Natural and Effective Solution for Long-Lasting Hydration and Plumpness of the Skin Using Core-Shell Ion Complex

Shimatani, Mitsuru[1*]; Isojima, Tatsushi[1]; Ohshima, Mariko[1]; Wang, Dannie[1]; Edagawa, Mai[1]; Cruz, Adriana[2]; Liu, Juan[3]; Itoh, Miho[1]; Saito, Makoto[1]; Ikeda, Yuichi[1]; Asanuma, Hidehiko[1]; Simonnet, Jean-Thierry[4]

[1] L'Oréal Research and Innovation, Tokyo, Japan; [2] L'Oréal Research and Innovation, Clerk, USA; [3] L'Oréal Research and Innovation, Pudong, China; [4] L'Oréal Research and Innovation, Chevilly-Larue, France

* Mitsuru Shimatani, KSP R&D B1213, 3-2-1, Sakado, Takatsu-ku, Kawasaki 213-0012, Japan, +81-44-812-2537, mitsuru.shimatani@loreal.com

Abstract

This study presents a novel core-shell ion complex formulation designed to overcome the limitations of conventional hyaluronic acid (HA) formulations and unlock the full potential of this powerful humectant. Inspired by nature's designs, we created a bioinspired structure from epidermal cells and extracellular matrix, wherein an ionic complex core composed of polyepsilon-lysine (PLYS) and phytic acid (PA) that is emulsified within a protective HA shell called HA Core-Shell Ion Complex. This unique structure addresses the challenges of conventional HA formulations, such as tackiness, uneven film formation, and poor water resistance, by reducing HA entanglement and promoting the formation of a smooth, uniform, and long-lasting film on the skin. Furthermore, the incorporation of polyglyceryl fatty acid esters (PGFEs) dramatically enhanced the surface hydrophilicity and homogeneity of the HA Core-Shell Ion Complex, resulting in superior long-lasting moisturizing effects. The result of consumer home in-use test demonstrated that the novel HA complex formulation significantly improved perceptions of skin firmness, plumpness, and the appearance of smoothness compared to conventional HA formulations. Remarkably, these benefits persisted after 3 days of non-use. This breakthrough technology significantly expands the application of HA in cosmetics and paves the way for a new generation of high-performance cosmetic products.

Keywords: Hyaluronic acid, Core-Shell structure, Ion complex, Skin firmness, Long-lasting

1. Introduction

It is well-established that intrinsic and extrinsic factors, such as chronological aging, ultraviolet radiation, and dehydration, contribute to the degradation of skin's structural integrity. This degradation manifests as a loss of elasticity and firmness, leading to the formation of wrinkles, sagging, and other visible signs of aging.

With the growing number of people living in urban areas, increased exposure to various external aggressors and aging populations, it's becoming increasingly challenging for cosmetics research to offer products that effectively protect the skin over the long term, bring sustained moisturizing properties, preserve elasticity, and protect the skin from external aggressors to prevent the signs of aging. Thus, there is a need for a new formula that is both effective and gentle to protect skin vulnerability against its environment.

Many active ingredients have demonstrated their anti-aging and moisturizing effectiveness, but this can often be compromised by formulations that are not perfectly adapted to the environmental changes to which we are more and more exposed.

This is the case with HA topical formulations which gives skincare sustained moisturizing properties and confers skin anti-ageing benefits. These types of formulations are often susceptible to removal via friction, or degradation by sweat, diminishing their efficacy and can sometimes leave undesirable tacky films on skin.

In this context, our challenge was to develop a new formulation technology that enhances the sustained effects of active ingredients while minimizing stress during use. Moreover, the objective of this innovative formulation was to provide lastingness and resilience to external stimuli after application and a pleasant sensorial experience.

Finally, to align ourselves with the new challenges of sustainability in cosmetic industry, we decided to achieve this challenge by leveraging a unique synergy of natural ingredients, and thus achieve lastingness of the product and giving resilience to external aggressors.

This study reports the successful development of a breakthrough formulation technology comprising exclusively natural ingredients and its application to the cosmetic formulation using hyaluronic acid (HA) .

In the body, HA plays a crucial role, particularly in the skin. As a major component of the extracellular matrix, HA maintains tissue elasticity and flexibility and contributes to skin hydration and plumpness by retaining substantial water content. Although present in lower amounts compared to the dermis, HA is also a component of the epidermis. It has been reported that HA significantly decreases in the epidermis with age, and this is considered one of the contributing factors to the decline in skin elasticity [1]. Therefore, we focused on the structure of youthful epidermis (Figure 1a). Observing the structure of HA in the skin, with epidermal cells at the core and HA shell as the matrix, provides elasticity and flexibility.

We hypothesized that mimicking this structure in cosmetics could enhance the performance of

HA. In this study, we selected a combination of PLYS and PA to form the liquid ion complex, representing the core in our biomimetic approach (Figure 1b).

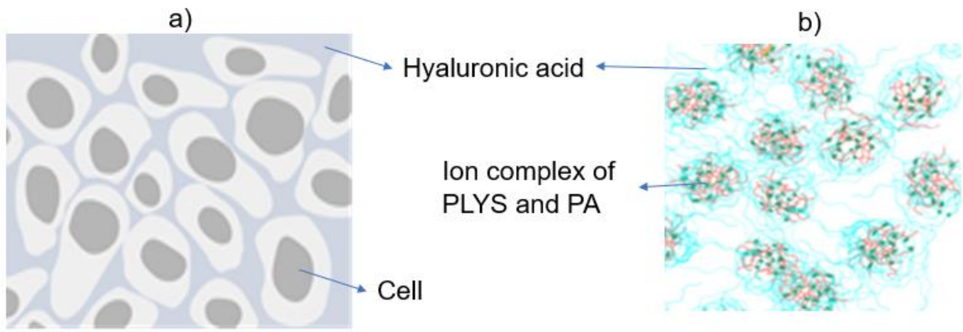


Figure 1. Epidermis structure (a) and Image of HA Core-Shell Ion complex (b)

HA, classified as a glycosaminoglycan, comprises repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine linked by β-1,4 and β-1,3 glycosidic bonds. HA forms a unique ribbon-like structure through intramolecular hydrogen bonding and interactions with water molecules. This ribbon structure creates hydrophobic patches due to the alignment of hydrogen atoms at axial positions, thus engaging in hydrophobic interactions in aqueous solutions. Especially in high molecular weight HA molecules, these hydrophobic interactions and entanglement effects are pronounced, resulting in high viscosity and stickiness [2-5].

PLYS is a unique cationic polypeptide produced by the fermentation of Streptomyces albulus [6], with a molecular weight of approximately 4000 Da and 25-35 L-lysine residues linearly linked via ε-amino and α-carboxyl terminals. PLYS exhibits antimicrobial properties, including antiviral, antifungal, and antibacterial characteristics [7], and is utilized as a preservative and antimicrobial agent in the cosmetic and food industry. According to Personal Care Products Council, it is recognized as a skin and hair conditioning agent [8].

PA, a natural organic acid found in the seeds and grains of plants such as nuts and rice, is primarily composed of six phosphate groups and inositol. It possesses antioxidant and mineral chelating properties [9] and is utilized a chelating agent, exfoliant and humectant, according to Personal Care Products Council [8]. And it is used as an antioxidant and stabilizer in food preservation and processing. PA, with its six phosphate groups, binds to various functional molecules, exhibiting unique properties. These characteristics are detailed in reviews by Wang R and Guo S [9] and Oatway L et al [10]. Furthermore, PA acts as a crosslinker by binding to polycations such as chitosan [11,12] and forming hydrogen bonds with polyanions like alginate [13] and HA [14].

The application of a PLYS-PA complex in cosmetics leverages the individual efficacy of both components. We hypothesize that this complex, formed at neutral pH, generates a film capable of conforming and accumulating on the uneven surfaces of skin and hair.

The HA Core-Shell Ion Complex, with PLYS and PA ion complex as the core and HA as the shell, is designed to maintain its structure during film formation, thereby functioning as a matrix for HA. This structure has been previously reported [15].

To further enhance moisturization, polyglyceryl fatty acid esters (PGFEs) were incorporated into the HA Core-Shell Ion Complex as a key material. PGFEs, derived from plant oils, are natural ingredients formed from glycerin and fatty acids. PGFEs are expected to have moisturizing effects.

The film properties were evaluated using multiphoton microscopy, contact angle measurements, and texture analysis. The formulation's efficacy was assessed through Dermal Torquemeter measurements, three-dimensional (3D) imaging analysis, and a quantitative consumer home in-use test. The results demonstrate the superior functionality of the cosmetic formulations developed through this research.

2. Materials and Methods

2.1 Material

The main ingredients used in this study are as follows:

Sodium Hyaluronate (HA): 1,100 kDa

Polyepsilon-Lysine (PLYS): 4 kDa

Phytic acid (PA)

Polyglyceryl fatty acid ester (PGFEs): HLB 5 and 15

Fluorescein-labeled hyaluronic acid (FL-HA): 800 kDa

2.1.1 Preparation of HA Core-Shell Ion Complex formulation

In an aqueous solution of PLYS, HA was dissolved while maintaining a pH above 10.

PA was then added, and the pH was adjusted to 7.

PGFEs and other cosmetic ingredients were added to complete the preparation.

The compositions of the HA Core-Shell Ion Complex formulation are shown in Table I.

Table I. Compositions of the HA Core-Shell Ion Complex formulation

	HA Core-Shell Ion Complex formulation / mass %	**Conventional HA formulation** / mass %
Sodium hyaluronate (1,100 kDa)	0.50	0.50
Polyepsilon-Lysine (4 kDa)	0.25	-
Phytic acid	0.15	-
Polyglyceryl fatty acid esters	3.5	-
Humectants, Preservatives, Stabilizers, Solvents	Q.S.	Q.S.

2.2 Characterization of the film of HA Core-Shell Ion Complex formulation

The properties of the cosmetic film formed by the HA Core-Shell Ion Complex formulation were evaluated. The cosmetic film formed by conventional HA formulation was used as a comparison.

2.2.1 Ex-vivo visualization of HA residue using fluorescein-labeled HA

To assess the water resistance of the cosmetic film and film retention on the skin formed by the HA Core-Shell Ion Complex formulation, 20% of the high molecular weight HA in the formulation was replaced with fluorescein-labeled HA. To investigate the individual contributions of the core-shell ion complex and PGFEs to the water resistance of the formulation, we prepared two separate formulations, each containing only one of these components.

The labeled HA-containing HA Core-Shell Ion Complex formulation was applied to the substrate at a rate of 2 mg/cm^2, dried to form a cosmetic film, and observed using a multiphoton microscope (A1RMP/FN1, Nikon, Tokyo, Japan). After rinsing with a fixed amount of water at a constant rate and air-drying, the film was re-observed with the multiphoton microscope to visualize the retention of labeled HA.

2.2.2 Evaluation of surface hydrophilicity and water resistance of the cosmetic film on the skin using contact angle measurement

The surface hydrophilicity of the cosmetic film formed by the HA Core-Shell Ion Complex formulation was evaluated using a Mobile Surface Analyzer (MSA Flex, KRUSS, Hamburg, Germany). First, the contact angle of pure water on the skin of the forearm was measured. Then, after applying 2 mg/cm^2 of the formulation to the same area, drying to form a cosmetic film, and measuring the contact angle, the film was rinsed with water and air-dried. The contact angle was measured again, and the changes in contact angle under each condition were evaluated.

2.2.3 Evaluation of the peel force of the film

The tackiness of the cosmetic film of the HA Core-Shell Ion Complex formulation was evaluated using a Texture analyser (TA.XTplusC Texture Analyser, Stable Micro Systems, Surrey, UK). Peel force measurements were employed to quantify the degree of tackiness.

To conduct the analysis, a circular specimen of artificial skin (Sappler™, Idemitsu Technofine) with a diameter of 2 cm was excised. The formulation was then uniformly applied onto the Sappler™ at a concentration of 2 mg/cm^2. Following air-drying, the specimen was affixed to the cylindrical probe of the texture analyser. A second piece of artificial skin was secured to the base platform of the instrument. The peel force required to separate the two surfaces was measured after ensuring complete contact. This procedure was repeated 5 times to obtain replicate measurements.

2.3 In vivo performance evaluations

2.3.1 Dermal Torquemeter Measurements (DTM)

Skin firmness was evaluated using a Dermal Torquemeter (TORQUEMETER™, Dia-Stron, Andover, UK). Measurements were performed on the participants' forearms at baseline (T0) and 4 hours post-application (T4h). A circular area with a diameter of 4 cm (12.56 cm^2) was selected for the application of the formulation at a dosage of 2 mg/cm^2.

The DTM conditions were set to a torque of 10 mNm, a twisting time of 10 seconds, a rest period of 10 seconds, and a single cycle. Immediate extensibility (Ue) and immediate tonicity (Ur) were obtained from the measurements. The Ur/Ue, representing skin firmness, was calculated at both T0 and T4h. The difference in Ur/Ue between T4h and T0 was used to determine the change in skin firmness over time.

The test included 40 female participants aged between 41 and 65 years of European origin who perceived a lack of skin firmness.

The study adhered to the protocol in accordance with the most recent version of the World Medical Association Declaration of Helsinki, local regulations, and Intertek procedures, which are based on the ICH Guidelines for Good Clinical Practice.

2.3.2 Product use test with advanced 3D imaging analysis

An objective evaluation and visualization based on empirical data were conducted to compare the Long-lasting and immediate effects on the skin of the HA Core-Shell Ion Complex formulation compared to the conventional HA formulation using an advanced 3D imaging analysis system [16].

The study recruited 10 female volunteers aged between 25 and 45 years, each of whom applied both test formulations to their face. Facial imaging was conducted using a 3D imaging analysis system prior to the initial application, immediately after application and after 24 hours. The evaluation focused on the following parameters:

Visualization and Quantification of Film: The state of cosmetic film formation on the skin surface immediately after application and after 24 hours were visualized using high-precision 3D scanning technology. The uniformity and distribution of the film were quantitatively evaluated.

Skin Smoothness: The 3D imaging analysis captured the fine texture of the skin surface, quantitatively assessing parameters such as roughness, smoothness, and fineness of texture to evaluate changes in the skin surface condition due to the formulations.

Evaluation of Persistence: The residual state of the cosmetic film after 24 hours was assessed using 3D imaging analysis to evaluate the persistence of the formulations.

2.3.3 Consumer home in-use test

The test recruited participants from across the United States, targeting women aged 18 to 70, excluding those with sensitive skin, and encompassing all skin types, ethnicities, and skin tones. However, the target group consisted of users of anti-aging formulation concerned with signs of aging.

This study employed a blind, randomized, controlled design to evaluate the efficacy of the HA

Core-Shell Ion Complex formulation compared to the conventional HA formulation. A total of 362 participants were randomly assigned to one of two groups: a test group (N=177) receiving the HA Core-Shell Ion Complex formulation and a control group (N=185) receiving a conventional HA formulation. Both groups were instructed to apply their assigned formulation at home for a period of 4 weeks. Participants completed self-assessment questionnaires after week 4, covering aspects related to signs of aging, such as skin firmness, plumpness, and appearance. Additionally, to verify the persistence of effects, self-assessments were conducted again 3 days after discontinuing the product use.

3. Results

3.1 Characterization of HA Core-Shell Ion Complex formulation

3.1.1 Ex-vivo visualization results of HA residue using fluorescein-labeled HA

In the cosmetic film after application, the presence of fluorescent substances was confirmed across the entire applied area for both formulations (Figure 2a, c). After rinsing, no significant change in fluorescence intensity was observed in the HA Core-Shell Ion Complex formulation (Figure 2b). In contrast, a decrease in fluorescence intensity was observed in the conventional HA formulation (Figure 2d).

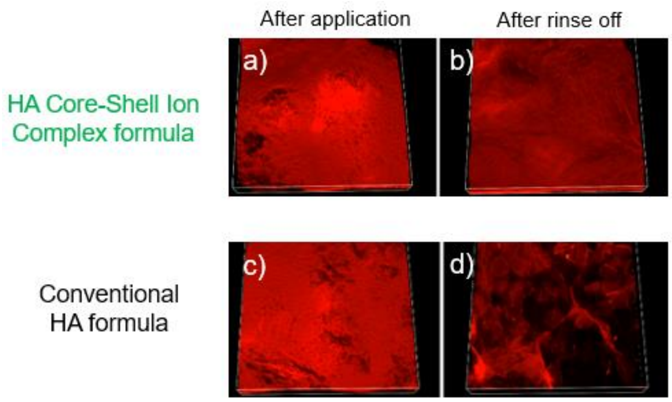


Figure 2. Multiphoton microscope observation

3.1.2 Contact angle measurement results

The hydrophilicity of the bare skin is more than 90° since normal skin is hydrophobic. The contact angles of the bare skin were 102° / 104° (Figure 3a, 3d). The cosmetic film formed by the HA Core-Shell Ion Complex formulation on the arm showed a contact angle of 17° before rinsing (Figure 3b), indicating high hydrophilicity. Moreover, the contact angle did not change significantly after rinsing, maintaining its initial hydrophilicity (Figure 3c).

On the other hand, the cosmetic film formed by the conventional HA formulation showed a larger contact angle which is 56° compared to the HA Core-Shell Ion Complex formulation before rinsing (Figure 3e), confirming some degree of hydrophilicity. However, after rinsing, the contact angle changed significantly, reaching values almost equivalent to bare skin (Figure 3f).

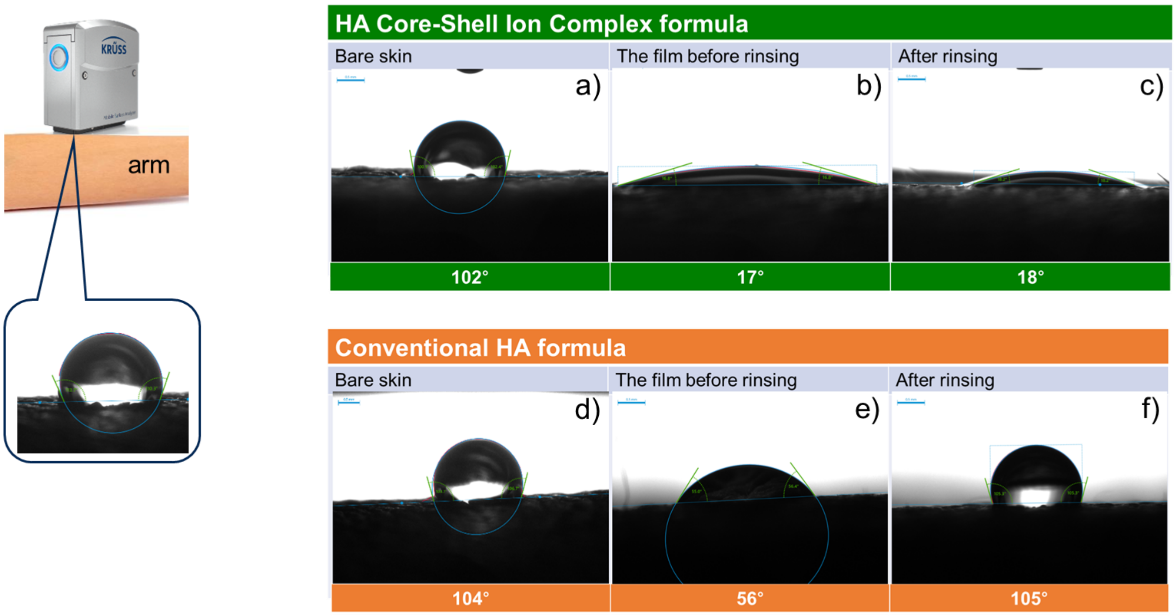


Figure 3. Contact angle measurement results

3.1.3 The result of the peel force of the film

The cosmetic film formed by the HA Core-Shell Ion Complex formulation exhibited a tendency for reduced half of peel force when compared to that of the conventional HA formulation (Figure 4).

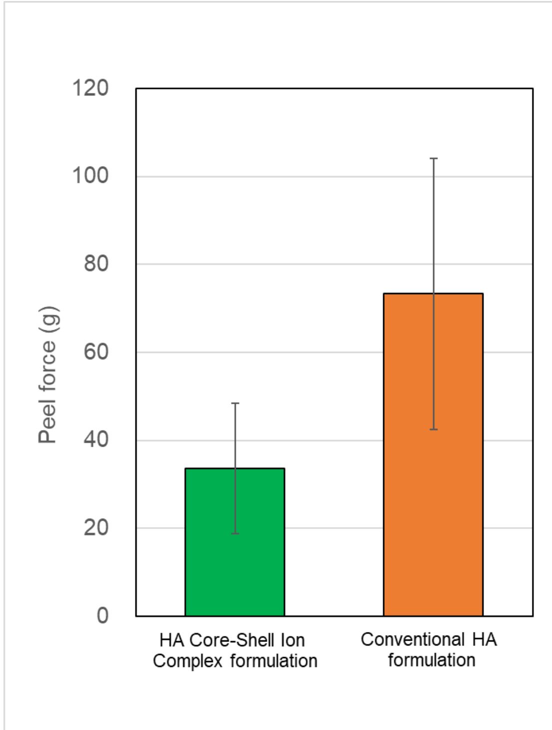


Figure 4. Peel force measurement results

3.2 Performance of HA Core-Shell Ion Complex formulation

3.2.1 Results of DTM

Application of the HA Core-Shell Ion Complex formulation resulted in a statistically significant increase in the Ur/Ue at 4 hours post-application compared to T=0 ($p < 0.05$), demonstrating a more than two-fold improvement in skin firmness compared to the conventional HA formulation (Figure 5).

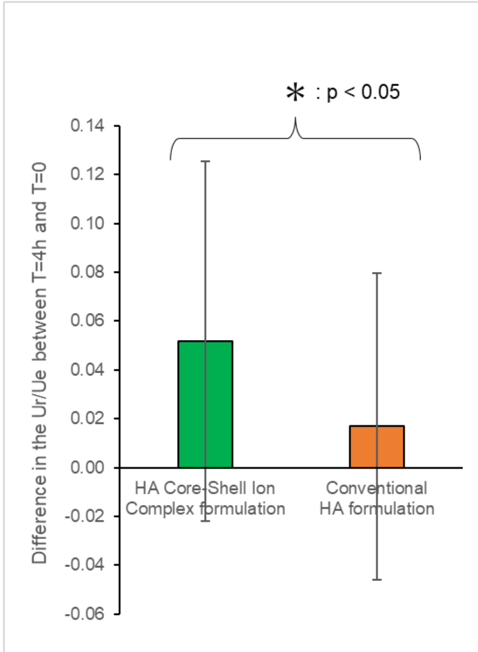


Figure 5. Difference in the Ur/Ue between T=4h and T=0

3.2.2 Product use test with advanced 3D imaging analysis

Figure 6 presents the results of the 3D imaging analysis following the application of the HA Core-Shell Ion Complex formulation in 10 participants. It was observed that the HA Core-Shell Ion Complex formulation formed a uniform cosmetic film on the skin surface (Figure 6a). In contrast, the conventional HA formulation exhibited non-uniform in the cosmetic film formation (Figure 6b).

Furthermore, after 24 hours, the cosmetic film of the HA Core-Shell Ion Complex formulation was kept uniform on the skin, as shown in Figure 6c. On the other hand, the cosmetic film of conventional HA formulation had disappeared after 24 hours (Figure 6d).

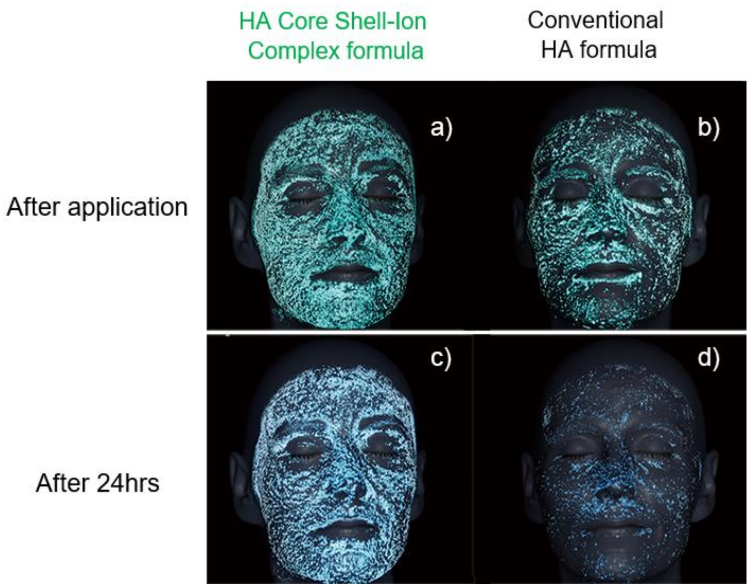
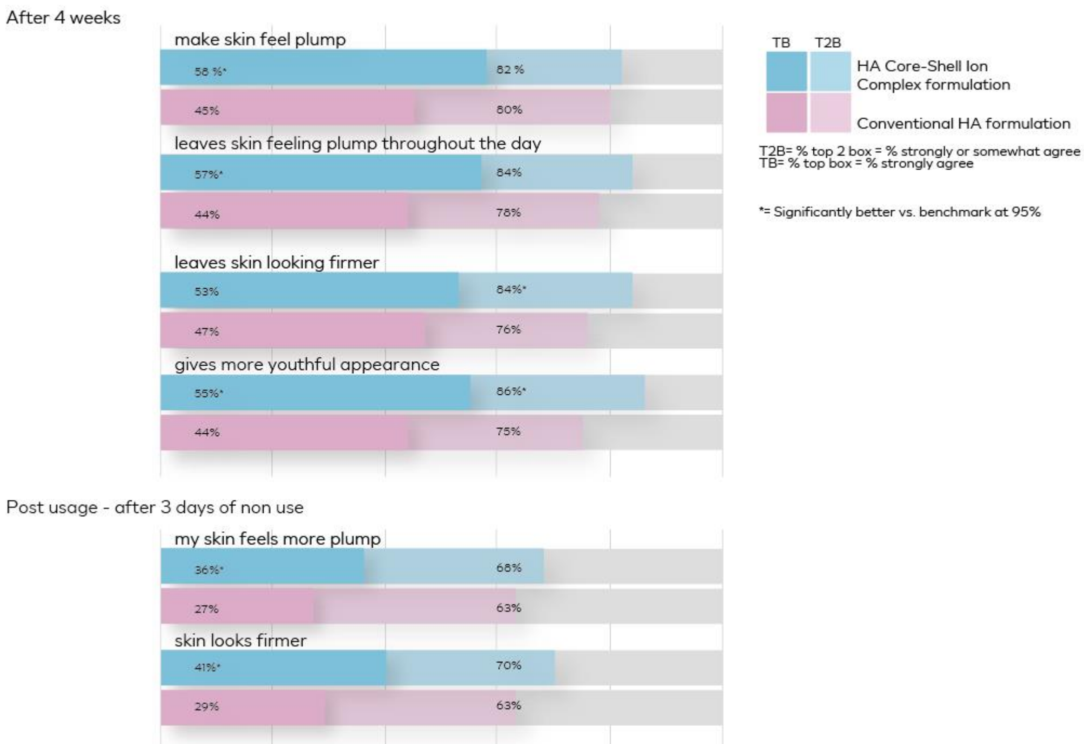


Figure 6: 3D imaging analysis

3.2.3 Results of the consumer home in-use test

The consumers perceived a significant improvement in skin plumpness and firmness with the HA Core-Shell Ion Complex formulation compared to the conventional HA formulation (Table II). Furthermore, this perception was maintained for 3 days after discontinuation of product use.

Table II: Consumer test results



4. Discussion

With the aim of maintaining skin firmness, as well as suppressing wrinkles, we revisited hyaluronic acid (HA), a widely used as cosmetic ingredient [17], and investigated the lastingness of its moisturizing effect. In this study, we attempted to sustain the moisturizing effect of HA and improve skin firmness by mimicking the role that HA plays in the extracellular matrix. Specifically, to mimic the structure of HA in the extracellular matrix, a liquid ion complex core mainly composed of the polycation PLYS and the crosslinker PA was designed to resemble a cell, with HA serving as the surrounding shell (matrix). This resulted in the development of a novel HA Core-Shell Ion Complex.

The formation of the core-shell structure suggests that the HA constituting the shell layer exhibits a conformation with reduced molecular entanglement compared to its state in an aqueous solution where it does not form the core-shell structure. Therefore, cosmetics formulated with the HA Core-Shell Ion Complex are expected to provide a lighter and less tacky texture compared to conventional HA-containing cosmetics.

To elucidate the structure of the HA core-shell ion complex, we performed structural observations using fluorescence microscopy in Figure 7a and stained transmission electron microscopy (TEM) in Figure 7b. For fluorescence microscopy, HA chemically modified with fluorescein (molecular weight: 800 kDa; green fluorescence, wavelength: 550 nm) was mixed at 20% as marker for visualization. As shown in Figure 7a, the complex exhibited a wide size distribution, ranging from large size of approximately 10 μm to small size of several micrometers. To examine the detailed structure, stained TEM observation using ruthenium tetroxide was conducted, and the results are presented in Figure 7b. This observation clearly revealed that the complex possesses a distinct core-shell structure. Furthermore, the zeta potential measurement yielded a negative value of -40 mV, suggesting that the shell of the structure is composed of HA [15].

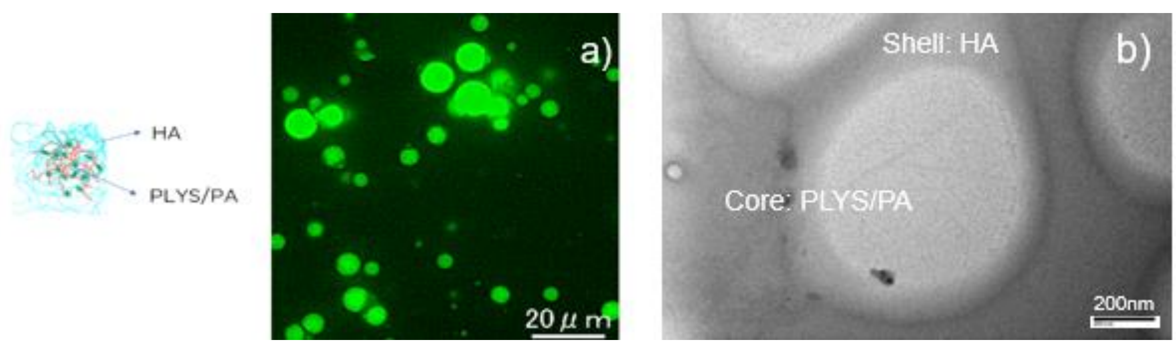


Figure 7. Microscope observation and image of HA Core-Shell Ion Complex
a) Fluorescence microscope observation of HA Core-Shell Ion Complex by BZX-710 (Keyence corporation, Tokyo, Japan). b) Stained TEM image by H-7600 (Hitachi High-Technologies Corporation, Tokyo, Japan). The sample was stained with ruthenium tetroxide.

Our challenge was to develop a new formulation technology that enhances the sustained effects of active ingredients while minimizing stress during use. Moreover, the objective of this innovative formulation was to provide lastingness and resilience to external stimuli after application. To address the challenges of lastingness and resilience against external stimuli, we first developed a formulation with the HA Core-Shell Ion Complex. To maximize the hydrating effects of HA, nonionic surfactants called PGFEs were added to the formulation. However, there was a concern about the PGFEs, due to their hydrophilic nature, could increase hydrophilicity of the film. This could lead to a decrease in the film's durability and resilience. To validate this hypothesis, we conducted contact angle measurements on the skin (Figure 3). The results demonstrated that the HA Core-Shell Ion Complex formulation maintained a high level of hydrophilicity. Notably, even after rinsing, the film retained its hydrophilic properties, indicating its resilience to water. To gain a deeper understanding of this phenomenon, we employed multiphoton microscopy (Figure 2).

To further assess the film's performance, we evaluated its tackiness using a texture analyser. The results clearly indicated that the film formulated with the HA Core-Shell Ion Complex exhibited significantly less peeling force, which directly corresponds to tackiness, compared to the film formed with a conventional HA formulation (Figure 4).

The resulting observations revealed a synergistic effect between the HA Core-Shell Ion Complex and the PGFEs. This combination enhances the film's resilience to water, preserving its integrity and promoting long-lasting effects. Furthermore, it suggests a mechanism that reduces HA entanglement, leading to a smoother and more homogenous film formation.

The effects of the HA Core-Shell Ion Complex and PGFEs are discussed below.

The remarkable mechanical resilience of the HA Core-Shell Ion Complex from a unique mechanism involving PLYS/PA liquid ion complexes that form within the cosmetic film. HA, naturally prone to entanglement, forms a network within the film. This entanglement typically generates internal stress, which can lead to uneven film formation and compromise its properties. However, the presence of deformable liquid ion complexes effectively mitigates this issue. These complexes act as shock absorbers, buffering the stress and allowing the film to withstand deformation, ultimately enhancing its overall toughness and resilience [15]. The formation of a polyion complex provides additional benefit: enhanced water resistance at neutral pH levels [15]. This characteristic further contributes to the film’s durability upon contact with moisture. Incorporation of PGFEs introduces molecular interactions that further enhance the film’s property. It is believed that the hydroxyl groups of PGFEs form hydrogen bonds with HA, and the alkyl chains of PGFEs assemble themselves by the hydrophobic interactions. These combinations of interactions cross-link the HA Core-Shell Ion Complex in the cosmetic film. This cross-linking is thought to enhance its mechanical strength of the film and improve water resistance.

Studies on the combination of surfactants and HA, such as the work by Yorke et al. on the development of conditioning shampoos using HA and bio-based surfactants primarily through rheological methods [18], and the study by Seres et al. on the examination of nanogels formed by the cationic surfactant CTAB and anionic HA, where CTAB and HA form nanogels through ion interactions and hydrophobic interactions of the surfactant [19], are relevant. Our research extends beyond the simple interaction between PGFEs and HA. It is an intriguing subject from the perspective of multiple crosslinking gels to investigate PGFEs’ interactions with the novel HA Core-Shell Ion Complex, with the PLYS and PA molecules, and with the ion complex formed by PLYS/PA.

The efficacy of the HA Core-Shell Ion Complex formulation was assessed by DTM. A statistically significant improvement ($P < 0.05$) in DTM measured skin firmness was observed after 4 hours post application compared to the conventional HA formulation (Figure 5). This observed increase in firmness is attributed to the formulation of a uniform hydrogel film on the skin's surface.

3D imaging analysis confirmed the superior uniformity of the HA Core-Shell Ion Complex formulation film compared to the film of conventional HA formulation (Figure 6a, 6b). It suggested that the uniform hydrogel film effectively enhances skin hydration, thereby contributing to the observed improvement in skin firmness. Notably, the film of HA Core-Shell Ion Complex formulation maintained its uniformity for 24 hours (Figure 6c).

Our research addressed the challenge of developing a new formulation technology that enhances the sustained effects of active ingredients. We anticipated that this innovative formulation delivers prolonged skin hydration and firmness benefits of HA to consumers. To test this hypothesis, a quantitative consumer in-use study was conducted, comparing the HA Core-Shell Ion Complex formulation to the conventional HA formulation. After 4 weeks of product use, a statistically significant improvement in self-evaluated skin firmness, plumpness, and more youthful appearance was observed in the group utilizing the HA Core-Shell Ion Complex formulation. Remarkably, these effects on skin firmness and plumpness persisted even after a 3-day product discontinuation period following the 4-week usage period, suggesting that the HA Core-Shell Ion Complex formulation may induce sustained enhancement of moisturizing and firming properties of HA.

The skincare effects of the HA Core-Shell Ion Complex formulation are discussed below.

The HA Core-Shell Ion Complex formulation mitigates the inherent tackiness associated with high molecular weight HA, thereby offering a more desirable and comfortable application experience. This formulation generates a uniform, highly hydrophilic hydrogel film on the skin surface, effectively retaining moisture and providing continuous hydration. The enhanced water resistance of this film contributes to prolonged skin hydration and firmness, delivering sustained benefits attributed to HA. Furthermore, the film exhibits resilience against external stimuli for up to 24 hours post-application, potentially contributing to a more youthful appearance.

5. Conclusion

This study detailed the development and efficacy of an unprecedented HA Core-Shell Ion Complex formulation, inspired by extracellular matrix structure of dermis, for enhanced delivery and prolonged benefits of HA. This innovative approach, meticulously designed through precise molecular interactions and a synergistic combination of PLYS/PA/HA and PGFEs, generates a unique hyperuniform hydrogel film matrix. This matrix surpasses conventional HA formulations in critical aspects, including reduced tackiness, enhanced uniformity, increased water resistance, and improved persistence. These characteristics translate to significant improvements in both measured skin firmness (DTM), and consumer-perceived benefits, such as improved skin firmness, plumpness, and youthful appearance, fulfilling key consumer needs in skincare. This versality of this technology paves the way for development of high-performance, next-generation cosmetic products across skincare, haircare, make-up, and even in complementary medicinal categories. By controlling HA entanglement and providing lastingness and resilience against external stimuli, this breakthrough unlocks the full potential of HA, ushering in a new era of advanced and efficacious natural solutions for cosmetic science.

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7. Conflict of Interest Statement

NONE.

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