PRESS RELEASE

May 2022
Shiseido Company, Limited

Shiseido Develops Technology to Control Hyaluronic Acid Volume
~The most-advanced Shape-Shifting HA Technology increases skin moisture~

Shiseido Company, Limited ("Shiseido") has developed "Shape-Shifting HA Technology" that controls the volume of hyaluronic acid (HA). HA forms a water retention film on the skin surface and exerts a high moisturizing effect, but at the same time, its very large molecular size hinders penetration into the stratum corneum after application. With the new technology, HA shrinks via the addition of magnesium ions (Mg ions) and dramatically increases its penetration into the stratum corneum compared to normal HA. In addition, this technology re-expands the shrunken HA ("Compact HA") via the addition of sodium metaphosphate, a type of chelating agent*1, resulting in restoration of the original properties of HA and increasing the water content in the stratum corneum. Some of these research results were presented at the 142nd Annual Meeting of the Pharmaceutical Society of Japan on March 26, 2022.

We at Shiseido have been conducting this research under the Inside/Outside approach of our R&D philosophy "DYNAMIC HARMONY". We aim to realize soft and dewy skin through the application of the Shape-Shifting HA Technology, the most advanced technology that controls the volume of high molecular HA to enhance its penetration and function in the stratum corneum.

*1 A chemical component that counteracts the properties of metal ions by capturing the metal ions in the surroundings.

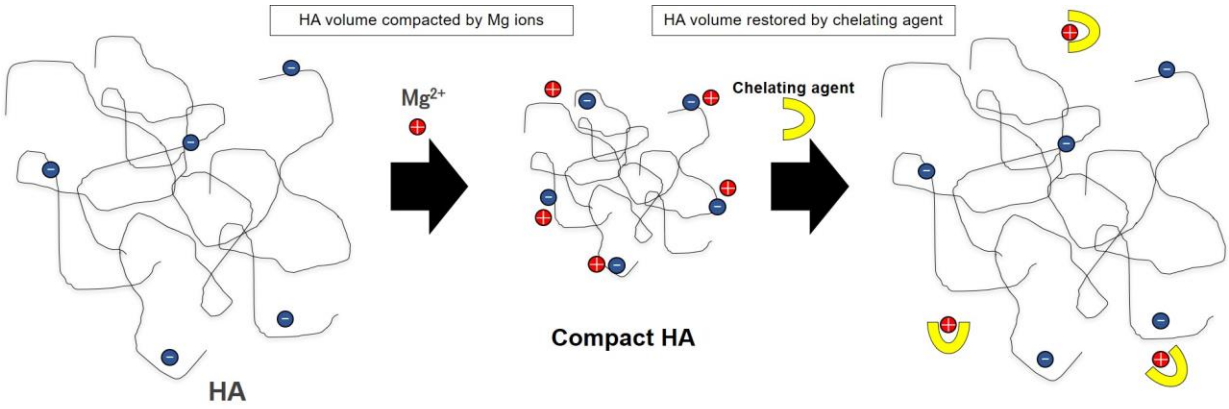

Figure 1. Shape-Shifting HA Technology controls HA volume (image)

Research Background

HA is a biopolymer with excellent water retention capacity and known to indicate various biological activities other than moisturizing the skin. Since the amount of HA in the epidermis decreases with age, it is important to deliver HA to the inner skin in order to maintain healthy skin. However, given that HA is large in molecular weight and the stratum corneum acts as a strong barrier, it was extremely difficult to make HA penetrate the skin. In addition, HA injections in cosmetic medicine, which deliver HA into the subcutaneous tissue directly as an invasive procedure, still pose the challenge of not applicable to the entire face. Therefore, we have developed a new technology that allows high molecular weight HA to penetrate into the skin in a non-invasive way and enables the penetrated HA to perform its original functions.

Technology to shrink hyaluronic acid and increase its penetration into the stratum corneum

We added various salts to aqueous HA solutions and measured their penetration amount into the stratum corneum. The results showed that the addition of magnesium chloride ($MgCl_2$) increased the amount of HA penetrated into the stratum corneum (Figure 2). Next, after having applied the HA labeled with green fluorescence onto the skin surface and observed cross sections with a fluorescence microscope, we successfully visualized that more HA had reached the deeper layer of stratum corneum via the addition of $MgCl_2$, compared to a HA solution without $MgCl_2$ (Figure 3). Furthermore, we added $MgCl_2$ to an aqueous HA solution and measured the HA volume, and it was confirmed that there was a decrease in HA volume (Figure 4), which suggests that $MgCl_2$ shrinks the HA volume and enhances the HA penetration in the stratum corneum.

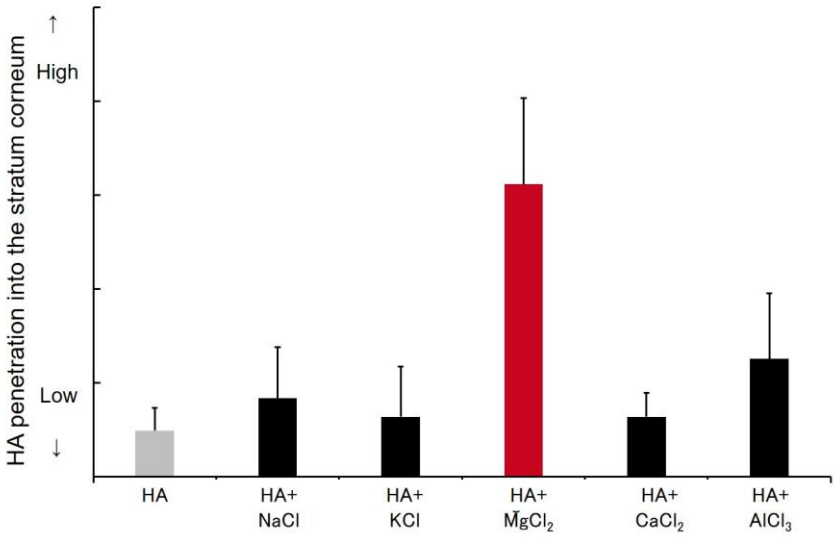

Figure 2. $MgCl_2$ enhances HA penetration into stratum corneum.

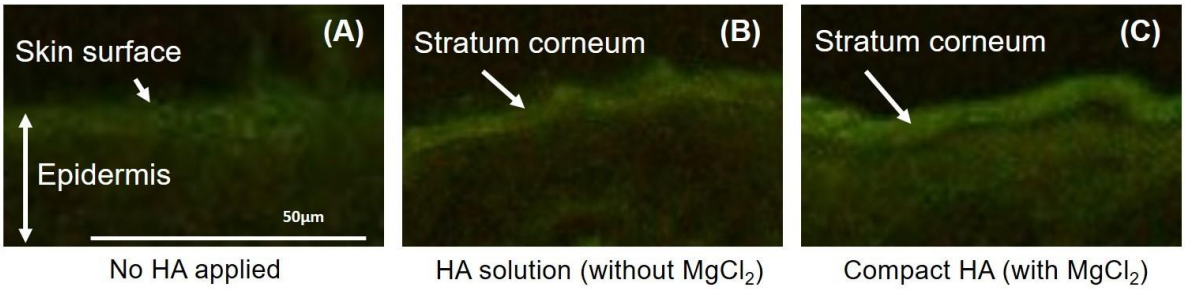

Figure 3. Scenes of HA penetrating into stratum corneum

Technology of re-expanding Compact HA and its effects on the skin

We added sodium metaphosphate (SMP), a chelating agent, to Compact HA and found that the volume of Compact HA increased, re-expanding to a volume equivalent to that of HA before it shrunk (Figure 4). Next, we compared the water content in the stratum corneum between when only Compact HA was applied onto the skin surface and when an aqueous SMP solution was additionally applied after Compact HA application. The results revealed that the addition of SMP to Compact HA significantly increased the water content in the stratum corneum (Figure 5). From these results, it is suggested that HA re-expands with the addition of SMP, restoring its water retention capacity and increasing the water content in the stratum corneum. The “Shape-Shifting HA Technology” refers to a series of technologies that improve the water retention capacity of the skin by shrinking the large HA molecule and creating Compact HA to allow it to be penetrated into the stratum corneum more easily and then re-expanding Compact HA via the application of chelating agents such as SMP.

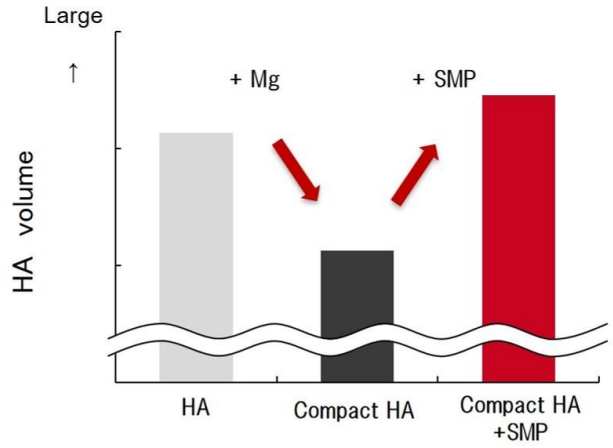

Figure 4. Addition of chelating agent increases the volume of Compact HA shrunken by $MgCl_2$

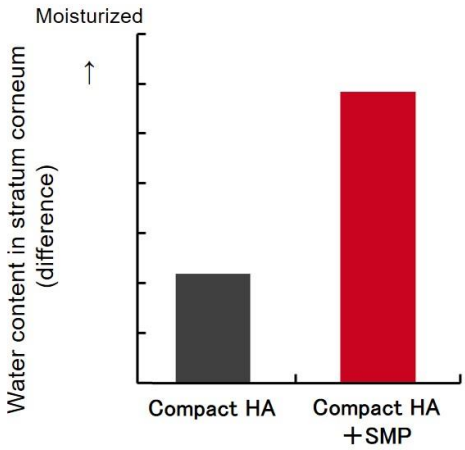

Figure 5. Compact HA re-expands, increasing water content in stratum corneum.

Future Prospects

We at Shiseido have further deepened our research on HA, a skin moisturizing component, and succeeded in developing an innovative technology that controls its volume, enhances its penetration into the stratum corneum, and its functionality. We will continue to utilize this technology to address a wide range of skin concerns as our key technology for future beauty care solutions in suit with our corporate mission, “BEAUTY INNOVATIONS FOR A BETTER WORLD”.

Shiseido’s R&D philosophy “DYNAMIC HARMONY”

Shiseido Formulates its Unique R&D philosophy “DYNAMIC HARMONY” (2021)
https://corp.shiseido.com/en/news/detail.html?n=00000000003252

The DYNAMIC HARMONY special website:
https://corp.shiseido.com/en/rd/dynamicharmony/

<Reference>

Researchers' Challenge

Researcher, Mika Fujii, Ph.D.

■ Research inspired by cosmetic medicine

Hyaluronic acid (HA) plays an important role in skin function and moisturizing, but the amount of HA in the epidermis decreases with age. Since HA is large in molecular weight, it is difficult to make HA penetrate the skin simply through application, and there have been many challenges in supplementing HA in the skin via cosmetics. In the cosmetic medicine, surgical injection is used as a method of supplementing HA, however, in addition to being invasive, HA injection can be administered only in the limited areas and not applicable to the entire face. Thus, we pursued our research with the hope of solving these problems and providing cosmetics that allow HA penetrate the skin in a non-invasive way.

■ The challenge of balancing HA penetration and skin moisturizing

HA is low in molecular weight, which is made by cutting HA chains to enhance its penetration rate, have already been used in the cosmetics field, however, during this process, the original moisturizing effect of HA is diminished. The challenge in developing this technology was to ensure that HA could penetrate the skin without reducing its molecular weight while also maintaining its moisturizing effect. At first, we were successful in shrinking HA while maintaining its structure, allowing for high HA penetration, however, the shrunken HA reduced its original moisturizing effect, failing to achieve both penetration and moisturizing effects. Thus, inspired by the principle of magnets, we found a way to make HA molecules re-expand and succeeded in restoring its water retention capacity. It took us three years to develop this technology, which is based on Shiseido's more than 30 years of research and expertise in HA.

■ Toward the development of even more effective solutions

It is essential to have any active ingredient be delivered to the tissue where it will exert its effect. Given that the skin is a tough barrier that prevents substances from entering the body, it is an eternal challenge to efficiently deliver active ingredients to the target areas. While understanding the characteristics of each active ingredient, we will continue to research new methods to maximize penetration into the skin and maximize its effect.