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# Stabilized composition of 26 mg/mL of high molecular weight HA for subcutaneous injection to improve skin quality

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## Abstract

**Aim:** Skin firmness is one of the key parameters to define skin quality and facial aging. Among the minimally invasive anti-aging strategies, hyaluronic acid (HA) injection is widely accepted to improve skin quality. While most of the available HA injectables are designed and intended for intradermal injection, a novel HA/sorbitol composition containing 2.6% high molecular weight hyaluronic acid stabilized by sorbitol was recently developed to be specifically injected into the adipose tissue to improve the quality of all skin layers, especially the skin firmness.

**Methods:** The HA/sorbitol composition was investigated versus product comparators in terms of biophysical properties, tolerance in subcutaneous tissue with *in vivo* implantation study, and skin firmness assessment on human skin explants.

**Results:** The HA/sorbitol composition was characterized by unique and differentiated biophysical properties, proper distribution and high tolerance of the gel composition into the adipose tissue, and the ability to efficiently improve skin firmness.



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**Conclusion:** The HA/sorbitol composition represents a new attractive solution to treat facial skin aging with an injection strategy specifically targeting the adipose tissue instead of the dermis, to improve the quality of the skin.

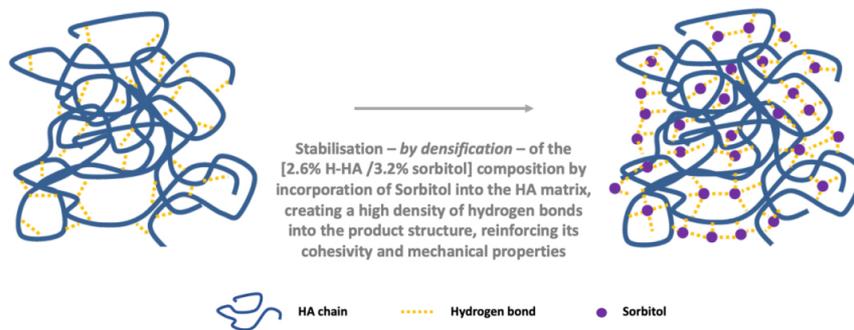
**Keywords:** Facial aging, hyaluronic acid, sorbitol, biophysical properties, skin quality

## INTRODUCTION

Skin aging is a complex and unavoidable biological phenomenon that starts in the third decade of life and is determined by intrinsic (chronological, hormonal, and genetic) and extrinsic factors (sun exposure, cigarette smoking, dietary habits, alcohol intake, pollution, and weather environment)<sup>[1]</sup>. It is a dynamic process that results in structural alterations of soft and bony tissues with modifications of various constituent layers from skin surface to subcutaneous adipose tissue<sup>[1-3]</sup>. Skin quality is important to human attractiveness and significantly influences the perception of age, health, and youth across ethnicities<sup>[4]</sup>. Minimally invasive procedures have revolutionized the treatment paradigm for both facial and body skin rejuvenation and the recent history of cosmetic surgery<sup>[5]</sup>. In these procedures, the demand for treatments with hyaluronic acid (HA) injectables is constantly on the rise, and a large consensus has been gained worldwide for these products in aesthetic medicine and dermatology<sup>[4-6]</sup>. This market demand has driven the research and development of new advanced HA formulations for different clinical indications and applications while offering improved safety, effectiveness, and patient satisfaction. In this context, a novel 2.6% H-HA/3.2% sorbitol composition [Figure 1] containing 52 mg of stabilized high molecular weight (H-HA) pure hyaluronic acid with 64 mg of sorbitol in phosphate-buffered solution was recently developed (Kylane Laboratoires, Switzerland). The viscoelastic gel composition is manufactured using a technology based on specific mixing and heating process steps. It starts with high molecular weight HA (higher than 1.8 MDa) and sorbitol to reach a homogeneous high concentration of H-HA combined and stabilized with sorbitol. This benefits from the reinforced cohesivity and biomechanical properties of the hydrogel complex. According to the Handbook of Pharmaceutical Excipients, sorbitol is widely used as an excipient in pharmaceutical formulations and is also used extensively in cosmetics and food products<sup>[7]</sup>. Its safety is widely accepted, and the reports of adverse reactions to sorbitol are largely due to its effect as an osmotic laxative when taken orally<sup>[7]</sup>. It occurs naturally in many edible fruits and berries and is metabolized in the liver to fructose and glucose<sup>[7]</sup>. Sorbitol is described in the FDA Inactive Ingredients Guide, for example, for intra-articular and intra-muscular injections. In combination with hyaluronic acid in injectables, sorbitol has demonstrated its high level of clinical safety and performance for intraocular<sup>[8]</sup> and intra-articular applications<sup>[9-11]</sup>. No specific side effects related to sorbitol have been reported with these injectable hyaluronic acid compositions, in accordance with the high safety profile of sorbitol<sup>[8-11]</sup>. The intended use of the 2.6% H-HA/3.2% sorbitol composition is the treatment of skin laxity and loss of skin elasticity due to skin aging. The composition is injected into the subcutaneous tissue, especially the superficial adipose tissue just below the dermal layer, with a recommended protocol of 2 treatment sessions at one-month intervals, followed, if necessary, by maintenance treatment sessions after six months. The composition acts by bringing to the skin a mild filling with structural support to enhanced mechanical properties and skin quality.

The purpose of this article is to investigate this novel 2.6% H-HA/3.2% sorbitol composition based on the following:

- We studied its key biophysical properties of cohesivity, elasticity, and viscosity.



**Figure 1.** Schematic representation of the 2.6% H-HA/3.2% sorbitol composition.

- We studied its tissue tolerance and safety by implantation in the subcutaneous adipose tissue with an *in vivo* animal model.

- We studied its performance by assessment of the firmness of human skin explants cultured with CO<sub>2</sub> humid incubator after implantation into deep skin tissues.

## METHODS

### Materials

The 2.6% H-HA/3.2% sorbitol composition (Kylane Laboratoires, Switzerland) was compared with 2 commercial injectable products intended for skin quality improvement:

- 1.6% L-HA + 1.6% H-HA (Profilo, IBSA, Italy) is a mixture of low molecular weight HA (0.08-0.10 million Daltons) at 16 mg/mL and high molecular weight HA (1.10-1.40 million Daltons) at 16 mg/mL into buffered sodium chloride solution<sup>[12]</sup>, indicated to be injected in the dermal/subcutaneous levels. This product was used as a comparator for the cohesivity, oscillatory shear stress, and flow tests and the *ex vivo* study.

- VYC-12L (Juvéderm Volite, Allergan, France) is a composition of 12 mg/mL of crosslinked hyaluronic acid with 3 mg/mL of lidocaine hydrochloride in phosphate-buffered solution indicated for intradermal injections only<sup>[13]</sup>. This product was used as a comparator for the cohesivity, oscillatory shear stress, and flow tests.

### Cohesivity test

The cohesivity test was performed according to the method described in the article by Sundaram *et al.*<sup>[14]</sup>. In agreement with this article, the assessment of the cohesivity for each tested product was ranked according to the Gavard-Sundaram Cohesivity Scale, with cohesivity scores from 1 (fully dispersed) to 5 (fully cohesive).

### Oscillatory shear stress test

The oscillatory shear stress test measures the elastic modulus  $G'$ . It was performed using a TA Instrument cone-plate rheometer at a temperature of 25 °C in shear-stress oscillation mode at 1.0% of strain, within the linear viscoelastic region, with a cone/plate aluminum geometry of 40 mm, 2°, and a 50 μm gap between the cone and the plate of the rheometer. The measurements were carried out in a frequency range of 0.1-5 Hz. The value of the elastic modulus  $G'$  was measured at the physiological oscillation frequency of 1 Hz.

### Flow test

The flow test measures the viscosity  $\eta$  of the gel. It was performed using a TA Instrument cone-plate rheometer at a temperature of 25 °C at 0.001 to 1000 s<sup>-1</sup> shear rate with a cone/plate aluminum geometry of 40 mm, 2°, and a 50  $\mu$ m gap between the cone and the plate of the rheometer. The value of the viscosity  $\eta$  was measured at the shear rate of 0.02 s<sup>-1</sup>.

### *In vivo* implantation study with animal model

The *in vivo* study evaluated the local tissue effects of the 2.6% H-HA/3.2% sorbitol composition after subcutaneous administration. The study was conducted under international standards [International Standards Organization (ISO) 10993] as mandated by regulatory agencies in an AAALAC international accredited facility registered with the French Department of Agriculture for animal housing, care, and investigations. In this study, the gel composition was injected into the subcutaneous tissue of 15 rats with a follow-up period of 28 days. The 15 rats each received four subcutaneous injections of the gel composition and 2 subcutaneous implantations of negative controls. The negative control was high-density polyethylene (HDPE) (CAS number: 9002-88-4), as recommended in the ISO 10993 Standard, Part 12. The injections were performed by a qualified and trained operator using standard aseptic techniques. Six sites on the back of each rat were injected subcutaneously. The gel composition was injected with a needle with a volume of 200  $\mu$ L. The negative control was implanted with a trocar inserted through the skin, perpendicular to the vertebral column, deep enough into the subcutaneous tissue to accommodate the negative control article and ensure that the implant was far from the implantation entry point. The sites were appropriately spaced to avoid merging them as much as possible. Immediately after the injections, the sites were peripherally marked with a surgical skin marker. The animals were observed daily for general health and to detect mortality and morbidity. In addition, a detailed clinical examination of the animals was conducted at least twice a month. This examination included but was not limited to general conditions, behavior and activity, locomotion, and posture. Marks were checked regularly. When necessary, the back of the rats was shaved and the marks were renewed. The injection sites were macroscopically examined at 6 h, 2 days, and 28 days. Any gross changes in tissues around each injection were recorded using the following parameters: size, shape, color, consistency, distribution, and any other observations, as appropriate. When visible, the properties of the injections (location and coloration) were described. Tissues at the injection sites and the surrounding tissues were harvested and fixed in 10% NBF (Carlo Erba) for histopathologic analysis. In addition, the draining lymph nodes (axillary and inguinal, four per animal) were macroscopically examined, sampled, and fixed in 10% NBF (Carlo Erba) for histopathologic analysis. As lymph nodes are organized in clusters, one to several lymph nodes could be collected at each sampling. After complete fixation in 10% NBF (Carlo Erba), the injected sites were dehydrated in alcohol solutions of increasing concentration, cleared in xylene, and embedded in paraffin. For all injected sites, one central transversal slide was cut with a microtome (4  $\mu$ m thickness). All created slides were stained with saffron-hematoxylin-eosin (SHE). The histopathologic qualitative and semi-quantitative analyses were conducted in accordance with the OECD Good Laboratory Practice regulations, ENV/MC/CHEM (98) 17 and the United States Food and Drug Administration Good Laboratory Practice regulations, 21 CFR 58. Qualitative and semi-quantitative histopathologic evaluations of the local tissue effects at the injection sites were conducted according to the standard ISO 10993, Part 6, by a pathologist (reactivity ranking calculations based on the scoring related to the presence of macrophages, lymphocytes, plasma cells, polymorphonuclear cells, giant cells, necrosis, fibrosis, neovascularization, fatty infiltrate, fibrin, hemorrhage, cell or tissue degeneration, and fibroplasia). The gel composition was evaluated and compared to the negative control articles.

### *Ex vivo* study of the firmness of human skin explants cultured with CO<sub>2</sub> humid incubator

This study was performed on biopsy, obtained from surgical residues after written informed consent from the donor, in full compliance with the Declaration of Helsinki and article L.1243-4 of the French Public

Health Code. The latter does not require any prior authorization by an ethics committee for sampling and using surgical waste. Six human skin explants with a round shape and a diameter of 38 mm were placed on a support, on which the skin was stretched [Figure 2]. These skin explants were obtained from an abdominoplasty (discarded abdominoplasty tissue) of a 44-year-old Caucasian woman with phototype II according to the Fitzpatrick classification. The supports were put in a tank containing a culture medium [composition: glucose (3.65 g/L), L-glutamine (0.66 g/L), HEPES (26 mM), Phenol Red (0.300 mg/L), fetal bovine serum (5%), fungizone (2.5 µg/mL), and gentamicin (50 µg/mL)] that was linked to a CO<sub>2</sub> humid incubator at 37 °C, 21% O<sub>2</sub>, 5% CO<sub>2</sub>, and 98% relative humidity by a peristaltic pump [Figure 2].

On Day 0 (D0), 2 skin explants were injected with the 2.6% H-HA/3.2% sorbitol composition, 2 skin explants were injected with the 1.6% L-HA + 1.6% H-HA composition, and 2 skin explants were not treated (reference). All injections were performed in the deep skin tissues of each skin explant with four injection sites of 25 µL per explant, forming a square with injection sites spaced 8 mm [Figure 3]. A cutometer study with measurements of the skin firmness R<sub>0</sub> in the middle of the square formed by the four injection sites was then carried out with a cutometer (MPA580, Courage & Khazaka) at different survival times for all the skin explants: Day 0 (before and after injection, D0), Day 1 (D1), Day 2 (D2), and Day 5 (D5). The measuring principle of the cutometer is based on the suction method, where negative pressure deforms the skin explant mechanically. The pressure is created in the device and draws the skin into the aperture of the probe, and, after a defined time, releases it again. The resistance of the skin explants to the negative pressure is defined as the skin firmness R<sub>0</sub>, and the lower the R<sub>0</sub>, the firmer the skin.

## RESULTS

### Measurement of cohesivity

The assessment of the cohesivity for the 3 tested products ranked according to the Gavard-Sundaram Cohesivity Scale, is described in Table 1, and pictures of cohesivity for the 2.6% H-HA/3.2% sorbitol composition are provided in Figure 4.

### Measurement of elastic modulus G' and viscosity η

The measured values of elastic modulus G' and viscosity η are summarized for the 3 tested products in Table 2.

### Investigation of the tolerance by implantation with *in vivo* animal model

All animals appeared clinically normal at the beginning and throughout this study. All rats gained weight as expected during the study.

Macroscopically, no major findings were observed in the surrounding tissues, and no major abnormality was observed in the draining lymph nodes during the study. A slight redness was observed at 6 h for the gel composition. Slight to moderate redness was observed at 6 h and 2 days for the negative control articles. At 6 h, the gel composition was visible and palpable, with a round shape. At 2 days, the gel composition was visible and palpable but with a softer consistency than at 6 h. The bleb was very dispersed and slightly bulging for all gel composition sites. At 28 days, the gel composition was not visible and not palpable. Therefore, it is hypothesized that the gel composition was spread out around the injection point throughout the study and became non-palpable in the injected area. The negative control was visible and palpable for the whole duration of the study.

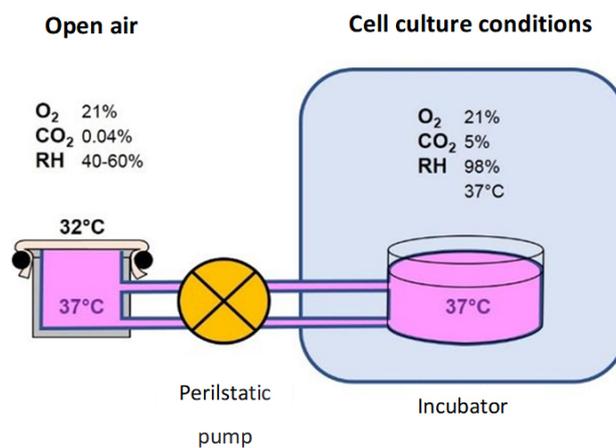
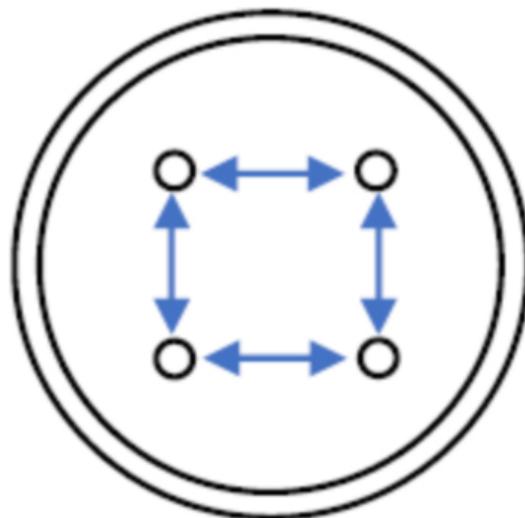
Microscopically, at 28 days, the sites injected with the gel composition showed slight local tissue effects that were slightly lower than those observed for the implanted negative control. The inflammatory reaction was

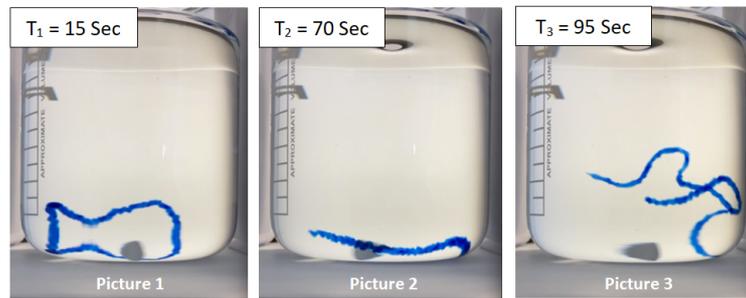
**Table 1. Scores of cohesivity for the three tested products**

Tested HA composition	Gavard Sundaram Cohesivity Scale (1-5)		
	15 Sec	70 Sec	95 Sec
2.6% H-HA/3.2% sorbitol	5	5	5
1.6% L-HA + 1.6% H-HA	5	4	4
VYC-12L	3	1	1

**Table 2. Elastic modulus G' and viscosity  $\eta$  for the three tested products**

Tested HA composition	Elastic modulus G' in shear-stress at 1 Hz (Pa)	Viscosity $\eta$ at 0,02 s <sup>-1</sup> (Pa.s)
2.6% H-HA/3.2% sorbitol	529	856
1.6% L-HA + 1.6% H-HA	47	31
VYC-12L	142	281

**Figure 2.** Schematic representation of the *ex vivo* study method with skin explants cultured with CO<sub>2</sub> humid incubator.**Figure 3.** Schematic representation of the product administration with four injection sites of 25  $\mu$ L per explant, forming a square with injection sites spaced 8 mm apart.



**Figure 4.** Photographs of the cohesivity for the 2.6% H-HA/3.2% sorbitol composition.

slight for the gel composition and negative for the control. Under the conditions of the study, the average score of the changes seen in the gel composition injected sites resulted in a reaction described as “null to minimal” when compared to the reactivity ranking scores of the negative control according to the reactivity ranking calculations of the pathologist.

**Figure 5** provides histopathologic photomicrographs of the injected area at 28 days after subcutaneous injection of the 2.6% H-HA/3.2% sorbitol composition, highlighting a proper and homogeneous anatomy of the adipose tissue in the injected area following the injection of the product.

#### **Investigation of the performance of the 2.6% H-HA/3.2% sorbitol composition on the skin firmness by *ex vivo* human skin explant model**

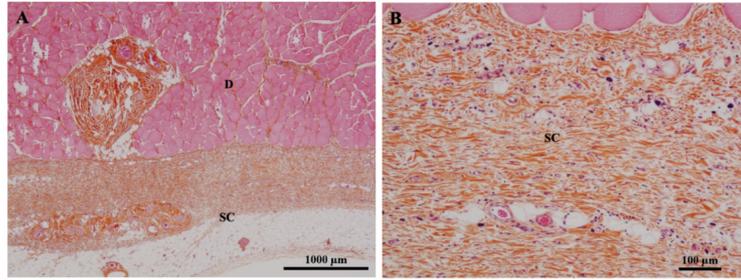
Cutometer study results of the skin firmness [**Figure 6**] demonstrate that the firmness (R0) of the reference skin explants (without any treatment) was quite stable over the five days of the study. On the contrary, the skin firmness increased significantly (i.e., R0 decreases) for the skin explants injected with both the 2.6% H-HA/3.2% sorbitol composition and the 1.6% L-HA + 1.6% H-HA composition from the product injection D0 and for the entire five-day duration of the study. On the other hand, the increase of the firmness (i.e., R0 decreases) was significantly greater for the 2.6% H-HA/3.2% sorbitol composition than for the 1.6% L-HA + 1.6% H-HA composition (i.e., 18.4% higher at D1 and 10.6% higher at D5) for the entire duration of the study, i.e., for the five-day follow-up.

## **DISCUSSION**

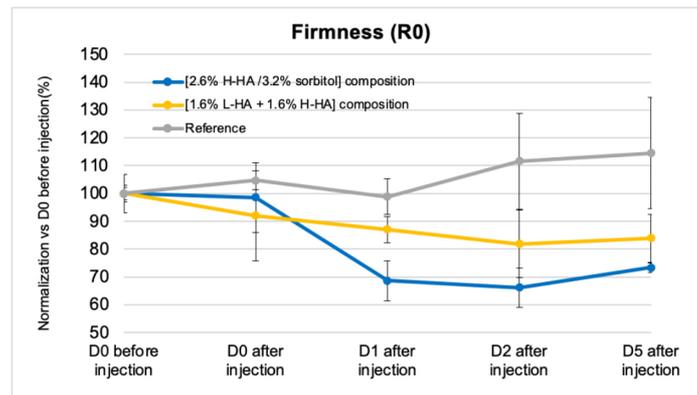
Human skin is composed of 3 distinct layers, namely epidermis, dermis, and hypodermis, each with varying degrees of specialization. The epidermis and dermis are well characterized, but very little attention has been given to the hypodermis/subcutaneous tissue<sup>[15]</sup> despite its key role in facial aging<sup>[3]</sup>.

While most skin quality boosters based on hyaluronic acid available on the market are designed for intradermal applications, the novel 2.6% H-HA/3.2% sorbitol injectable composition was specifically designed with tailored composition and biophysical features to be implanted into the subcutaneous tissue, with the aim to develop new treatment strategies specifically focused on the adipose tissue, especially the superficial adipose tissue, to significantly influence and improve the mechanical properties of the skin and treat skin aging.

The 2.6% H-HA/3.2% sorbitol product is characterized by a composition of a high content of pure hyaluronic acid with high molecular weight stabilized with sorbitol, which creates a very dense network of hydrogen bonds within the matrix of the sorbitol, hyaluronic acid, and water molecules [**Figure 1**]. This capacity of sorbitol to form strong and extensive hydrogen bonds capable of forming water and hyaluronic



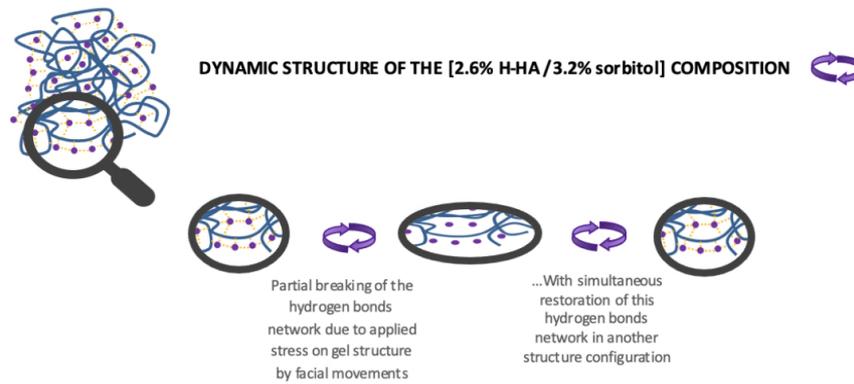
**Figure 5.** Histopathologic photomicrographs of the injected area 28 days after subcutaneous injection into rat model: (A) 2× magnification; and (B) 10× magnification. Slides were stained with saffron-hematoxylin-eosin (SHE). D: Dermis; SC: subcutaneous tissue.



**Figure 6.** Graph of the skin explant firmness measured for the two tested products and reference.

acid is evidenced in the literature<sup>[16,17]</sup>, notably through measurements of thermodynamic properties. This fact is consistent with the high stability observed with injectable hyaluronic acid and sorbitol products; for example, ophthalmic viscoelastic devices (OVD) containing hyaluronic acid and sorbitol are reported to benefit from better maintained viscoelastic properties versus injectable products without sorbitol, in the case of thermal treatment, light irradiation, or storage of the device at 25 °C<sup>[8]</sup>. On the other hand, cohesivity results of the 2.6% H-HA/3.2% sorbitol composition versus the non-crosslinked 1.6% L-HA + 1.6% H-HA composition and the crosslinked VYC-12L product demonstrate the high affinity which exists among the molecules of sorbitol, HA, and water within the gel. This offers a significantly higher cohesivity than the 2 tested products used as comparators in this article, independently of their HA concentrations, i.e., 12 mg/mL for the VYC-12L product and 32 mg/mL for the 1.6% L-HA + 1.6% H-HA product. It is important to mention that the 2.6% H-HA/3.2% sorbitol composition, which is not crosslinked but stabilized by the high density of hydrogen bonds formed by the sorbitol molecules within the viscoelastic gel, is characterized by a highly flexible structure. Indeed, within the gel, the hyaluronic acid chains are not linked by chemical covalent bonds generated by a crosslinker such as BDDE, but by hydrogen bonds, which are physical bonds of low energy that can be easily broken and restored depending on the mechanical actions applied to the gel product [Figure 7]. This is a key advantage to qualify a more natural behavior of the product in the skin and get a gel which behaves like the surrounding tissues.

The measurements of the elastic modulus  $G'$  and the viscosity  $\eta$  of the 2.6% H-HA/3.2% sorbitol composition highlight the fact that the HA/sorbitol stabilization provides very high elasticity and viscosity, significantly higher than the non-crosslinked 1.6% L-HA + 1.6% H-HA composition and the crosslinked

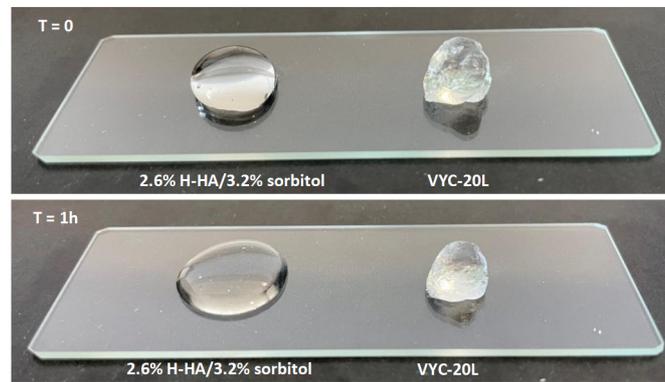


**Figure 7.** Schematic representation of the dynamic structure of the 2.6% H-HA/3.2% sorbitol composition.

VYC-12L product. These unique rheological features, combined with the high cohesivity, are essential biophysical properties for the composition to provide elasticity to the skin tissues that need to be treated for their laxity and loss of elasticity, and combined with a mild filler to fill the soft tissues. Even though the 2.6% H-HA/3.2% sorbitol composition is not crosslinked, its elastic modulus  $G'$  is higher than most other HA fillers, for example, the leading VYC-20L volumizer (Juvéderm Voluma, Allergan, France) with its  $G'$  of 318 Pa at 1 Hz<sup>[18,19]</sup>. Nevertheless, [Figure 8](#) shows that, even if its elasticity is higher than a HA filler volumizer, the viscoelastic behavior of the 2.6% H-HA/3.2% sorbitol composition is considerably different from the VYC-20L product, which is reasonable since the 2 products do not target the same objective (i.e., improvement of the skin quality by 2.6% H-HA/3.2% sorbitol composition versus the creation of high volume in tissues by VYC-20L HA filler). Notably, [Figure 8](#) shows that the spreadability of the 2.6% H-HA/3.2% sorbitol composition is high in comparison to HA fillers such as VYC-20L, and thus appropriate for smooth and homogeneous distribution in the adipose tissue without the goal of creating high volume but only to fill and lift the skin and to efficiently biostimulate the skin tissues. This is enabled by the high concentration of high molecular weight hyaluronic acid and its specific biophysical properties which foster contact with the surrounding tissues and boost their mechano-stimulation. In this respect, in the animal study with 15 rats, the macroscopic observation of the 2.6% H-HA/3.2% sorbitol composition highlights that the novel product does not behave as a traditional hyaluronic acid filler. The 2.6% H-HA/3.2% sorbitol composition spreads out in the skin tissue around the needle entry point. This feature is an advantage for the targeted clinical application because it enables treating the skin quality of a larger area versus a traditional hyaluronic acid filler.

The *in vivo* animal study with 15 rats demonstrated a high tolerance for the proper distribution of the viscoelastic 2.6% H-HA/3.2% sorbitol gel into the adipose tissue. It confirmed that the unique and differentiated composition and biophysical properties of the HA/sorbitol formulation specifically designed to be injected into the subcutaneous tissue, especially the superficial adipose tissue, ensure a high tolerance for the treatment to improve the skin quality, in line with the positive background of HA in dermatology and medical aesthetics over the last two decades. The outcome of this study is also consistent with the safety demonstration of the use of injectable HA/sorbitol viscoelastic formulations in other medical fields, such as in ophthalmology with OVD or rheumatology with intra-articular products for the treatment of osteoarthritis<sup>[8-11]</sup>.

The *ex vivo* study by cutometer follow-up of the treatment with 2.6% H-HA/3.2% sorbitol composition of human skin explants that were cultured with CO<sub>2</sub> humid incubator for five days demonstrated that the hydrogel complex of high molecular weight hyaluronic acid and sorbitol efficiently improves the skin



**Figure 8.** Photographs of 0.25 mL of 2.6% H-HA/3.2% sorbitol gel composition and VYC-20L HA filler after deposit on a glass slide (T = 0) and 1 h following this deposit (T = 1).

firmness over the entire duration of the investigation after implantation. This outcome is consistent with the biophysical properties of high cohesivity, elasticity, and viscosity of the product, showing that the 2.6% H-HA/3.2% sorbitol composition can lift the skin and bring firmness to it after deep tissue implantation.

Therefore, as part of the currently available solutions in the market to improve the skin quality in facial aging, the injectable 2.6% H-HA/3.2% sorbitol composition is demonstrated to be a new relevant treatment alternative with respect to the following:

- Current injectable skin quality booster products based on hyaluronic acid are designed for intradermal applications and not specifically for the treatment of the subcutaneous adipose tissue.
- Currently available solutions usually target the treatment of adipose tissue firmness, such as fat grafting or thread lifts. These solutions are usually significantly more invasive and complex in their administration protocol and require a longer recovery time; thus, they do not meet the wishes of all patients and physicians.

In conclusion, the 2.6% H-HA/3.2% sorbitol composition represents a novel, attractive solution to form the skin matrix and improve the skin quality in facial aging by focusing the treatment on the subcutaneous adipose tissue, with benefits not only at the level of the subcutaneous tissue but also more comprehensively in all skin layers, notably in the dermal layer. Additional evidence by investigation of the improvement in skin quality biological markers will be obtained to offer further insight into the treatment. The objective of this new investigation will be to study the biological effects on the dermal layer skin quality after the injection of the 2.6% H-HA/3.2% sorbitol composition in the adipose tissue. In addition, a clinical study of the 2.6% H-HA/3.2% sorbitol composition in facial treatment will be completed to support and evidence the high product tolerance and performance to improve skin quality and ensure patient satisfaction.

## DECLARATIONS

### Authors' contributions

Obtained all the experimental data: Gavard Molliard S, Bon Bétemps J

All authors contributed to design of the concept and writing of the article.

### Availability of data and materials

Experimental data were obtained by Kylane Laboratoires SA.

### Financial support and sponsorship

Kylane Laboratoires SA provided the logistical and financial support for the execution of this study.

### Conflicts of interest

Gavard Molliard S, Bon Bétemps J, Hadjab B are employed by Kylane Laboratoires SA. Other authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

The project authorization number from the Ethical Committee (France) associated with the *in vivo* animal study is: APAFIS#23401-2017050517312149 v17.

### Consent for publication

Not applicable.

### Copyright

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