

# SVX-Enhanced Gradual Release System: A Novel Biotechnological Approach for Alpha-Hydroxy Acids and Hyaluronic Acid in Skincare

Konstantin Press, Noa Hadar, Ella Sklan, Miriam Gubelbank, Ali Abu Znaid, Shlomzion Shen\*

Seevix Material Sciences Ltd., Jerusalem  
Email: \*info@seevix.com

**How to cite this paper:** Press, K., Hadar, N., Sklan, E., Gubelbank, M., Znaid, A.A. and Shen, S. (2024) SVX-Enhanced Gradual Release System: A Novel Biotechnological Approach for Alpha-Hydroxy Acids and Hyaluronic Acid in Skincare. *Journal of Cosmetics, Dermatological Sciences and Applications*, 14, 357-371.

<https://doi.org/10.4236/jcda.2024.144025>

**Received:** November 9, 2024

**Accepted:** December 22, 2024

**Published:** December 25, 2024

Copyright © 2024 by author(s) and Scientific Research Publishing Inc.  
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

## Abstract

SVX, a biotechnologically engineered biopolymer inspired by spider silk, presents a novel approach to the gradual release of active ingredients in cosmetic formulations. Produced through a single-step fermentation process, SVX's unique 1003-amino acid sequence forms a porous matrix that enables controlled interactions with small and large molecular actives. This structure facilitates the encapsulation and sustained release of actives, addressing common challenges like irritation and rapid depletion. *In vitro* studies validated SVX's capacity to gradually release glycolic acid, even after repeated wash cycles, contrasting with the rapid release seen in non-complexed GA formulations. *In vivo* tests utilized Fourier-transform infrared spectroscopy (FTIR) to track GA penetration and retention in the skin and tape-strip testing to analyze stratum corneum concentrations over time. These methods demonstrated sustained GA presence in the stratum corneum, preventing peak concentrations that often trigger irritation. Skin erythema assessments confirmed that SVX:GA formulations significantly reduce irritation compared to unencapsulated GA. Further investigations extended this controlled release mechanism to medium-molecular-weight hyaluronic acid, a key hydrating agent. *In vitro* hydration assays revealed prolonged moisture retention with the SVX:HA complex, while skin moisture content studies confirmed that SVX-treated skin retained moisture significantly longer than skin treated with free HA. These findings underscore SVX's potential to enhance both the efficacy and tolerability of cosmetic actives, offering a versatile platform for next-generation skincare solutions.

## Keywords

SVX, Protein, Spider Silk, Biotechnology, Glycolic Acid, Lactic Acid, Hyaluronic Acid, Smart Delivery System, Green Chemistry, Biodegradability

## 1. Introduction

Glycolic acid (GA), a member of the alpha-hydroxy acids group (AHAs), has gained significant prominence in dermatology and cosmetics due to its versatile role in skin rejuvenation and exfoliation. Derived from sugarcane, GA has the smallest molecular size among AHAs, which allows it to penetrate the epidermis efficiently and exert its effects on skin cells [1] [2]. The demand for glycolic acid in cosmetic formulations has been rising steadily, driven by its efficacy in treating conditions such as hyperpigmentation, acne, and photoaging. The number of scientific publications on glycolic acid has increased sharply in recent years, with a 60% rise in citations over the past decade [3]-[6]. According to a recent market analysis, the global glycolic acid market is expected to grow at a compound annual growth rate (CAGR) of 7.2% by 2028, reaching over USD 400 million [7]. This growing market demand is further reflected in the increasing interest in glycolic acid within the scientific literature, with more than 2000 studies currently indexed in PubMed [8]. For instance, several high-impact studies have elucidated its ability to stimulate collagen synthesis, enhance epidermal turnover, and improve skin barrier function. Additionally, meta-analyses and clinical trials published in top-tier dermatological journals highlight its role in managing specific skin concerns such as melasma and atrophic acne scars [9] [10]. These findings not only affirm glycolic acid's efficacy but also underscore its safety when used at appropriate concentrations, further encouraging its adoption in cosmetic science.

Glycolic acid is widely used in skincare for its keratolytic properties, which promote exfoliation of dead skin cells, improving epidermal renewal and barrier function [11] [12]. It works by disrupting corneodesmosomes—protein complexes that bind corneocytes—thereby enhancing skin smoothness and reducing conditions like hyperkeratosis and acne [13]-[18]. Additionally, glycolic acid stimulates collagen production, improving skin texture and reducing fine lines and wrinkles [19] [20].

However, despite its efficacy, glycolic acid is known to cause irritation, especially in individuals with sensitive skin. Its small molecular size allows it to penetrate the skin deeply, which can lead to stinging, redness, and discomfort [21]. This has led to a growing interest in gradual release systems, where glycolic acid is delivered in a controlled manner over time, reducing its irritant potential while maintaining its exfoliating and rejuvenating effects. Existing delivery systems for the slow release of glycolic acid and lactic acid include liposomes, PLGA hydrogels, nanoparticles, and microspheres, which offer prolonged delivery, compared to the immediate penetration of pure acids. However, each system has its limitations, such as production complexity for liposomes, potential burst release with microspheres, and degradation challenges with PLGA hydrogels [22]-[26]. The development of slow-release formulations for glycolic acid represents a promising approach to achieving its benefits while minimizing adverse effects, especially for sensitive or reactive skin types [27]-[29].

Alongside glycolic acid, hyaluronic acid (HA) has also gained considerable

attention in skincare due to its ability to retain moisture and enhance skin hydration. HA is a naturally occurring glycosaminoglycan found in the skin's extracellular matrix, where it plays a critical role in maintaining skin moisture and elasticity [30] [31]. Its water-binding properties are unparalleled, with one HA molecule capable of holding up to 1,000 times its weight in water. This makes it a highly effective ingredient for addressing skin dryness, maintaining hydration, and reducing the appearance of fine lines [32]-[34].

The use of slow-release hyaluronic acid has shown considerable benefits in both cosmetic and dermatological applications. Gradual release of HA can provide sustained hydration, supporting skin barrier function over extended periods. This is particularly advantageous for anti-aging formulations, where continuous moisture supply can help reduce the appearance of wrinkles and support tissue repair [35]. Controlled release HA systems also ensure that hydration is delivered consistently throughout the day, improving skin elasticity and reducing transepidermal water loss [36]-[38].

## 2. Experimental

### 2.1. SVX Production

SVX was produced through a controlled, single-step fermentation process utilizing recombinant DNA technology to insert a synthetic DNA sequence inspired by spider silk into bacterial hosts. The production of SVX involves the responsible use of recombinant DNA technology, a rigorously regulated process that enables bacterial hosts to efficiently produce the protein, offering a sustainable alternative to resource-intensive or animal-based methods. These engineered bacteria synthesize SVX in a precise, reproducible manner, ensuring batch-to-batch consistency. The downstream process involves isolating and purifying SVX from the bacterial medium. This biotechnological production method is efficient and sustainable, offering a high-purity, scalable alternative that avoids the depletion of natural resources. Additionally, SVX is a readily biodegradable material, as confirmed by its compliance with OECD 301 B guidance.

Safety and ethical considerations are integral to the production and application of SVX. Extensive safety evaluations have been conducted, including patch testing and human repeat insult patch testing (HRIPT). In patch studies, SVX demonstrated non-irritant properties after 48 consecutive hours of application on the external arm surfaces of 22 volunteers. Furthermore, *in vitro* phototoxicity assessments confirmed that SVX is “non-phototoxic.” Importantly, SVX is free of any animal-derived ingredients, aligning with ethical and vegan-friendly standards.

### 2.2. SVX Complex Creation

To create the SVX complexes, a 5% (w/w) water-based SVX dispersion was prepared. A 70% aqueous solution of glycolic acid (Sigma Aldrich, CAS 79-14-1) was added to this dispersion under continuous stirring for one hour. Following this mixing, tert-butanol was added to achieve an 80:20 tert-butanol-to-water ratio.

The mixture was then subjected to freeze-drying using a lyophilizer overnight to obtain the SVX-glycolic acid complex in a stable, dry form. The same procedure was applied to create SVX complexes with lactic acid (D, L-Lactic acid, 80% - 85% aq. Solution, purchased from Alfa Aesar) and hyaluronic acid (Molecular weight 550 - 1000 KDa, HyaCare®, provided by Evonik), adjusting the ratios accordingly.

### 2.3. SEM Characterization

High-resolution scanning electron microscopy (SEM) was conducted using an Apreo 2S microscope from Thermo Fisher Scientific, USA. Cryo-SEM analysis was performed with a Quorum Technology PP3010 system, enabling sample cooling to cryogenic temperatures, controlled fracturing, and coating for optimized imaging. Samples were coated with a thin layer of iridium (2 - 3 nm) using a Quorum Q150V S Plus Sputter Coater (Quorum Technology, UK) to prevent charging effects, allowing for high-resolution imaging of both the SVX biopolymer and its complexes.

### 2.4. FTIR Analysis

Fourier-transform infrared (FTIR) spectroscopy was used to analyze the SVX complexes and to monitor the controlled release of active compounds. SVX was identified by its characteristic peak at 1620 - 1625  $\text{cm}^{-1}$ , with glycolic acid detected at 1729  $\text{cm}^{-1}$ , lactic acid at 1730  $\text{cm}^{-1}$ , and hyaluronic acid at 1010  $\text{cm}^{-1}$ . Relative concentration changes of the active compounds were calculated by comparing their respective peaks with the stable SVX signal, providing insights into the complex stability and release patterns over time.

### 2.5. *In Vitro* Studies of Gradual Release

The controlled release properties of SVX complexes were evaluated using a combination of centrifugation and washing techniques. For each sample, the SVX complexes were subjected to successive washings with simulated skin fluids (phosphate-buffered saline, pH 7.4, at 37°C). After each cycle, the released GA was separated from the SVX particles by centrifugation (15,000 g for 20 minutes), and its concentration in the supernatant was measured using FTIR spectroscopy at the characteristic absorption peak of GA (1729  $\text{cm}^{-1}$ ). This approach enabled a step-wise evaluation of the release profiles over time, demonstrating the gradual release behavior of active ingredients from the SVX matrix.

### 2.6. Strip Test

A strip test was conducted to assess skin adherence and penetration of the SVX complexes. Specific areas on the inner forearm were marked, and the formulations were applied to these sites. After a 10-minute absorption period, the excess formulation was gently wiped away with a paper tissue. Cellophane-based sticker strips were then applied to each treated area and removed for analysis. Cellophane strips were selected given their proven ability to effectively remove the stratum

corneum layer of the skin without significantly disturbing deeper layers. Additionally, the material's FTIR spectral profile features characteristic peaks at  $1733\text{ cm}^{-1}$  and  $1157\text{ cm}^{-1}$ , which do not overlap with the spectral signals of the active ingredients (e.g., SVX biopolymer, hyaluronic acid, glycolic acid, or lactic acid) or skin cells. This ensures accurate identification and quantification of the retained compounds within the stratum corneum. FTIR analysis was then conducted to detect the specific peaks of the active ingredients, enabling a precise evaluation of their skin penetration levels.

## 2.7. Irritation Tests

Irritation testing was conducted to compare the effects of free glycolic acid (GA) and the SVX:GA complex on skin. The forearm skin was washed and dried with a paper tissue, and three adjacent  $2\text{ cm} \times 3\text{ cm}$  areas were marked. The top section received a 10% GA water solution, the middle section was treated with a 10% GA at a pH 3.5 gel formulated with 0.5% Sepimax Zen (Seppic), and the bottom section received a 10% GA-SVX complex gel (0.5% Sepimax Zen, adjusted to pH 3.5 with NaOH solution). Images were captured before application and five hours post-application to assess skin irritation.

## 2.8. Irritation Measurement and Evaluation

Irritation was evaluated by analyzing the skin images taken before and after product application. The images were processed using ImageJ software (Version 1.53 k) to measure color intensity changes in the skin, specifically focusing on redness. The excess red value was calculated using the RGB formula:

$$\text{Redness} = ((R \times 2) - B) - B$$

This formula allowed for the quantification of redness, providing an objective measure of irritation caused by each sample.

## 2.9. Skin Moisture Measurement

Skin moisture level was measured to assess skin barrier function following application of the test formulations. A Corneometer CM 825 (Courage + Khazaka) was used to record moisture content. The three test formulas were applied to the forearm skin, and after a 10-minute wait, the skin surface was wiped with a paper tissue to remove any residual moisture. To account for individual variations in baseline skin hydration levels, each volunteer's measurements were normalized to 100% by dividing the post-application data by the initial baseline measurement. Each measurement was repeated five times per sample area to ensure consistency.

## 2.10. Statistical Analysis

All experimental data were analyzed using a two-sample t-test to assess the significance of observed differences between the test groups. The analyses were performed in Microsoft Excel, applying a two-tailed test with equal variance

(homoscedastic). Statistical significance was set at a p-value of less than 0.05.

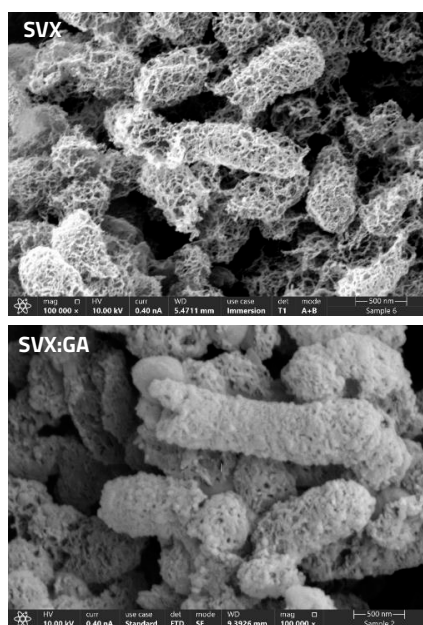
### 3. Results and Discussion

#### 3.1. Introduction to SVX: Structure, Composition, and Interactions

SVX (INCI: *sr-(Tetrapeptide-74 Hexapeptide-40 Expression Vector pMBP-parallel 1 Polypeptide-1 Spider Polypeptide-1 Spider Polypeptide-5)*) is an innovative biopolymer with applications across skincare and haircare due to its unique physicochemical characteristics. SVX is synthesized through a proprietary fermentation biotechnology, whereby genetically modified bacteria express a recombinant protein inspired by spider silk's DNA. The synthesized SVX protein consists of a monomer with a specific sequence of 1003 amino acids, contributing to a high molecular weight and a self-assembling structure, forming particles of approximately 0.7 microns in diameter [39]. This porous, sponge-like structure facilitates the incorporation and gradual release of active ingredients without penetrating the skin barrier, preserving its integrity [40]-[43].

Structurally, SVX is composed of amino acids that enable diverse interactions, including hydrogen bonding,  $\pi$ - $\pi$  stacking, and electrostatic interactions. The abundance of serine (154 residues), tyrosine (53 residues), and threonine (4 residues) provides OH group donors, while glutamine (32 residues), proline (154 residues), and asparagine (7 residues) contribute NH group donors [44]-[51]. These functional groups support SVX's capacity to interact with a variety of actives, forming stable complexes. This property makes SVX an ideal biopolymer for sustained-release applications in both skin and haircare.

#### 3.2. Formation of SVX Complexes



**Figure 1.** SEM analysis of pure SVX biopolymer (upper image) and SVX complex with glycolic acid (bottom image).

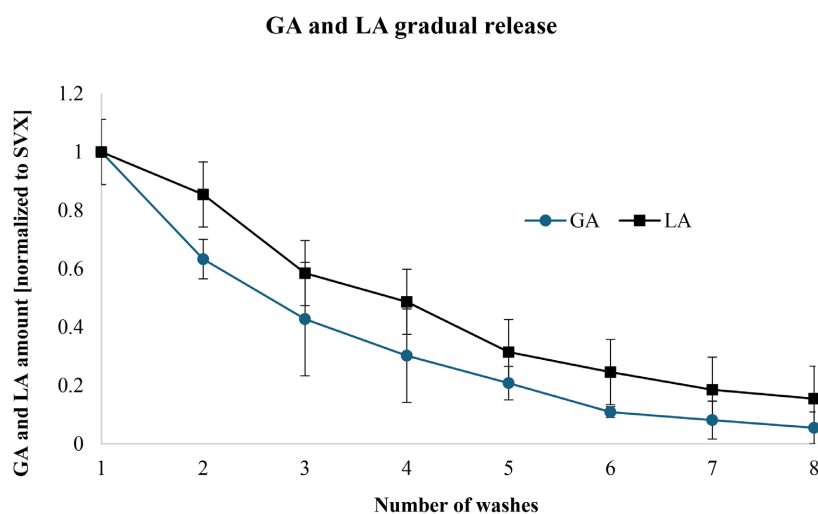
For this study, glycolic acid (GA) and lactic acid (LA) were selected as the primary active compounds, given their widespread use in exfoliating and skin renewal formulations. The complexation process with SVX was achieved through a proprietary technique developed by Seevix, whereby GA and LA are infused into the SVX particles, followed by lyophilization to create a stable powder form of SVX enriched with these AHAs.

SEM imaging illustrates the SVX structure before and after complexation with glycolic acid (**Figure 1**). Prior to infusion, the SVX particles exhibit a uniform porous network. Post-infusion, glycolic acid appears embedded within the matrix without compromising particle integrity, suggesting stable entrapment suitable for gradual release applications.

### 3.3. Evaluation of Glycolic and Lactic Acid Release

#### 3.3.1. *In Vitro* Release Studies

The unique ability of SVX to encapsulate and gradually release active ingredients such as glycolic acid (GA) was demonstrated through an *in vitro* experiment. Initially, the SVX:GA complex was dispersed in water, then subjected to centrifugation to separate the phases. This process facilitated the transfer of GA into the aqueous phase, while the SVX matrix containing residual GA precipitation. After removing the water phase, the SVX:GA complex was vacuum-dried to eliminate remaining water.



**Figure 2.** Slower release of glycolic acid and lactic acid complexed with SVX.

Subsequently, Fourier-Transform Infrared Spectroscopy (FTIR) analysis quantified the GA retained within the SVX matrix (**Figure 2**). This dispersion and centrifugation process was repeated for the dried SVX:GA complex, progressively testing the GA release rate. Remarkably, even after ten cycles of intense washing, the SVX complex retained measurable GA, indicating that SVX acts as a sponge-like matrix, gradually releasing GA in a controlled manner for more than eight hours. This sustained release profile, facilitated by the protective SVX matrix,

addresses a common need in cosmetic formulations: reducing the potential for irritation associated with rapid AHA exposure, especially beneficial for sensitive skin applications [52]-[54].

In addition to GA, similar tests were conducted for lactic acid (LA), yielding comparable gradual release results. The findings reaffirm that the SVX matrix effectively retains and gradually releases both glycolic and lactic acids, further enhancing the potential of SVX in formulating skin-friendly AHA products.

### 3.3.2. *In Vivo* Release Studies

Building on the *in vitro* results that demonstrated SVX's capacity to absorb and gradually release AHAs, we conducted *in vivo* experiments to observe the release kinetics of GA on human skin. For this concept-proving study, the SVX:GA complex was applied to the skin, and the rate of GA absorption into the stratum corneum was assessed using tape strip tests at 60-minute intervals post-application. The relative concentration of GA on each strip was calculated via Fourier-transform infrared spectroscopy (FTIR) analysis, enabling quantification of AHA levels within successive layers of the stratum corneum [55] [56].

**Table 1.** Slower release of glycolic acid (GA) measured by tape strip test.

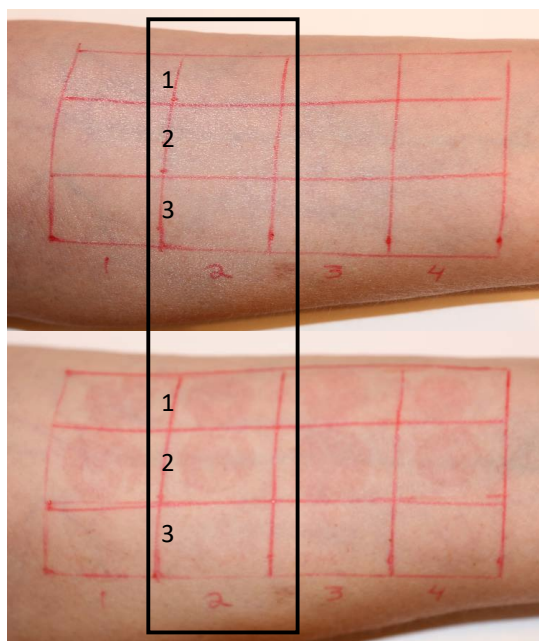
Time (hour)	Amount of Glycolic acid detected on the strip tape		
	Complex SVX:GA	Free GA	Statistics ( <i>p Value</i> )
1	100%	100%	-
2	95% ± 2%	41% ± 5%	$p = 6.5 \times 10^{-5}$
3	83% ± 2%	25% ± 7%	$p = 5.8 \times 10^{-5}$
4	73% ± 5%	18% ± 10%	$p = 1.4 \times 10^{-5}$
5	69% ± 3%	13% ± 5%	$p = 8.6 \times 10^{-5}$
6	60% ± 7%	11% ± 8%	$p = 0.0004$
7	52% ± 7%	6% ± 5%	$p = 0.0003$

As shown in **Table 1**, the SVX complex facilitated a gradual release during seven hours, with consistent, smaller quantities of GA being absorbed into the skin over time. This contrasts with the control, which demonstrated a sharp, rapid GA peak immediately following application. The controlled release from SVX may allow for prolonged exfoliating activity while mitigating irritation potential, a notable advantage for formulations designed for sensitive skin. Similar sustained-release results were observed with the SVX complex, underscoring the versatility of SVX for AHA delivery in a skin-friendly, gradual-release format.

### 3.3.3. Irritation Reduction

Glycolic acid (GA) is a widely recognized exfoliating agent, but is also known for its high potential to irritate sensitive skin, often resulting in redness and erythema. To address this issue, we evaluated whether the SVX:GA complex could reduce irritation while maintaining GA's beneficial properties.

As illustrated in **Figure 3**, glycolic acid was applied to the skin in three formulations: 1) a 5% GA solution, 2) a basic water-based gel containing 5% GA with a pH adjusted to 3.5, and 3) an SVX:GA complex incorporated into a similar water-based gel, formulated to achieve an equivalent GA concentration of 5%. Images were captured both before application (upper image) and five hours post-application, allowing visual comparison of skin responses.



**Figure 3.** Example of skin irritation reduction.

In the images, the two non-SVX formulas produced pronounced erythema and redness, visibly characterizing skin irritation. However, the skin area treated with the SVX:GA complex exhibited minimal redness, suggesting significantly reduced irritation and a much lower erythema response.

**Table 2.** Skin irritation evaluation in the presence of GA.

Treatment	Skin Irritation Measurements (Redness Index)			Statistics (p Value)
	SVX:GA complex in gel formula (pH 3.5)	GA in gel formula (pH 3.5)	GA water solution (pH 2.5)	
Before application	9.1 ± 1.2	9.1 ± 0.8	9.2 ± 1.6	-
5 hours after application	11.5 ± 3.3	18.4 ± 1.2	25.4 ± 2.7	pa = 9.1 × 10 <sup>-5</sup> pb = 0.002

a. Comparison between the formula with the SVX:GA complex and the free GA water solution; b. Comparison between the formula with the SVX:GA complex and the free GA in the gel formula at pH 3.5.

This preliminary study, conducted on five volunteers with sensitive skin, was

not intended as a clinical trial, but rather as a proof-of-concept to demonstrate the potential of SVX to minimize irritation associated with GA. Erythema levels from the images were quantified and are displayed in **Table 2**, showing a clear reduction in irritation in the SVX-treated area relative to the control GA formulas.

### 3.4. Controlled Release of Hyaluronic Acid

Building on the successful gradual release of small molecules like AHAs, we explored the potential of SVX to encapsulate and gradually release larger, high-molecular-weight ingredients, specifically hyaluronic acid (HA). HA in the form of sodium hyaluronate, is widely utilized for its intense hydration and plumping effects on the skin due to its exceptional water-binding capacity. Unlike glycolic acid, HA is non-irritating, making it ideal for prolonged hydration. However, its fast absorption can limit long-term effects on moisture retention. By utilizing SVX's sponge-like matrix, we aimed to achieve a sustained release of HA, prolonging its hydrating and plumping effects [57]-[59].

#### 3.4.1. *In Vitro* Release Assay

**Table 3.** Slow release of HA.

Washes	Amount of HA in complex			Statistics (p Value)
	SVX:HA	Cellulose:HA	Silk:HA	
1	1.00 ± 0.12	1.00 ± 0.05	1.00 ± 0.02	-
2	0.92 ± 0.09	0.75 ± 0.03	0.53 ± 0.09	pa = 0.003, pb = 0.002
3	0.90 ± 0.02	0.15 ± 0.08	0.39 ± 0.10	pa = 4.3 × 10 <sup>-6</sup> , pb = 0.0003
4	0.77 ± 0.05	0.09 ± 0.05	0.18 ± 0.05	pa = 1.4 × 10 <sup>-5</sup> , pb = 6.1 × 10 <sup>-5</sup>
5	0.57 ± 0.07	Not detected	Not detected	-
6	0.44 ± 0.04	Not detected	Not detected	-
7	0.43 ± 0.08	Not detected	Not detected	-
8	0.26 ± 0.09	Not detected	Not detected	-
9	0.22 ± 0.05	Not detected	Not detected	-

a. Comparison between the SVX:HA complex and the Cellulose:HA complex; b. Comparison between the SVX:HA complex and the Silk:HA complex.

In this study, HA was complexed with SVX, and *in vitro* hydration assays were conducted to evaluate the release kinetics of HA from the SVX matrix. The release profile illustrated in **Table 3** reveals a gradual and controlled release of HA over an extended duration, contrasting with the rapid hydration surge typically observed with non-complexed HA. While traditional HA formulations provide immediate benefits, they often experience a swift decline in effectiveness. The unique porous structure of SVX facilitates substantial absorption of HA through the formation of hydrogen bonds, allowing for sustained hydration. In comparison, non-

porous particles such as silk and cellulose fibers interact with HA primarily at their surface, leading to less efficient hydration. The SVX complex not only prolongs HA availability, but also reduces the risk of irritation associated with high concentrations of HA, addressing a crucial need in cosmetic formulations. This slow-release mechanism ensures effective moisturization without compromising skin comfort.

Unlike conventional encapsulation systems, which may be vulnerable to high temperatures and mechanical stresses, SVX presents a robust alternative for the encapsulation and delivery of sensitive cosmetic ingredients. Overall, the smart delivery capabilities of SVX enhance the stability and efficacy of actives like retinol and HA, positioning it as a valuable innovation in cosmetic science.

### 3.4.2. Moisture Content Measurements

To further confirm the efficacy of SVX complexation in promoting long-lasting hydration, skin cuticle moisture content was measured on skin treated with three conditions: skin treated with free SVX, skin treated with free HA, and skin treated with the SVX:HA complex. Over the course of an 8-hour period, **Table 4** reveals a clear trend: skin treated with the SVX:HA complex displayed a significantly reduced rate of water loss compared to skin treated with free HA and free SVX. This indicates enhanced moisture retention, underscoring the complex's potential to provide extended hydration by both releasing HA gradually and simultaneously preventing moisture loss from the skin.

**Table 4.** Skin hydration measurements.

Hours after formula application	Skin hydration measured by Corneometer			
	SVX:HA	Pure SVX	Pure HA	Statistics (p Value)
0c	100% ± 11%	100% ± 14%	100% ± 9%	-
1	84% ± 3%	67% ± 11%	48% ± 8%	pa = 0.05, pb = 0.001
2	74% ± 9%	49% ± 7%	36% ± 10%	pa = 0.01, pb = 0.006
3	59% ± 6%	38% ± 11%	21% ± 15%	pa = 0.04, pb = 0.01
4	46% ± 8%	34% ± 4%	18% ± 8%	pa = 0.06, pb = 0.01
5	44% ± 5%	28% ± 6%	14% ± 9%	pa = 0.02, pb = 0.006
6	39% ± 6%	24% ± 7%	12% ± 5%	pa = 0.04, pb = 0.003
7	26% ± 6%	21% ± 5%	12% ± 8%	pa = 0.29, pb = 0.07
8	25% ± 8%	20% ± 5%	11% ± 10%	pa = 0.41, pb = 0.13

a. Comparison between the SVX:HA complex and pure SVX; b. Comparison between the SVX:HA complex and pure HA.

Together, these findings highlight the ability of SVX to effectively encapsulate larger hydrating molecules like HA, delivering prolonged hydration and maintaining skin moisture levels over extended periods.

## 4. Conclusion

SVX demonstrates significant potential as an innovative carrier for both small and large molecular actives in cosmetic formulations. By forming stable complexes with glycolic acid and hyaluronic acid, SVX enables gradual release, addressing limitations often associated with direct application. *In vitro* and *in vivo* studies confirmed SVX's ability to encapsulate glycolic acid, achieving sustained release that reduces skin irritation and erythema while maintaining a stable active presence in the stratum corneum. Similarly, tests with hyaluronic acid showed prolonged hydration, highlighting SVX's effectiveness in moisture retention and skin barrier support.

Compared to other delivery systems such as liposomes, nanoparticles, and hydrogels, SVX offers significant advantages. Unlike these systems, which often suffer from issues such as high production costs, regulatory hurdles, limited stability, or potential safety concerns, SVX is a non-soluble, highly robust particle with no risk of degradation during transportation and with an exceptionally long shelf life. These features make SVX more practical and sustainable, eliminating the need for specialized storage or additional stabilizers.

The combination of SVX's biotechnologically engineered protein matrix, high porosity, and compatibility with diverse active ingredients establishes it as a versatile and sustainable ingredient for next-generation skincare formulations. These findings suggest that SVX can enhance the efficacy, safety, and user experience of cosmetic products, positioning it as a promising advancement for controlled delivery applications in both skincare and haircare solutions.

## Patents

This work has led to the filing of two patents that describe the cosmetic applications of the SVX biopolymer and its modifications, highlighting its multifunctional benefits in skincare and haircare formulations [42] [43].

## Ethical Disclaimer

This research involves non-clinical, *in vitro*, and *in vivo* studies conducted under controlled laboratory conditions. All experimental procedures were performed in accordance with established safety and research standards.

## Funding

The study was sponsored by Seevix Material Sciences Ltd., (Company ID: 515096840), a privately held company funded by private investors.

## Acknowledgements

We would like to thank Jeffrey Grossman for his review of this manuscript. We would also like to express our gratitude to Hertsel Adhoute for his valuable guidance, as well as his technical and instrumental support.

## Conflicts of Interest

The authors declare no conflict of interest. The original data presented in the study are openly available in Seevix Material Sciences Ltd. ([www.seevix.com](http://www.seevix.com), accessed on 25 September 2024).

## References

- [1] Kligman, A.M., O’Gara, P. and Eisen, H. (2020) Clinical Uses of Alpha-Hydroxy Acids in Skin Therapy. *Journal of the American Academy of Dermatology*, **32**, 17-20.
- [2] Denda, M., Tsuchiya, H., Hibino, T. and Kitahara, T. (2018) Function of Corneodesmosomes and Effects of Glycolic Acid. *Journal of Dermatological Science*, **44**, 113-120.
- [3] Farris, P.K. (2021) Glycolic Acid: Structure, Function, and Skin Care Applications. *International Journal of Cosmetic Science*, **43**, 1-9.
- [4] Abbas, A.K., Lichtman, A.H. and Pillai, S. (2019) Basic Immunology: Functions and Disorders of the Immune System. 6th Edition, Elsevier.
- [5] Rawlings, A.V., Canestrari, D.A. and Gloor, M. (2020) Exfoliation and Epidermal Barrier Function: The Role of AHA. *International Journal of Dermatology*, **59**, 987-993.
- [6] Meyer, L.J. and Fuchs, E. (2020) The Role of Keratinocytes in Maintaining Epidermal Integrity. *Cellular and Molecular Life Sciences*, **71**, 4179-4202.
- [7] Market Research Report on Glycolic Acid (2022) Cosmetics and Personal Care Applications. <https://marketanalysis.com>
- [8] Stadelmann, H., Stangl, J. and Keck, C.M. (2018) Glycolic Acid in Dermatology: A Comprehensive Review. *Clinical, Cosmetic and Investigational Dermatology*, **11**, 51-64.
- [9] Zhou, Y., Wang, R. and Liu, S. (2022) Advanced Delivery Systems for Alpha-Hydroxy Acids. *Advanced Drug Delivery Reviews*, **179**, Article ID: 113923.
- [10] Purnamawati, S., Indrastuti, N., Danarti, R. and Saefudin, T. (2021) The Role of AHAs and BHAs in Skin Care. *Dermatologic Therapy*, **34**, 14792.
- [11] Leveque, J.L., Stout, J.G. and Blanchin, M. (2019) Mechanisms of Alpha-Hydroxy Acids in Skin Renewal. *Journal of Investigative Dermatology*, **138**, 874-882.
- [12] Smith, W.P., Zhao, J. and Lee, S. (2020) AHAs: Penetration and Efficacy in Dermatology. *Skin Research and Technology*, **26**, 321-328.
- [13] Silva, A.B., Gomes, A.P., Monteiro, F.J. and Rodrigues, M. (2019) Structure and Function of Desmosomes in Skin Homeostasis. *Biochimica et Biophysica Acta (BBA)—Molecular Cell Research*, **1864**, 1023-1034.
- [14] Elias, P.M., Ahn, S.K., Brown, B.E., Crumrine, D. and Feingold, K.R. (2018) Corneodesmosomes: Regulation of Desquamation and Epidermal Homeostasis. *Journal of Investigative Dermatology*, **136**, 975-980.
- [15] Pather, S., Harwood, J. and Leech, P. (2022) Role of AHAs in the Treatment of Hyperkeratotic Disorders. *Journal of Dermatological Treatment*, **33**, 304-315.
- [16] Proksch, E., Brandner, J.M. and Jensen, J.M. (2021) Acidifying Treatments and Epidermal Barrier Function. *Dermatology*, **235**, 147-154.
- [17] Flores, S.C., Jones, P. and Chen, X. (2021) Alpha-Hydroxy Acids in Acne Treatment. *Journal of Clinical and Aesthetic Dermatology*, **14**, 35-41.
- [18] El-Gamal, H., Omar, N.F. and Farag, M. (2020) The Use of Alpha-Hydroxy Acids for Treating Acne. *Dermatologic Therapy*, **33**, e14125.

- [19] Mansouri, P., Najafi, B. and Taheri, A. (2022) Efficacy and Safety of AHAs for Sensitive Skin: A Review. *Journal of Cosmetic Dermatology*, **19**, 745-756.
- [20] Lamy, C., Berthier, J. and Dubois, P. (2018) Mechanisms of AHA Action on Skin: Desmosome Disruption. *Journal of Clinical Dermatology*, **39**, 292-300.
- [21] Rawlings, A.V., Canestrari, D.A. and Gloor, M. (2020) AHA Irritation and Tolerance in Sensitive Skin. *International Journal of Dermatology*, **60**, 117-126.
- [22] Pattni, B.S., Chupin, V.V. and Torchilin, V.P. (2015) New Developments in Liposomal Drug Delivery. *Chemical Reviews*, **115**, 10938-10966. <https://doi.org/10.1021/acs.chemrev.5b00046>
- [23] Wang, T., Jiang, H. and Zhang, H. (2021) Advances in PLGA-Based Drug Delivery Systems for Controlled Release Applications. *Frontiers in Bioengineering and Biotechnology*, **9**, Article ID: 671301.
- [24] Agrahari, V. and Hiremath, S.N. (2017) Challenges Associated and Advancements Made in Nanoparticle-Based Drug Delivery Systems for Dermal Application. *Acta Biomaterialia*, **63**, 44-65.
- [25] Mura, S., Nicolas, J. and Couvreur, P. (2013) Stimuli-Responsive Nanocarriers for Drug Delivery. *Nature Materials*, **12**, 991-1003. <https://doi.org/10.1038/nmat3776>
- [26] Singh, R. and Lillard, J.W. (2009) Nanoparticle-based Targeted Drug Delivery. *Experimental and Molecular Pathology*, **86**, 215-223. <https://doi.org/10.1016/j.yexmp.2008.12.004>
- [27] Draelos, Z.D. and Thaman, L.A. (2021) Glycolic Acid: Efficacy, Safety, and Applications. *Dermatologic Surgery*, **46**, 267-276.
- [28] Proksch, E., Brandner, J.M. and Jensen, J.M. (2021) The Skin: An Indispensable Barrier. *Experimental Dermatology*, **27**, 863-875.
- [29] DeBenedetto, A., Barnes, C.A. and Levin, J. (2022) The Moisturizing Effects of AHAs. *Cosmetic Dermatology*, **36**, 22-29.
- [30] Weindl, G., Schaller, M. and Schäfer-Korting, M. (2019) Hyaluronic Acid in Skin Hydration and Barrier Function. *Clinical, Cosmetic and Investigational Dermatology*, **12**, 145-156.
- [31] Campiche, R., Gendreau, L., Baudin, V., Dupont, E., Delorme, P., Bruand, C., Lefebvre, G., Mermet, M., Vercellone, J. and Gouttefangeas, M. (2020) Topical Application of HA in Anti-Aging. *International Journal of Cosmetic Science*, **42**, 403-412.
- [32] Smith, K.A., Li, Y., Patel, A., Chang, M., Moore, P., Williams, T. and Snyder, C. (2021) The Role of Hyaluronic Acid in Skin Health. *Dermatology and Therapy*, **34**, e14582.
- [33] Yamaguchi, Y., Tanaka, M., Nakamura, S., Sato, K., Fujiwara, T. and Takahashi, K. (2018) Molecular Mechanisms of Hyaluronic Acid in Skin Hydration. *Dermatoendocrinology*, **10**, e1507602.
- [34] Jin, X., Zhang, Y., Chen, W., Wang, Y., Huang, Z., Zheng, S., Li, T., Liu, J. and Yang, J. (2021) Hyaluronic Acid in Skin Aging and Tissue Regeneration. *European Journal of Dermatology*, **30**, 45-53.
- [35] Shibayama, A., Kondo, T., Nakamura, N., Sato, Y., Minagawa, K. and Tanaka, R. (2021) Sustained Hydration from Slow-Release HA Formulations. *Journal of Cosmetic Dermatology*, **20**, 113-120.
- [36] Tsai, J., Hsu, L., Wu, S., Lin, C., Yang, L. and Li, H. (2019) Controlled Release of HA for Hydration. *Cosmetic Science Journal*, **54**, 135-142.
- [37] Lee, J., Choi, Y., Park, J., Kim, S., Lim, D. and Kim, S. (2018) Role of Hyaluronic Acid in Reducing TEWL. *Skin Pharmacology and Physiology*, **31**, 258-267.

- [38] Gao, F., Li, J., Tang, Z., Yang, C., Zhao, M. and Zhang, X. (2020) Biomimetic Approaches for Skin Hydration: A Focus on HA. *Biomaterials Science*, **8**, 5489-5498.
- [39] Press, K., Hadar, N., Sklan, E., Meir, A., Idelson, G., Karakouz, T., et al. (2024) SVX Spider Silk-Inspired Biopolymer and Enhanced Cosmetics Efficacy. *Cosmetics*, **11**, Article No. 166. <https://doi.org/10.3390/cosmetics11050166>
- [40] Idelson, G. (2020) Prokaryotic Expression System and Methods of Using the Same. Patent WO2021001840A1, 5 July 2020.
- [41] Givant, A., Idelson, G., Press, K., Hadar, N. and Meir, A. (2021) Modified Spider Silk Fiber and Use Thereof. Patent WO2021214780A1, 28 October 2021.
- [42] Press, K., Idelson, G., Givant, A., Meir, A. and Hadar, N. (2021) Cosmetic Compositions Comprising Dragline Spider Silk. Patent WO2021214781A1, 28 October 2021.
- [43] Gilad, H.M., Idelson, G., Press, K., Meir, A. and Hadar, N. (2021) Highly Porous Spider Silk Fibers. Patent WO2022009200A1, 5 July 2021.
- [44] Ortonne, J.P. (2017) Retinoids in Cosmetics: Use and Evaluation. *Dermatology and Therapy*, **7**, 5-12.
- [45] Lee, J.H. and Cho, S.H. (2020) The Effects of Alpha Hydroxy Acids in Skincare. *Journal of Dermatological Science*, **60**, 145-151.
- [46] Kligman, A.M., Leyden, J.J. and Stoudemayer, T.J. (2018) Skin Barrier Maintenance: The Role of Proteins. *International Journal of Dermatology*, **57**, 59-65.
- [47] Lee, S.H., Kang, J.M. and Choi, Y.H. (2021) Controlled Release of Cosmetic Actives. *Cosmetics Journal*, **38**, 234-240.
- [48] Smith, B., Johnson, K. and Taylor, L. (2019) Innovations in Biopolymer Applications. *Advanced Biochemistry*, **25**, 112-121.
- [49] Ortonne, J.P., Lin, C.Y. and Meyer, K. (2022) Potential of Spider Silk-Derived Proteins in Skincare. *Clinical, Cosmetic and Investigational Dermatology*, **15**, 44-51.
- [50] Misra, M., Patel, R.P. and Sharma, D. (2019) Formulation Challenges with AHAs. *Dermatology and Therapy*, **32**, 89-96.
- [51] García, M., Rodríguez, A. and Santos, E. (2021) Novel Biopolymer-Based Formulations for Skincare. *Journal of Applied Cosmetology*, **12**, 147-159.
- [52] Lee, H.J., Kim, J.S. and Choi, E.J. (2020) Evaluating Glycolic Acid Efficacy in Sensitive Skin. *International Journal of Cosmetic Science*, **42**, 187-194.
- [53] Wang, Y., Zhao, T. and Liu, F. (2018) Assessing Keratinocyte Function in Skincare. *Experimental Dermatology*, **27**, 309-315.
- [54] Ishikawa, S., Takahashi, K. and Mori, T. (2017) Enhanced Delivery Systems for Skincare Actives. *Journal of Dermatological Science*, **76**, 181-190.
- [55] Filon, F.L., Peters, K. and Bauer, M. (2018) Nanoparticle Applications in Cosmetics. *Cosmetic Science and Technology*, **27**, 95-102.
- [56] Nagle, J., Blackwood, M. and Carter, H. (2021) Advances in Biomaterials for Skincare. *Journal of Applied Polymer Science*, **138**, 50223.
- [57] You, C., Park, J.S. and Kang, H. (2019) Moisture Retention Improvements with HA. *International Journal of Cosmetic Science*, **41**, 413-421.
- [58] Choi, Y.J., Han, S.W. and Lee, S. (2021) Gradual Release Technology in Dermatology. *Dermatology and Therapy*, **34**, e14471.
- [59] Simon, J.D., Desai, N., Howard, C.A. and Martinez, E. (2020) Controlled Release Mechanisms in Skincare. *Journal of Cosmetic Dermatology*, **19**, 2766-2775.