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Development and Characterization of a Novel Transfersome System for Enhanced Dermal Delivery of Active Ingredients in Cosmetic Formulations

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Abstract
Consumer demand for effective anti-aging cosmetics is increasing, but limited skin absorption of active compounds often hinders their efficacy. We selected bakuchiol, a plant-derived retinol alternative, and hyaluronic acid (HA) as representative anti-aging actives and developed stabilized transfersome carriers to enhance their skin penetration. Transfersomes produced via high-pressure homogenization exhibited small nanoparticle sizes for both bakuchiol and HA formulations, maintaining stability for one month under various storage conditions. Encapsulation of bakuchiol and hyaluronic acid in transfersomes resulted in significantly greater skin penetration, as confirmed by Franz cell diffusion tests and fluorescence microscopy. After 4 weeks of treatment, participants' self-assessments showed significant improvements in satisfaction with both skin hydration and elasticity, supporting the effectiveness of the transfersome serum. This study demonstrates the potential of transfersome technology for developing advanced anti-aging skincare products with enhanced efficacy.

1. Introduction
The effective delivery of active ingredients across the skin barrier presents a persistent challenge in both the cosmetic and pharmaceutical sciences.[1,2] Among various innovative approaches, transfersome technology has emerged as a promising strategy for enhancing the transdermal permeation of bioactive compounds. Transfersomes, with their flexible lipid bilayer structure, can effectively penetrate the skin's lipid matrix, promoting deeper absorption of active ingredients. [3,4] These vesicles typically comprise phospholipids and nonionic surfactants, with the phospholipid composition being a critical determinant of membrane stability and drug penetration. Further optimization is required to maximize the potential of transfersomes and meet growing consumer demand for effective anti-aging solutions. To address this, we selected bakuchiol, a plant-derived retinol alternative, and HA, a highly effective moisturizing agent, as anti-aging actives and developed stabilized transfersome carriers for these compounds, aiming to enhance their skin penetration efficiency. [5,6] Our study demonstrate the superior efficacy of these optimized transfersomes in ameliorating signs of skin aging, offering a promising approach for advanced anti-aging skincare formulations.

2. Materials and Methods
2.1. Development of transfersome
Transfersome carriers were prepared using hydrogenated lecithin (Lipoid GmbH, Germany), polyglyceryl emulsifiers (Talyo Kagaku, Japan), beta-sitosterol (HSF Biotech, China), dimethyl

isosorbide (Novaphene, India) as a skin permeation enhancer, and other components such as glycerine and preservatives. The formulations were processed using a high-pressure homogenizer at 1000 bar with bakuchiol (Sytheon, USA) or hyaluronic acid (HA) (Hyundai bioland, Korea).

2.2. Assessment of stability

The stability of transfersome formulation was evaluated over a 4-week period under various storage conditions, including room temperature (25 °C), high temperature (50 °C), freeze-thaw cycles, and temperature cycling conditions. The freeze-thaw test was conducted by alternating storage of the samples at −15 °C for 6 days followed by 25 °C for 1 day, with observations made after repeated cycles. For the temperature cycle test, formulations were stored sequentially at 25 °C, 45 °C, and −15 °C, each for 8 hours, and the cycle was repeated over the study period. Formulations were visually evaluated for physical instability, including phase separation, precipitation, or gelation. Additionally, the particle size and polydispersity index (PDI) of the transfersomes were measured using dynamic light scattering (DLS) with a Zetasizer Nano ZS (Malvern Instruments, UK). [7]

2.3. Skin permeation

The skin permeation efficiency of bakuchiol and HA-loaded transfersomes was assessed using two distinct methodologies: a Franz-type diffusion cell assay and a 3D artificial skin model. The skin permeation of bakuchiol was evaluated using Franz-type diffusion cells (Lab Fine Instruments, Korea) equipped with Strat-M® artificial membranes (Merck, Germany), which are designed to mimic the barrier properties of human skin. The receptor chamber was filled with a mixture of purified water and ethanol (1:1, v/v) and maintained at 32 °C throughout the 24-hour experiment. The test formulation was applied to the donor compartment, and after 24 hours, the receptor solution was collected. The amount of bakuchiol permeated was quantified using high-performance liquid chromatography (HPLC). To evaluate the penetration of HA, a 3D artificial skin model was utilized. [8,9] The model was constructed in a 12-well cell culture plate by embedding a dermal equivalent composed of human dermal fibroblasts and collagen. Human keratinocytes were then seeded onto the surface to form the epidermal layer. After 3–4 days of submerged culture, the inserts were exposed to an air–liquid interface for an additional two weeks to allow full epidermal differentiation. Transfersomes loaded with fluorescein isothiocyanate (FITC)-labeled HA were applied to the outer surface of the 3D skin model (200 µL per sample). After 4 hours of incubation, the skin models were fixed in 4% formaldehyde for 1 hour and rinsed with phosphate-buffered saline (PBS). The tissues were then embedded in O.C.T. compound and cryosectioned at a thickness of 20 µm using a cryostat microtome (CM1850, Leica, Germany). Nuclear staining was performed using DAPI, and fluorescence distribution was visualized via fluorescence microscopy (Nikon Eclipse Ti2, Japan). The intensity of FITC fluorescence, indicating the degree of HA penetration, was quantified using the ImageJ program.

2.4. Skin improvement

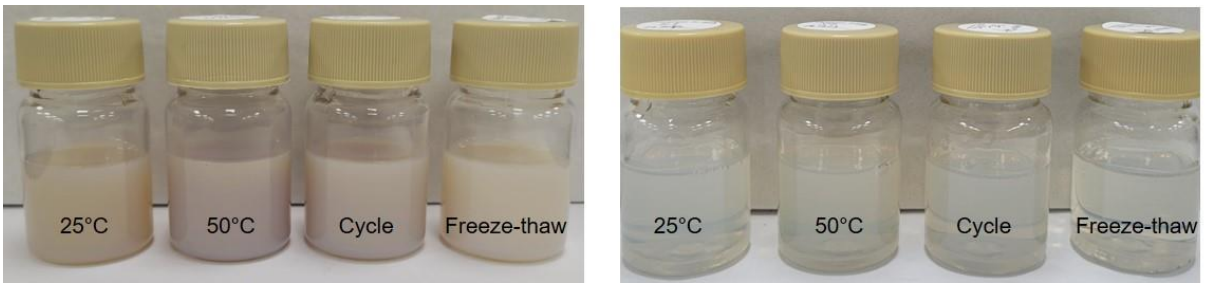
To evaluate the perceived anti-aging efficacy of the bakuchiol and HA-loaded transfersome formulations, a consumer satisfaction study was conducted with twenty participants, who applied the formulations twice daily (morning and evening) after facial cleansing for four weeks. After the application period, participants rated perceived improvements in skin hydration and elasticity using a 5-point scale

3. Results

3.1. Stability of Transfersome Formulations

The physical stability of bakuchiol and HA-loaded transfersomes was evaluated over a 4-week period under various storage conditions. As shown in Figure 1a, the bakuchiol-loaded transfersome formulation remained homogeneous in appearance without signs of separation or gelation across all tested conditions. Similarly, Figure 1b showed that the HA-loaded

transfersome remained clear and stable visually. The formulation compositions are provided in Table I.



(**a**) (**b**)

Figure 1. Visual appearance of transfersome formulations after 4 weeks of storage. (a) Bakuchiol-loaded transfersome (b) HA-loaded transfersome

Table I. Composition of bakuchiol and hyaluronic acid transfersome formulations.

Ingredients	Bakuchiol Transfersome	Hyaluronic acid Transfersome
Polyglyceryl-10 Laurate	-	-
Polyglyceryl-10 Oleate	-	2.5
Polyglyceryl-5 Oleate	10	2.5
Hydrogenated Lecithin	3	1.5
Glycerin	50	50
Phytosterols	0.1	0.1
Bakuchiol	10	-
Sodium Hyaluronate	-	0.1
Caprylic/Capric Triglyceride	10	10
Dimethyl Isosorbide	3	1
Water	To 100	To 100
Preservative	q.s*	q.s

* q.s : quantum sufficit

To further confirm the physicochemical stability of the transfersomes, particle size and polydispersity index (PDI) were measured using Dynamic Light Scattering (DLS), which calculates particle size distribution by analyzing the Brownian motion of particles. [10] Immediately after preparation, the bakuchiol-loaded transfersomes showed a particle size of 68 nm, while the HA-loaded transfersomes measured 135 nm. Although particle sizes increased slightly, both formulations maintained stability. As shown in Table II, the bakuchiol-loaded transfersomes exhibited particle sizes ranging from between 106.3 nm (freeze-thaw) to 142.4 nm (50 °C), with PDI values consistently maintained at low levels (0.116–0.155) even after 4 weeks of storage. Similarly, the HA-loaded transfersomes (Table III) showed particle sizes between 99.05 nm at 25 °C and 129.6 nm at 50 °C, and PDI values ranging from 0.131 to 0.162. These indicate that both formulations maintained relatively uniform particle distributions under various storage conditions, supporting their physicochemical stability.

Table II. Particle size and PDI measurements of bakuchiol transfersomes after 4 weeks of storage.

	Bakuchiol Transfersome	
	Particle size	**PDI**
25 °C	117.7 nm	0.122
50 °C	142.4 nm	0.116
Cycle	118.7 nm	0.138
Freeze-thaw	106.3 nm	0.155

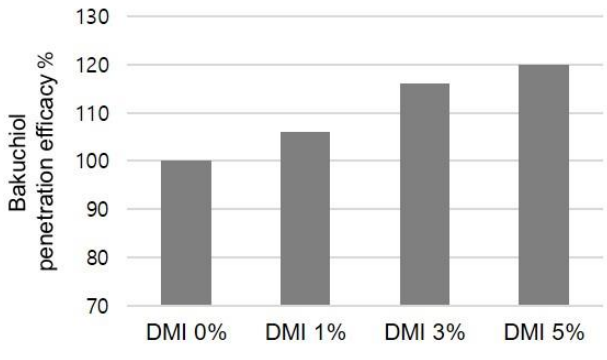
Table III. Particle size and PDI measurements of hyaluronic acid transfersomes after 4 weeks of storage.

	Hyaluronic acid Transfersome	
	Particle size	**PDI**
25 °C	99.05 nm	0.159
50 °C	129.6 nm	0.162
Cycle	120.3 nm	0.135
Freeze-thaw	116.7 nm	0.131

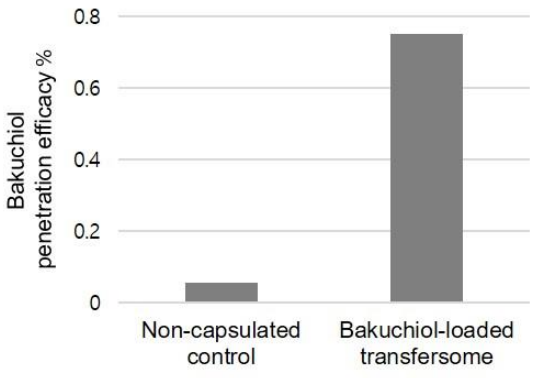
3.2. Skin Permeation

The skin permeation-enhancing effect of dimethyl isosorbide (DMI) was evaluated by incorporating it into the formulation at various concentrations. As shown in Figure 2a, DMI led to a concentration-dependent increase in the in vitro permeation of bakuchiol. Specifically, the addition of 1%, 3%, and 5% DMI resulted in approximately 6%, 16%, and 20% increases in skin permeation, respectively, compared to the formulation without DMI. While the transfersome containing 5% DMI exhibited the highest permeation efficiency, it was not stable. In contrast, formulations with 1% and 3% DMI demonstrated both enhanced permeation and good stability, indicating optimal balance between efficacy and stability. These results further supported the role of DMI as an effective permeation enhancer, likely by disrupting intercellular lipid packing and thereby facilitating the transdermal absorption of bakuchiol. [11,12]

As shown in Figure 2B, bakuchiol-loaded transfersomes demonstrated significantly enhanced skin permeation compared to non-capsulated control containing the same concentration of bakuchiol. Franz cell diffusion studies revealed that the control showed a permeation rate of 0.055%, whereas the transfersome formulation achieved a markedly higher rate of 0.752%, confirming the superior delivery efficiency of the transfersome.



(**a**)



(**b**)

Figure 2. Enhanced skin permeation of bakuchiol using transfersomes (Franz diffusion cell test). (a) Effect of DMl concentration on bakuchiol permeation. (b) Comparison of bakuchiol permeation between transfersome and non-capsulated control.

Skin permeation of HA was evaluated using a 3D artificial skin model with FITC-HA. As shown in Figure 3a, the transfersome exhibited deeper penetration of FITC-HA into the skin layers compared to the non-capsulated control. ImageJ analysis revealed a 196.9% increase in fluorescence intensity compared to the control, confirming that transfersome delivery significantly enhanced skin permeation (Figure 3b).

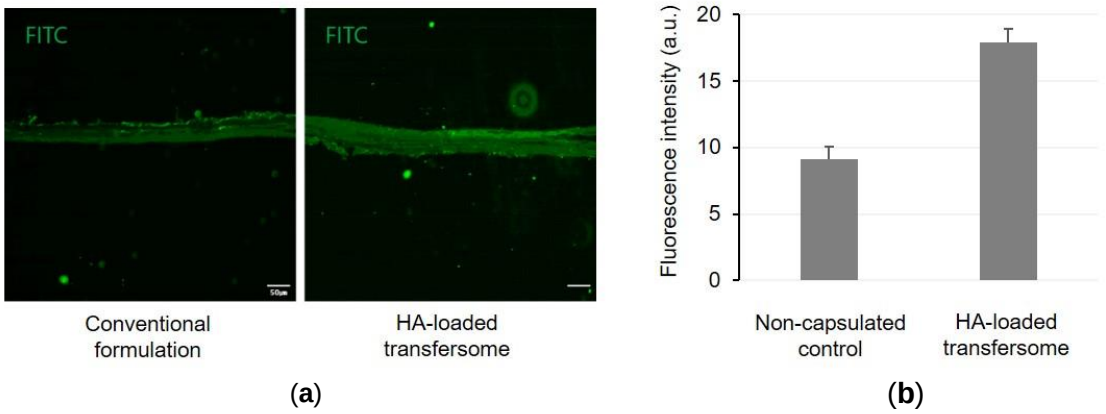


Figure 3. Enhanced skin permeation of FITC-HA via transfersomes. (a) Fluorescence microscopy images showing FITC-HA penetration in a 3D skin model (transfersome vs. non-capsulated control). (b) Quantitative fluorescence intensity analysis using ImageJ software.

3.3. Skin Improvement

Consumer satisfaction was assessed after four weeks of applying the bakuchiol and HA-loaded transfersome serum. The serum compositions for both the control and transfersome groups are detailed in Table IV. Participants who applied the transfersome formulations reported significantly higher satisfaction compared to those using the control formulation. The mean score for skin hydration was 4.5 in the transfersome group versus 3.5 in the control group (Figure 4a). For skin elasticity, the transfersome group rated 4.3, while the control group rated 3.0 (Figure 4b). These findings indicate a clear consumer preference for the transfersome formulations and support their potential to improve perceived signs of skin aging.

Table IV. Composition of control and transfersome serum.

Ingredients	Control serum	Transfersome serum
Water	To 100	To 100
Disodium EDTA	0.02	0.02
Glycerin	20	20
Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.2	0.2
Polysorbate 60	1	1
Potassium hydroxide	0.2	0.2
Bakuchiol	0.5	-
Sodium Hyaluronate	0.01	-
Bakuchiol-loaded transfersome	-	5

HA-loaded transfersome	-	10
Preservative	q.s*	q.s

* q.s : quantum sufficit

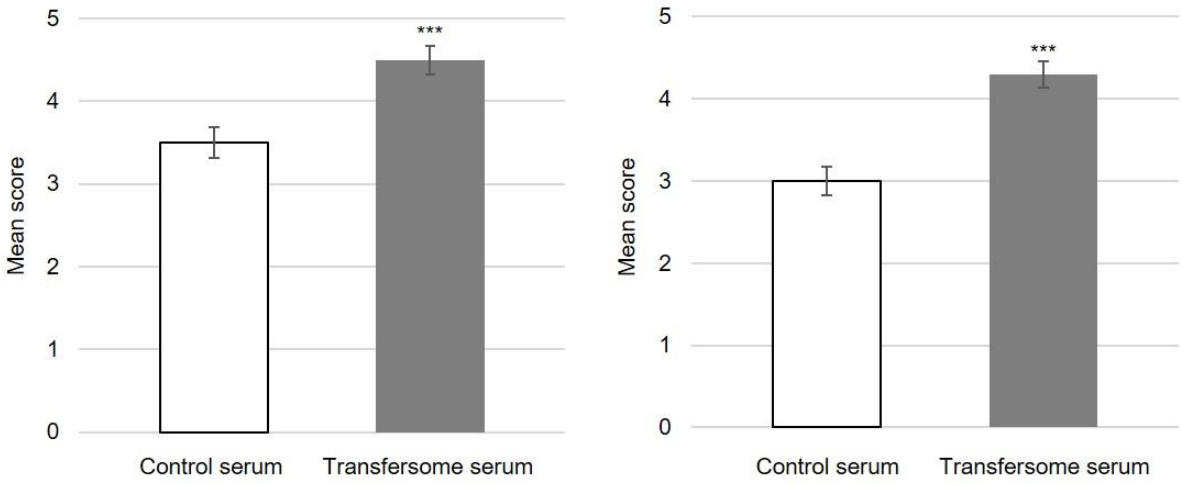


Figure 4. Consumer satisfaction scores after 4 weeks of application. (a) Skin hydration. (b) Skin elasticity. (***p < 0.001, n=20, mean ± SD)

4. Discussion

This study aimed to develop stable transfersome formulations for bakuchiol and hyaluronic acid (HA) to improve skin delivery efficiency. The results confirmed that both formulations maintained good stability over 4 weeks under various conditions, with consistent particle sizes below 150 nm and low PDI values, indicating good vesicle distribution.

Skin permeation tests showed that transfersomes significantly enhanced the delivery of both active ingredients. Bakuchiol transfersomes achieved a permeation rate of 0.752%, compared to 0.055% in the non-capsulated control. Similarly, HA transfersomes showed a 196.9% increase in fluorescence intensity in a 3D artificial skin model, suggesting more effective skin penetration. The addition of DMI improved permeation in a concentration-dependent manner. Although 5% DMI resulted in the highest permeation, it was not stable. In contrast, formulations containing 1–3% DMI maintained both effective delivery and good stability, suggesting that this range represents an optimal concentration for delivery efficiency and physical stability.

Application of the transfersome serum for 4 weeks demonstrated significant perceived improvement, with mean hydration and elasticity scores of 4.5 and 4.3, respectively, on a 5-point scale. These results demonstrate the potential of the transfersome system to enhance the efficacy of anti-aging cosmetics through improved transdermal penetration of bakuchiol and HA, which increases skin absorption and overall effectiveness.

5. Conclusion

In conclusion, the developed transfersome systems significantly enhanced the skin delivery of bakuchiol and HA, improving both stability and efficacy. These findings support the applicability of such systems in advanced cosmetic formulations aimed at anti-aging benefits.

6. Acknowledgments

None

7. Conflict of Interest Statement

None

8. References

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