices have demonstrated the potential of SP to increase skin permeability to therapeutic agents [14,15].

The cosmetics industry could benefit significantly from these technological advances by providing more effective antiaging products. This approach has been explored in various studies highlighting its potential for improved drug retention and delivery efficacy. Despite ethical concerns, the use of animal or isolated animal skin models to assess percutaneous absorption of molecules has been frequently reported. These models are generally more widely available than human skin and have proven to be important in basic research to improve our understanding of the processes, pathways, and driving forces of various agents across the skin barrier. However, there are many different types of skin models and experimental conditions, such as skin temperature and application volume, are variable. Therefore, in vitro and animal models are important tools for screening a range of drug formulations, evaluating enhancement of skin permeation and mechanism of action of carrier systems, and estimating the skin transport ranking of a range of drug molecules. Membranes, which are typically silicone-based polymeric materials, have been used primarily for percutaneous and topical delivery studies; however, despite certain advantages, they cannot completely replace human or animal skin to predict skin absorption in vivo and, in general, do not have a barrier.

The purpose of this study was to investigate the effect of noninvasive EP with SP on skin barrier function and the penetration of active ingredients in an ex vivo model. Skin samples were treated with noninvasive EP or SP or both and with ampoules for 3 minutes. The results showed that the oxidation reactivity significantly increased after being treated simultaneously with EP and SP and penetration from the ampoules. EP with SP reversibly decreased the skin barrier function. The ampoules can penetrate the skin only slightly via passive diffusion. However, when the skin was subjected to EP or SP or a combination of the two, the penetration rate of the ampoules was significantly higher than that of the control treatment. When only EP was applied, the transdermal delivery of ampoules was significantly enhanced compared to passive diffusion ($p < 0.05$). This is possibly because EP pretreatment promotes enhanced macromolecular transport through permeabilized skin by creating new aqueous pathways.

SP is an enhancement technique that temporarily increases skin permeability, enabling the noninvasive delivery of several therapeutic agents. Our study examines

transdermal drug delivery using two physical methods of enhancement: ultrasound (SP) and electric pulses (EP), alone or in combination. Our results showed a significant enhancement of ampoule delivery after 3 minutes of ultrasound application. We also experimented with combinations of the two enhancement methods, hoping for synergistic effects. The results showed a dramatic improvement in delivery when a combination of these methods was used compared with a single method. The mechanism of action of both methods involves the creation of aqueous pathways in the SC, leading to a synergistic increase in skin permeability. We established and characterized a new viable skin penetration model for drug and formulation development. The model allows the determination of drug concentrations in different layers of the viable epidermis and dermis, as well as the generation of information on skin metabolism. In particular, this model is suitable for supporting the rational ranking and selection of dermatological formulations in a drug development project. Another important factor for a penetration/permeation model is the skin barrier properties.

In this study, we confirmed the effectiveness of once-daily, 3-minute per-use ("boost" mode) EP plus SP, which involves simultaneous application of electric fields and ultrasound, using an *ex vivo* model. During follow-up at immediate, 3-day, 2-week, and 4-week follow-ups, most subjects in the combined device group showed significant improvements in all parameters compared with the control group. In particular, this method can have different effects depending on the function of each cosmetic used, and its greatest advantage is that it can deliver active ingredients with high molecular weights deep into the skin. Therefore, it is necessary to conduct clinical trials for a better understanding.

There were problems with some of the research methodologies, and we identified areas for further research. Further research is warranted to address these limitations and to enhance the understanding of EP with SP in facial treatments. Future studies should employ standardized treatment protocols, larger sample sizes, and longer follow-up periods to generate more robust evidence. Although this study and the available evidence do not indicate any adverse effects, the long-term risks of EP with SP of various compounds remains unknown.

Cell experiments showed that HAA alone or HAA with a EP or SP could significantly improve the proliferation and collagen secretion of HDFs. Type I collagen is the most abundant protein found in skin connective tissue, and along with other types of collagen (III, V, and VII), elastin, proteoglycans, fibronectin, and other extracel-

lular matrix proteins, it helps maintain the skin structure. Therefore, HAA can stimulate collagen synthesis and secretion by fibroblasts during the wound-healing process, and thus has potential utility in regenerating aged skin.

Validating safety and minimizing discomfort and adverse effects are key concerns that need to be addressed. Research on solid lipid nanoparticles and other nano-sized particles will be conducted to ensure their safety and efficacy in topical applications. Establishing standardized protocols for combining EP and SP is necessary to ensure consistent outcomes across various applications. Studies on the synthesis of hyaluronic acid nanoparticles have offered insights into how standardization can be achieved. Moreover, dermatology can provide enhanced personalized treatment options for various skin types and conditions by leveraging the personalized capabilities of these technologies.

In conclusion, this study shows that the combination of HAA and a device that applies EP or SP results in faster, deeper, and greater skin absorption of cosmetic products, as evidenced by the numerical and visual data obtained through Raman spectroscopy. These studies showed that administering HAA using EP with SP has a beneficial effect on skin absorption. This approach has potential benefits in clinical dermatology applications, warranting further research and development to optimize these techniques for broader and more effective applications. Continued exploration in this field is crucial for developing highly effective non-invasive skin care and treatment solutions.

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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. Tae-Rin Kwon, Jungwook Kim, Soo Min Kim, Hyoung Jun Kim, Jungkwan Lee are employees of LG Electronics, but they have no conflict of interest to declare. 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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