Received: 19 December 2023 | Revised: 17 January 2024 | Accepted: 4 February 2024

DOI: 10.1111/jocd.16225

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

Arc-poration improves transdermal delivery of biomolecules

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Abstract

Background: To increase skin permeability, various transdermal delivery techniques have been developed. However, due to the stratum corneum as a skin barrier, transdermal delivery remains limited.

Aims: In this study, we evaluated efficacy and safety of arc-poration as a novel technique disrupting the stratum corneum.

Results: Optical images and histological analysis using reconstituted human skin and porcine skin showed that the treatment of arc-poration created micropores with an average diameter of approximately 100 μm only to the depth of the stratum corneum, but not viable epidermis. In addition, the Franz diffusion cell experiment using reconstituted human skin showed a remarkable increase in permeability following pretreatment with arc-poration. Clinical results clearly demonstrated the enhancement of the skin-improving effect of cosmetics by pretreatment of arc-poration in terms of gloss, hydration, flakiness, texture, tone, tone evenness, and pigmentation of skin, without causing abnormal skin responses. The concentration of ozone and nitrogen oxides generated by arc-poration was below the permissible value for the human body.

Conclusions: Arc-poration can increase skin permeability by creating stratum corneum-specific micropores, which can enhance the skin-improving effect of cosmetics without adverse responses.

KEYWORDS
arc discharge, arc-poration, skin permeability, stratum corneum, transdermal drug delivery

1 | INTRODUCTION

The transdermal drug delivery system (TDDS) is emerging as an attractive alternative for drug delivery via oral administration or subcutaneous injection.[1] Especially in skin diseases, TDDS is an effective administration route that can be applied directly to skin lesions and avoids the side effects of conventional administration routes.[2] The most critical step in TDDS is passing the drug through the two epidermal skin barriers: the stratum corneum and the tight junctions on the stratum granulosum. The stratum corneum strictly prevents the penetration of external substances and pathogens.[3] Nevertheless, small molecules with molecular weight less than 500 Da and moderate lipophilicity can penetrate the stratum corneum to some extent.[1,4] The tight junctions obstruct molecules that pass through the stratum corneum from penetrating deep into the skin.[5] However, the tight junction is less strict than the stratum corneum because it can selectively allow ions, uncharged molecules, and macromolecules to pass through the

charge-selective pore and leak pathways.[6] This suggests that the most important challenge for the TDDS is to disrupt the stratum corneum.

To increase the permeability of macromolecules, various active delivery techniques have been developed, including iontophoresis, sonophoresis, electroporation, thermal ablation, and microneedle.[7] Of those techniques, only microneedle and thermal ablation techniques can create micropores on the skin. The microneedle procedure has gained popularity as a technique that allows effective penetration of drugs in the skin with a controlled release, but the occurrence of abnormal skin responses cannot be ruled out because it is an invasive method.[8,9] In contrast to thermal ablation using radiofrequency, which generates micropores with a certain diameter in the depth of the epidermis,[10] thermal ablation with lasers allows controlling the depth of the micropores by controlling the thermal energy applied to the skin, although an additional masking process is required for a certain diameter.[11,12] As stratum corneum-specific disruption and minimizing the damage are important, it is crucial to develop a technique that can control both the depth and diameter of micropores.[13]

Dielectric barrier discharge is a nonthermal plasma that occurs between the high voltage cathode and anode electrodes. In the TDDS, dielectric barrier discharge enhances the penetration of molecules by etching the stratum corneum.[14,15] However, dielectric barrier discharge damages a large area of the stratum corneum and produces harmful substances, such as ozone and nitrogen oxides, when plasma is generated, so there is a possibility for abnormal skin responses and respiratory disorders.[8,16] Unlike dielectric barrier discharge, arc discharge transmits thermal energy generated by high current. When dielectric breakdown occurs for the ignition of arc discharge, thermionic emission is induced in the cathode area by high current density and thermal electrons transmit to anode area.[17,18] In addition, the erosion of electrodes generated by arc discharge shows in areas sized between tens and hundreds of micrometers.[19,20] Therefore, arc discharge could be an alternative technique to apply to TDDS. Previously, we reported that arc discharge could support transdermal delivery along with electroporation.[21] In this study, we investigated the characteristics of micropores created by an arc discharge-based device and the penetration of biomolecules through those micropores.

2 | MATERIALS AND METHODS

2.1 | Device

Skin micropores were generated using the arc-poration device (MEDICUBE AGE-R ATS AIR SHOT, APR Co., Ltd.) developed and manufactured by Easytem Co., Ltd. The device consists of five outputs depending on duty cycle (10%–90%). Level 5, which has a 90% duty cycle, was used in this study. To efficiently generate the skin micropores, the device was kept in contact with the skin by tapping, sweeping, or brushing.

2.2 | Cosmetics ingredients

The ingredients in the MEDICUBE Deep Vitac Ampoule are as follows: water, ascorbic acid, butylene glycol, dipropylene glycol, propanediol, dicaprylyl carbonate, propylene glycol dicaprylate/dicaprate, diisopropyl sebacate, polysorbate 60, glutathione, glycerin, (−)-alpha-bisabolol, glyceryl stearate, panthenol, citric acid, chitosan, pullulan, sodium gluconate, sodium hyaluronate, *helianthus annuus* (sunflower) seed oil, dimethicone, disodium EDTA, ethylhexyl methoxycinnamate, guar hydroxypropyltrimonium chloride, sodium metabisulfite, tris (tetramethylhydroxypiperidinol) citrate, xanthan gum, cyclopentasiloxane, dimethicone/vinyl dimethicone crosspolymer, *Phaseolus Radiatus* seed extract, *Citrus Paradisi* (grapefruit) fruit extract, *Opuntia Ficus-Indica* fruit extract, *Myrciaria Dubia* fruit extract, beta-carotene, *Daucus Carota Sativa* (carrot) seed oil, *Curcuma Longa* (turmeric) root extract, *Terminalia Ferdinandiana* fruit extract, beta-glucan, *Betula Platyphylla Japonica* Bark extract, ethylhexylglycerin, *Rumex Crispus* root extract, sodium hydroxide, fragrance, linalool, limonene, and 1,2-hexanediol.

Whereas the MEDICUBE Super Cica Cream is composed of the following ingredients: water, butylene glycol, glycerin, caprylic/capric triglyceride, cyclohexasiloxane, pentylene glycol, 1,2-hexanediol, dipropylene glycol, *Limnanthes Alba* (meadowfoam) seed oil, *Theobroma Grandiflorum* seed butter, *Melia Azadirachta* leaf extract, *Melia Azadirachta* flower extract, *Ocimum Sanctum* leaf extract, hydrolyzed hyaluronic acid, *Centella Asiatica* leaf extract, *Centella Asiatica* root extract, *Centella Asiatica* extract, *Curcuma Longa* (turmeric) root extract, *Theobroma Cacao* (cocoa) seed extract, *Corallina Officinalis* extract, *Glycyrrhiza Uralensis* (Licorice) extract, ethylhexyl olivate, panthenol, ectoin, hydrogenated polydecene, sodium acrylates copolymer, cetearyl olivate, sorbitan olivate, polyglyceryl-4 oleate, hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, synthetic beeswax, dimethicone/vinyl dimethicone crosspolymer, hydroxyacetophenone, salicylic acid, ethylhexylglycerin, dipotassium glycyrrhizate, sodium phytate, sorbitan isostearate, polyglyceryl-10 oleate, hydrogenated lecithin, silica, dextrin, allantoin, polyglyceryl-10 stearate, madecassoside, tocopherol, ceramide NP, asiatic acid, asiaticoside, madecassic acid, and xanthan gum.

2.3 | Skin micropore formation using arc-poration device

For the micropore formation in the porcine skin, a porcine skin was kept at room temperature until the surface was dry. The frozen porcine skin was purchased from a butcher and used in the experiment. Prior to the arc-poration treatment, the porcine skin was marked with stamp ink so the micropores could be easily detected. After the arc-poration treatment, the micropores were observed under a microscope, and their diameters were calculated. To determine the depth of the micropores, a reconstituted human skin (Neoderm, Tegoscience Inc.) was used. After the arc-poration treatment, a

reconstituted human skin was fixed with 4% formaldehyde and then embedded with paraffin. The paraffin block was sliced to a thickness of 5 μm. These sections were deparaffinized with xylene and then dehydrated with alcohol. The sections were stained with hematoxylin and washed in water. Next, the sections were stained with eosin and rehydrated with EtOH-Xylene steps. After mounting with Canada balsam solution, stained sections were observed under a microscope (CX31, Olympus).

2.4 | Permeation test using Franz diffusion cell

The Franz diffusion cell system was used to determine the penetrance of caffeine after the arc-poration treatment. Phosphate-buffered solution and a magnetic stirrer were placed in the receiving compartment of the Franz diffusion cell. Reconstituted human skin that had or had not received arc-poration treatment were placed between a donor chamber and a receptor chamber, followed by the addition of a 2.2% caffeine solution on the surface of the reconstituted human skin. At each time point, samples were collected from the receiving compartment and analyzed to determine the concentration of caffeine using HPLC. The experiments were duplicated.

2.5 | Clinical evaluation of arc-poration

2.5.1 | Study design

1. Study type: Split-face study.
2. Method: After using the arc-poration device only on the left side of the face, cosmetics was applied evenly on the entire face.
3. Assessment: The difference between the skin properties after applying cosmetics compared with the baseline was evaluated. The difference after applying cosmetics with pretreatment using the arc-poration device compared with the baseline was evaluated. The difference between skin properties of the cosmetics-treated and arc-poration device–pretreated groups was evaluated.

2.5.2 | Study participants

The number of participants was selected based on the test method guidelines established by the Ministry of Food and Drug Safety of the Republic of Korea to demonstrate cosmetics labeling advertisements, and minimum 23 participants were required for this study while considering 15% dropout rate to obtain more than 20 effective datasets. Twenty two Korean adult women aged 20–60 years were registered as participants, and 21 subjects, excluding one dropout, completed the study. The average age of the participants was 48.762 ± 6.715 years, and all individuals provided written informed consent.

2.5.3 | Inclusion criteria

People meeting the following criteria were included in the study.

1. Korean women aged 20–60 years.
2. People having rough skin with visible pores.
3. Healthy individuals with no acute or chronic physical conditions, including skin diseases.
4. Individuals who could be followed up during the study period.
5. People who were informed of the purpose, contents, and other aspects of the research by the research manager or a person delegated by the research manager, who understood the information, and voluntarily signed an agreement to participate in the study.

2.5.4 | Exclusion criteria

People meeting the following exclusion criteria were excluded from this study.

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1. Women who were pregnant or lactating or those who were likely to be pregnant.
2. People who were sensitive to beauty devices, such as patients with neurological diseases and artificial heart transplants.
3. People with sensitive skin.
4. Drug addicts; alcoholics; or patients with mental illness, mental retardation, etc.
5. People with skin abnormalities, such as tattoos, scars, erythema, and dilated capillaries in the study area.
6. People who were using a steroid-containing lotion for at least a month for the treatment of skin diseases.
7. People who underwent skin treatment in the study area within the last 6 months.
8. People who used the same or similar medications in the study area within the last 3 months.
9. People who were deemed inappropriate for this study by the research manager.

2.5.5 | Dropout criteria

If the any of the following criteria were met by a participant or if a study participant expressed the intention to dropout from the study, the study participant was excluded from the study and their data were deleted and excluded from the analysis.

1. Withdrawing the consent to participate in the study.
2. Failing to show up on the study visit date.
3. Not adhering to the prescribed method for using the research product.

4. Taking other medication that may affect the studied skin area.
5. Experiencing skin reaction at the study site after using the research product.
6. Using the same type of cosmetics or similar medicines in the study area.
7. Experiencing severe adverse reaction and damage after participating in the study.
8. Research manager determining that a participant could no longer participate in the study.

2.5.6 | Treatment and assessment

After cleansing their face, all participants were treated with the arc-poration device for 2 min to the left side of the face four times a week (every Tuesday, Thursday, Saturday, and Sunday) for the 4 weeks study period. Additionally, the MEDICUBE Deep Vitac Ampoule and MEDICUBE Super Cica Cream were applied to the whole face twice each day (every morning and night) after cleansing the face during the study period. Prior to the skin evaluation, all individuals washed the study area with the same detergent in an indoor space under constant temperature (22°C ± 2°C) and humidity conditions (50% ± 10% relative humidity) without direct sunlight and waited for at least 30 min.

Skin gloss, dermal hydration, skin flakiness, or skin tone were evaluated using Mark-Vu (PSI Plus Co., Ltd.)/SkinGlossMeter (Delfin Technologies Ltd.), MoistureMeterD Compact (Delfin Technologies Ltd.), Visioscan VC 20plus (Courage+Khazaka Electronic GmbH), and Mark-Vu/Chromameter CR-400 (Konica Minolta Sensing, Inc.), respectively. Skin tone evenness, pigmentation, pore tightening, and texture were evaluated using Antera 3D.

2.5.7 | Statistical analysis

For the statistical analysis of this study, IBM SPSS Statistics 27 software (IBM Co., USA) was used. To analyze the significance of the evaluation results, the paired *t*-test and Wilcoxon signed-rank test were used for preuse and postuse comparisons according to the human body application test and normality test results of each item. In the case of group comparison, the independent *t*-test and Mann–Whitney *U*-test were used. Statistical significance was defined by a p-value of <0.05 in the 95% confidence interval.

2.6 | Measurement of ozone, nitrogen oxide, and nitrogen dioxide

To measure the concentration of ozone and nitrogen oxides, the arc-poration device was placed on a jig and operated at level 5 for 5 min. Then, a sampling tube was installed within 5 mm of the device's application region, and the maximum concentration was measured during the device's operation time. The concentrations of ozone and nitrogen oxides were measured using the ozone concentration tester (2B Technologies) and NOx analyzer (rbr Messtechnik GmbH), respectively.

3 | RESULTS

3.1 | Development of arc-poration device

To disrupt the stratum corneum, we developed an arc-poration device (Figure 1). In this device, the penetration of biomolecules into the skin can be promoted through micropores created by an arc discharge that is ignited by high voltage-induced dielectric breakdown (Figure 1A, left panel). Since the breakdown voltage of air is known to be approximately 3 kV/mm[22] and the applied voltage generally used in handheld electronic devices is very low, we used transformer in which the voltage applied to the primary coil was elevated to the winding ratio of the secondary coil via electromagnetic induction to generate high voltage from low applied voltage (Figure 1A, left panel). As a result, 3.3 Vdc of the applied voltage was transformed to 1.91 ± 0.4 kVpp of alternating current (AC) voltage (Figure 1A, right top panel). To prevent severe burning of the skin caused by thermal energy of continued arc discharge, we also generated pulsed arc discharge using 20 Hz of burst frequency, applying duty cycle in the range of 10%–90%, regulating the burning period (Figure 1A, right bottom panel). Although the output voltage was elevated to 1.91 ± 0.4 kVpp, it was not sufficient to ignite an arc discharge between the electrode and the skin surface. Since dielectric breakdown strength reportedly decreases as the frequency increases,[23] we applied a frequency of 90 kHz as a carrier frequency into the burst frequency to ignite the arc discharge efficiently (Figure 1A, right bottom panel), and then the output carrier frequency was measured at 74.17 ± 0.36 kHz under the no load condition (Figure 1A, right top panel). Figure 1B describes the process of arc-poration once the device contacts the skin. Initially, one of electrodes is in contact with the skin surface as a ground electrode. Once the other electrode enters within the distance where dielectric breakdown can occur, an arc discharge is generated, and micropores are created on the skin surface by the thermal energy. When both electrodes contact the skin surface, the AC current drops due to high skin resistance and flows between the two electrodes through the skin (Figure 1A, right top panel). From the moment one electrode is detached from the skin, an arc discharge occurs and micropores are created on the skin until that electrode is outside the range where dielectric breakdown can occur. Through this mechanism, micropores can be easily created by sweeping, brushing, or tapping the skin with the arc-poration device (Figure 1B).

3.2 | Skin micropore generation using arc-poration device

To analyze the ability of arc-poration to create micropores, we applied this device to both porcine skin and reconstituted human skin

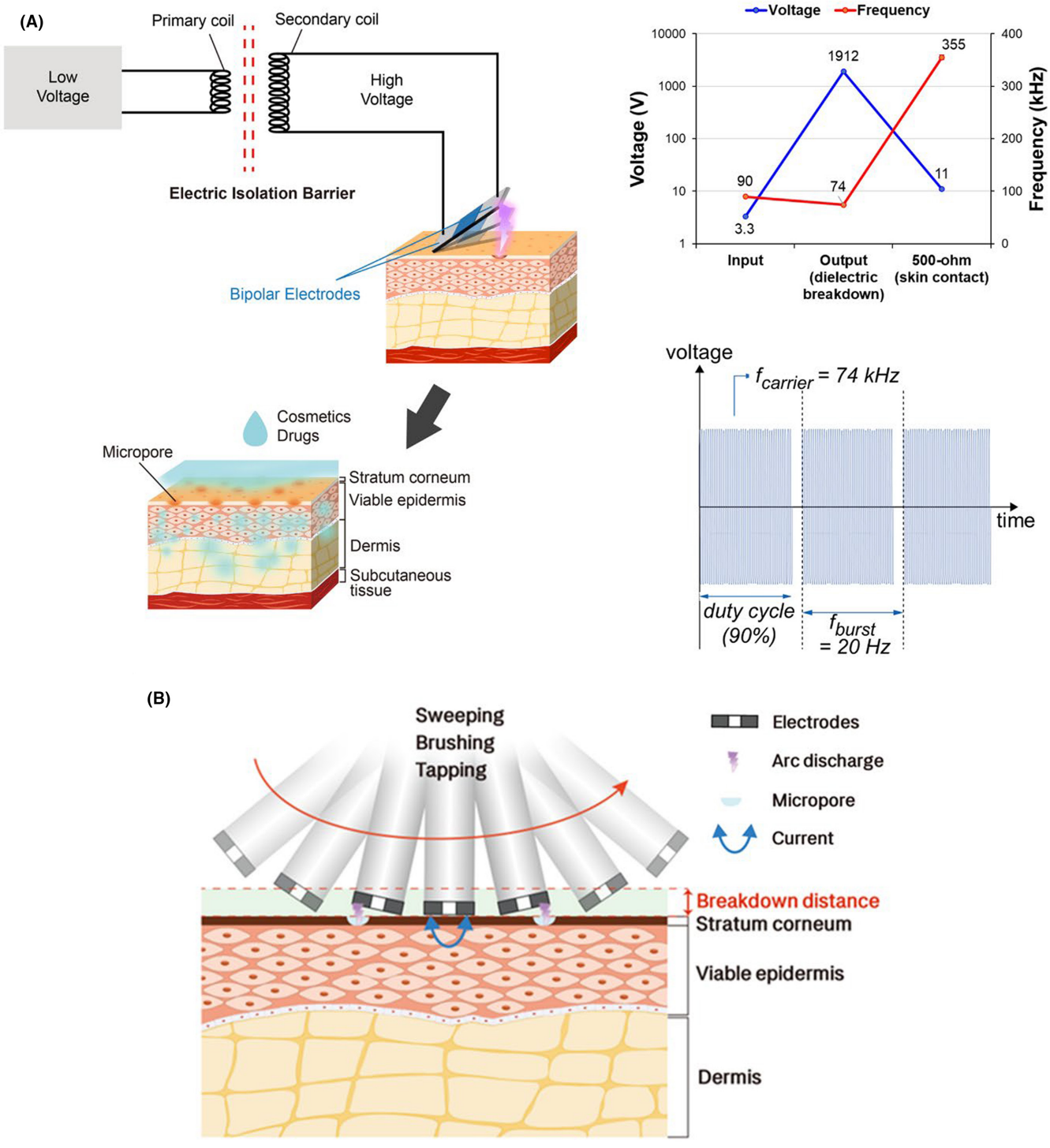


FIGURE 1 Development of arc-poration device. (A) Schematic diagram of transdermal delivery system using arc-poration (left panel). Changes in voltage and frequency at the indicated step are shown (right top panel). Data are expressed as mean ± SD ($n = 5$). Schematic diagram of carrier frequency in burst frequency used in this study are shown (right bottom panel). (B) Schematic diagram for a process of arc-poration on the skin surface.

(Figure 2). Since a porcine skin has many pores, stamp ink was applied before the arc-poration treatment to distinguish newly created micropores (Figure 2A, top panel). As expected, several newly created micropores with an average pores' diameter of 97.45 ± 19.33 μm were observed on the porcine skin treated with arc-poration (Figure 2A), which is similar to the diameter of the pores generated by microporation[10] or microneedle.[24] Similarly, our histological analysis showed that arc-poration created micropores on reconstituted

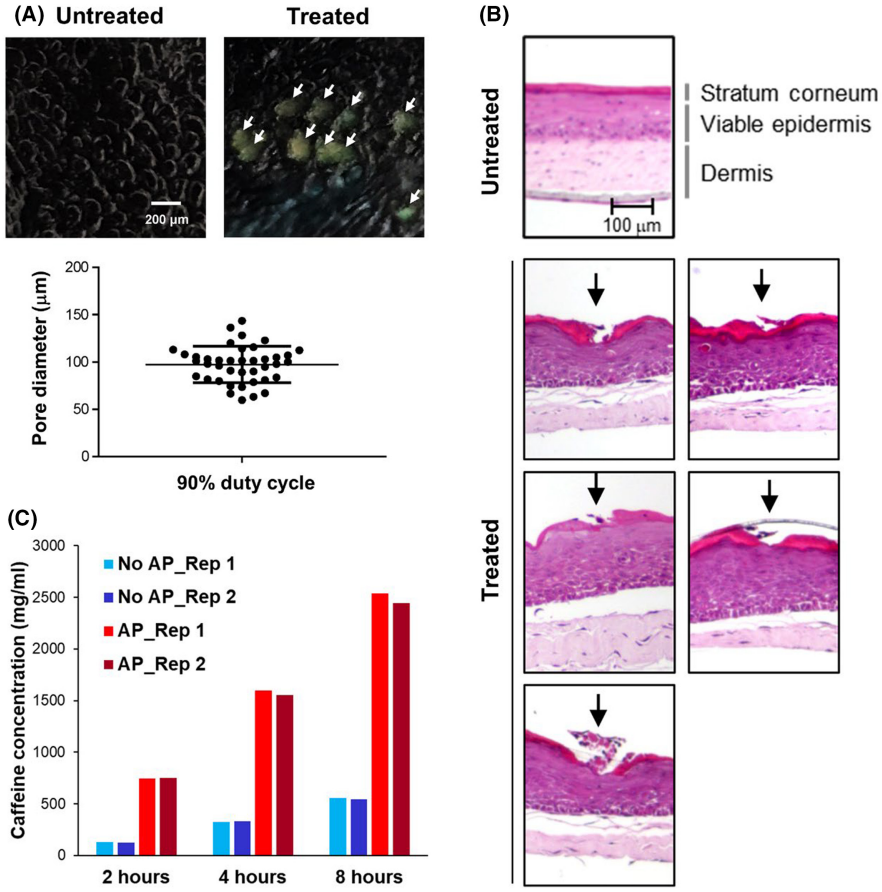


FIGURE 2 Arc-poration creates micropores and increases permeability on the skin. (A) Microscopic images of untreated and Arc-poration-treated porcine skin are shown. Arrows indicate the micropores (top panel). The micropores' diameter was calculated (bottom panel). Error bars represent standard deviation ($n = 40$). (B) Microscopic images of H&E-stained reconstituted human skin (top panel) and arc-poration-treated reconstituted human skin (bottom panel) are shown. Arrows indicate the micropores. (C) The skin permeability through arc-poration-treated (AP) or nonarc-poration-treated (No AP) reconstituted human skin was analyzed with caffeine using the Franz diffusion cell experiment. At each indicated time point, samples were taken, and the caffeine concentration was analyzed using HPLC. The experiment was duplicated.

human skin and the micropores were formed only on the stratum corneum (Figure 2B). Together, these data suggest that arc-poration can disrupt the skin barrier that prevents substance penetration, making a channel for transdermal delivery.

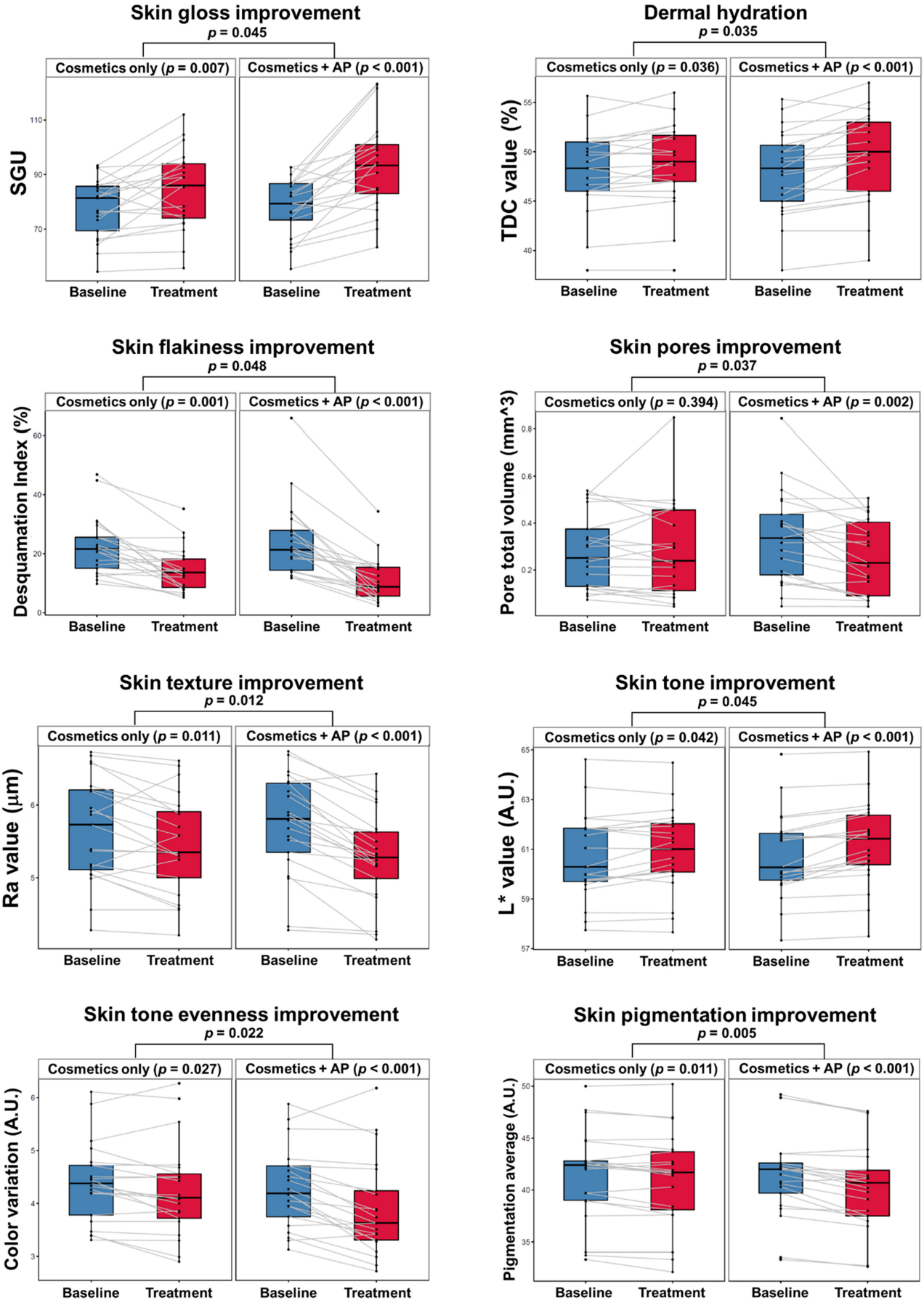
3.3 | Increased permeability of caffeine by arc-poration treatment

Given the stratum corneum's function as a skin barrier, it can be assumed that the stratum corneum-specific micropores created by the arc-poration facilitate the penetration of biomolecules into the skin. Therefore, we performed a Franz diffusion cell experiment with both arc-poration-treated and nonarc-poration-treated reconstituted human skin. Caffeine, which is widely used in dermatological applications, was used as a test substance to measure permeability.[25] The concentration of caffeine penetrated through the stratum corneum to the dermal layer was measured using HPLC. At 2, 4, and 8 h after caffeine treatment, the average concentrations of permeated caffeine are 5.9, 4.8, and 4.5-fold higher in arc-poration-treated sample than those in the nontreated sample, respectively (Figure 2C). This result indicates the enhancement of transdermal delivery through stratum corneum-specific micropores.

3.4 | Clinical evaluation of arc-poration treatment

Next, we investigated whether increased skin permeation through the stratum corneum-specific micropores enhanced the clinical effect of active ingredients. Two types of cosmetics containing antioxidants and anti-inflammatory, moisturizing, and soothing ingredients were applied after pretreatment or nontreatment of arc-poration (Figure 3). After 4 weeks of application of the study products, significant improvements in skin gloss, dermal hydration, skin flakiness, skin texture, skin tone, skin tone evenness, and skin pigmentation were observed in the application area (cosmetics only area) in comparison to that at baseline, confirming the skin improvement effects of cosmetics. These were further improved when arc-poration device was used together with cosmetics (AP area); these significant improvements in the AP area were statistically higher than those in the cosmetic area ($p < 0.05$; Figure 3). The evaluation of skin pore tightening after 4 weeks showed that the pore volume in the

FIGURE 3 Arc-poration enhanced the skin improvement effect of cosmetics. After 4 weeks of cosmetics usage in the absence or presence of arc-poration treatment, skin gloss improvement, dermal hydration, skin flakiness improvement, skin pores improvement, skin texture improvement, skin tone improvement, skin tone evenness improvement, and skin pigmentation improvement was measured compared to baselines. Data are expressed as mean ± SD ($n = 21$).



cosmetics only area decreased compared to that at baseline, but the difference was not statistically significant. In contrast, the AP area showed significant improvement in skin pore tightening ($p=0.002$), which was statistically significantly different from that of the cosmetics only area ($p<0.05$; Figure 3). These clinical results indicate that the skin improvement effect of cosmetics is enhanced by pretreatment of arc-poration.

3.5 | Safety evaluation

Finally, we analyzed the safety of the arc-poration device from its early stages of development. First, when the device contacts the skin, the voltage drops so that a microcurrent that is below the standard allowable current for the human body flows. Second, the pain that may occur due to low-frequency electrical stimulation was excluded by using high frequencies.[26] Third, skin damage caused by the thermal energy of arc discharge was minimized by applying high frequency to shorten the duration.[27] Last, arc-poration device was insulated through an isolation transformer to prevent electrical shocks caused by unexpected events (Table 1 and Figure 1). Within 5 mm of the device's application region, the ozone concentration generated by the device's use was 0.004 ppm (Table 1), which is less than 0.1 ppm (the minimum value among the occupational short-term exposure limit values[28]). The concentrations of nitrogen oxide and nitrogen dioxide produced by the device's use were less than 1 ppm, which is below Occupational Safety and Health Administration exposure limits. Besides, we observed no abnormal skin responses in the application area before or after the arc-poration treatment during the study period (Table 1). Taken together, these data indicate that the arc-poration device is a safe device, which minimizes damage and generates harmful substances below the allowable level.

4 | DISCUSSION

Based on the thermal effect of arc discharge, we developed a handheld device that can create micropores on the skin surface using a modified arc discharge. We named this technique arc-poration, which means creating micropores via arc discharge. Experiments performed on reconstituted human skin and porcine skin demonstrated that the micropores formed by arc-poration were limited to the stratum corneum and arc-poration created micropores with the diameter of approximately 100 μm (Figure 2), which is similar to the diameter of micropores formed by thermal ablation or microneedle. Interestingly, these diameters were achieved without the masking steps required to adjust the diameter of the micropores during thermal ablation, indicating that arc-poration is a unique tool for creating stratum corneum-specific micropores of a particular size. In addition, our clinical results show that the skin improvement effect of cosmetics is enhanced by the pretreatment of arc-poration in all aspects, including melanogenesis and collagen synthesis (Figure 3), suggesting that arc-poration may facilitate the penetration of biomolecules into the skin for its skin improvement effects.

One of the important aspects of facial devices is safety. All safety criteria, including intensity of electrical stimulations and concentration of hazardous substances, were below the permissible value for the human body (Table 1), providing that the arc-poration device is a safe device, which minimizes damage and generates harmful substances below the allowable level. Another important consideration with facial device is eye safety. In arc discharge, the conditions of dielectric breakdown vary depending on the humidity. The breakdown voltage increases as the humidity increases.[29] Since human eyes are always wet, arc discharge does not occur in the eyes when using the arc-poration device, suggesting the device's safety for the eyes.

In this study, we demonstrated that arc-poration, an arc discharge-based technique, can selectively create micropores on

TABLE 1 Evaluation of safety after arc-poration treatment.

Risk factor	Control subject	Required value (preferred value)	Observed value
Electric stimulations[a]	Contact current	<100 mA	22.04 ± 0.54 mA
	Pain	>20 kHz	354.98 ± 4.29 kHz
	Thermal damage	50–500 kHz	74.17 ± 0.36 kHz
	Electric shock	Insulation	Isolation transformer
Hazardous substances	Ozone	<0.1 ppm	0.004 ppm
	Nitrogen oxide	<25 ppm	<1 ppm
	Nitrogen dioxide	<5 ppm	<1 ppm
Abnormal skin responses	Erythema	(Not observed)	Not observed
	Edema	(Not observed)	Not observed
	Scaling	(Not observed)	Not observed
	Itching	(Not observed)	Not observed
	Stinging	(Not observed)	Not observed
	Burning	(Not observed)	Not observed
	Tightness	(Not observed)	Not observed
	Prickling	(Not observed)	Not observed

[a]These data were obtained from Figure 1A.

the stratum corneum, thereby increasing skin permeability and skin improvement effect of cosmetics. Although clinical trials were conducted with cosmetics, it would be expanded to therapeutic macromolecules. To demonstrate the possibility of an arc-poration device as a therapeutic use in the future, we will evaluate skin permeability and efficacy of various biologics after arc-poration pretreatment.

AUTHOR CONTRIBUTIONS

Conceptualization, S.K., J.H.H., and J.W.S.; Methodology, S.K., J.H.H., H.G.K., D.S., and J.W.S.; Investigation, S.K., J.H.H., E.P., H.G.K., J.L., and J.W.S.; Data curation, S.K., E.S.O.; Writing—Original draft preparation, S.K.; Writing—review and editing, S.K., E.S.O., J.H.H., E.P., H.G.K., J.L., D.S., and J.W.S.; Visualization, E.P.; Supervision, S.K. and J.W.S. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was conducted in accordance with the Declaration of Helsinki. This study methodologies were approved by the ethics committee of APR on 03/24/2022 (IRB approval code: 70094430-2202-HR-011-07). Informed consent from all participants were acquired before conducting the study.

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How to cite this article: Kim S, Han J-H, Park E, et al. Arc-poration improves transdermal delivery of biomolecules. *J Cosmet Dermatol*. 2024;00:1-9. doi:10.1111/jocd.16225