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Enhancing Retinol Efficacy: Addressing Challenges with Solid Lipid Particle Technology

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1. Introduction

Retinol has become a prominent choice in anti-aging skincare, praised for its ability to rejuvenate the skin. Retinol has emerged as a leading trend in anti-aging skincare, capturing the attention of both consumers and dermatologists alike.

As a potent derivative of vitamin A, retinol is renowned for its remarkable ability to rejuvenate the skin by promoting cell turnover and stimulating collagen production. This powerful ingredient not only helps reduce the appearance of fine lines and wrinkles [1, 2] but also improves skin texture and tone [3], making it a superhero ingredient in many skincare routines. However, its use in cosmetics presents several challenges.

This molecule, while powerful in its effects, is known for its instability due to oxidation [4], its poor bioavailability due to its high lipophilic nature [5] and its potential to cause skin irritation [6, 7].

To address these issues, we developed an innovative specific solid lipid particles (SLP) technology. SLPs is known to provide several advantages over other particle types, including the ability to protect active ingredients, whereas allowing the release of the encapsulated molecule.

2. Materials and Methods

The SLP technololgy

Retinol with the antioxidant blend (D-L-alpha tocopherol and Pentaerythrityl Tetra-di-t-butyl Hydroxyhydrocinnamate) is entrapped into a solid wax matrix (cetyl palmitate) surrounded by several surfactant layers which are semi-solid at room temperature (Fig 1).

INCI name: Water (and) Cetyl Palmitate (and) Glycerin (and) Ceteareth-12 (and) Polysorbate

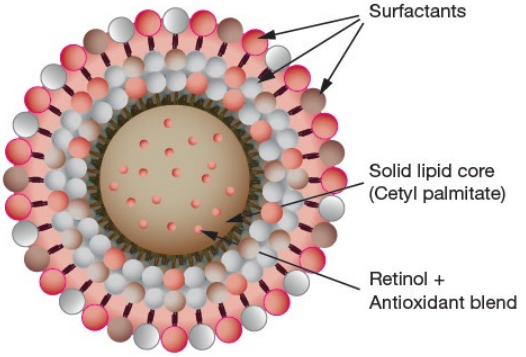

Figure 1. Schematic representation of a SLP particle

20 (and) Retinol (and) Glyceryl Stearate (and) Pentylene Glycol (and) Ceteareth-20 (and) Cetearyl Alcohol

Stability in real-life study

To prove the efficacy of this specific SLP technology regarding retinol stabilization, we evaluated the content of retinol formulated in a cream in a real-life study.

SLP technology was formulated at 2% in an O/W emulsion. Similarly, a market benchmark was formulated at 3%, to obtain an equivalent content of ~1% retinol, in the same O/W emulsion base. The formulations were stored in 50 ml plastic jars without inert gas protection and stored at room temperature.

Each day (except the weekend), 0.2 to 0.4 g of the cosmetic formulations were taken to mimic real-life conditions of use. Retinol quantification was carried out by HPLC dosage each month for 4 months (study was ended after total consumption of the product).

Bioavailability of retinol: collagen I stimulation

The bioavailability of retinol encapsulated in SLPs was evaluated through the measurement of collagen I on skin explants *vs* non-encapsulated retinol.

Human skin explants (n=3/condition, abdominoplasty from a 52-year-old Caucasian woman) were kept in survival in proprietary supplier culture medium (37°C, 5% CO_2).

Tested products:

- Gel base formula: hydroalcoholic gel based on 1.5% carboxymethylcellulose gel (CMC) and 4% ethanol (to dissolve retinol in the aqueous gel).
- Non-encapsulated retinol (Sigma, R7632) was tested at 0.1%
- SLP-retinol was tested at 2% which is equivalent to 0.1%% of pure retinol.

The condition “untreated control” corresponds gel base formula.

Treatment:

On D0, D3, and D4, tested products were applied topically at a rate of 2 mg/cm² except for the untreated control. At D4, skin samples were frozen at -80°C.

The frozen samples (n=3 biopsies/condition) were cut into 7-µm-thick sections and were mounted on Superfrost plus silanized glass slides. Immunostainings were performed with anti-collagen type I polyclonal antibody (Abcam ref. ab138492-1001). Quantification was performed by image analysis.

Results are expressed as the mean stimulation synthesis in % (percentage) normalized with the condition “Vehicle control”, standard deviation (SD). The statistical comparison of the variation between treated and untreated epidermises was done using Student’s t test, following Sigmaplot software recommendations (Systat Software Inv. USA). The threshold of significance was set to 5% ($p<0.05$).

Interleukin-8 (IL-8) expression

Irritation potential was monitored by measuring pro-inflammatory response of fibroblasts.

Normal human dermal fibroblasts (NHDFs) were maintained in DMEM supplemented with 10% heat-inactivated fetal bovine serum and 1% antibiotics at 37°C under a humidified atmosphere of 95% air and 5% CO_2.

When reached 80-90% confluence, NHDFs cells were digested and seeded to several 96-well plates at the density of 5000 cells per well.

Tested products:

- SLP-Retinol was diluted in culture medium and tested at 0.005% (eq. to 0.00025% retinol).
- a solution containing 0.005% of empty particles (SLP without retinol) and 0.00025% non-encapsulated retinol was tested in parallel.

The cells were treated with test samples (n=3) for 48h. After 48h treatment, the cell supernatants were collected and measured for IL-8 concentrations using ELISA kits (R&D Systems). IL-8 expression was quantified by the absorbance at 450nm using a microplate reader. Data were presented as the mean ± SD and analyzed with Student t test.

3. Results

After 4 months of real-life use, the SLP formulation achieved an 83% retention rate, significantly surpassing the 46% retention of the market benchmark (Fig 2).

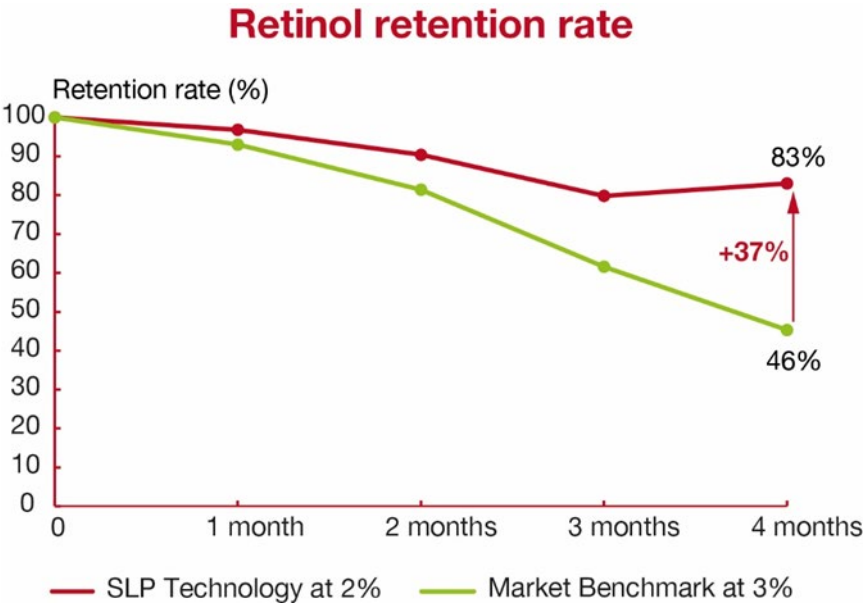

Figure 2. Retinol retention rate of SLP technology *vs* market benchmark formulated in a O/W formulation.

Regarding retinol bioavailability, collagen I was increased by 43% after SLP application, matching the level of non-encapsulated retinol (Fig 3), showing that SLP technology not only protects but also effectively releases retinol in the skin

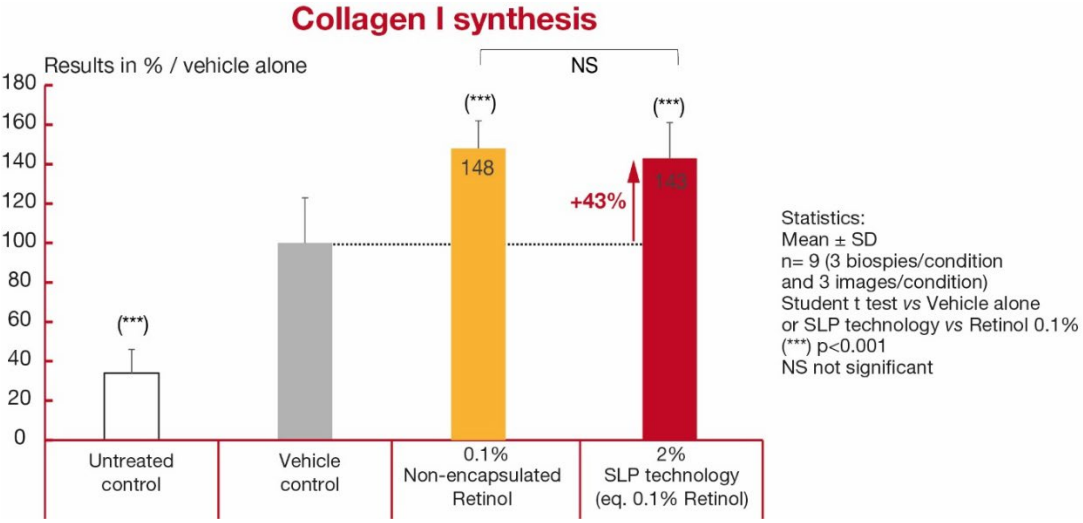

Figure 3. Evaluation of Collagen I synthesis by immunostaining after application of non-encapsulated retinol and retinol encapsulated with our SLP technology

Furthermore, a retinol irritation potential was avoided with the SLP technology. No stimulation of Il-8 secretion was observed with encapsulated retinol whereas the non-encapsulated retinol (free Retinol and empty solid lipid particles) significantly induced IL-8 by +47% ($p<0.01$) *vs* untreated control.

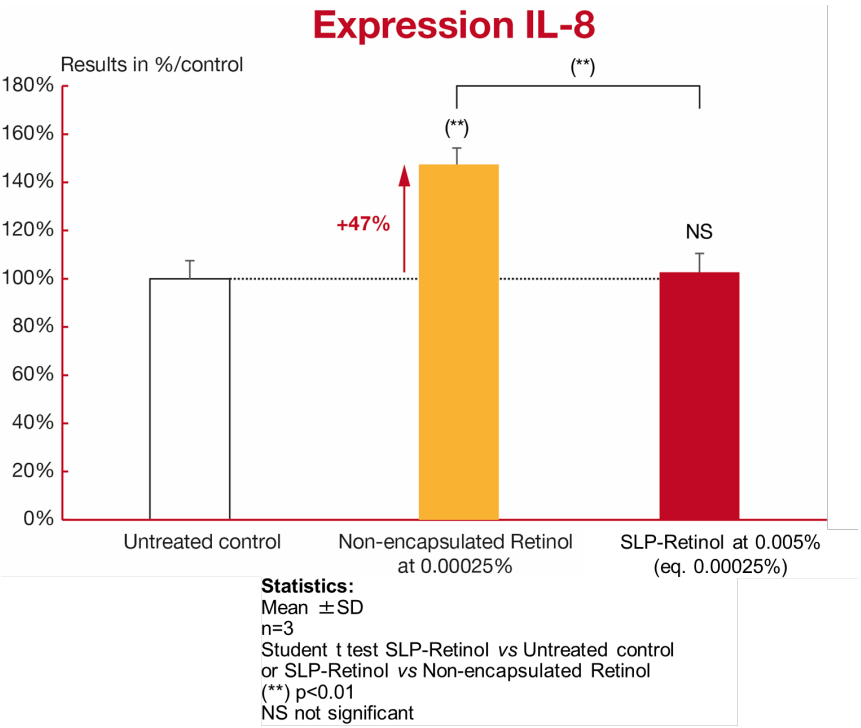

Figure 4. Effect of non-encapsulated retinol and SLP-Retinol on IL-8 secretion by fibroblasts, both conditions with the dose of 0.00025% retinol

4. Discussion

Solid lipid particles (SLPs) are used in various fields such as cosmetics, pharmaceuticals, and food industries. They are composed of lipids, often combined with surfactants to enhance their stability and bioavailability. SLPs offer many advantages over other types of particles, including their ability to protect active substances, long-term stability, and ease of preparation.

This SLP-retinol are solid lipid particles loaded with pure retinol co-encapsulated with an optimized antioxidant blend based on D-L-alpha tocopherol and Pentaerythrityl Tetra-di-t-butyl hydroxyhydrocinnamate. Retinol with the antioxidant blend is entrapped into a solid wax matrix (cetyl palmitate) surrounded by several surfactant layers which are semi-solid at room temperature which helps minimize exposure to oxygen.

Various factors affect the stability of retinol, such as the ingredients of the cosmetic formulation, the pH, the presence of antioxidants, and the conditions under which the cream is stored, including exposure to light and heat [4]. Therefore, it is recommended to use oxygen-impermeable packaging, like aluminum packaging, and to incorporate inert gases such as Nitrogen or Argon for the storage of retinol-based active ingredients to maintain their quality and efficacy [8].

In this study, we confirmed that SLP-retinol helps to strongly stabilize retinol in cosmetic formulations (without the use of inert gas, airless or aluminum packaging)

Other drawback of retinol is the skin irritation that may occur on some individuals with retinol-containing products, characterized by mild erythema and peeling of the *stratum corneum*, often referred to as “retinoid dermatitis” [9]. Specific pro-inflammatory cytokines are believed to play a significant role as key mediators of this irritation due to retinol [6]. Notably, interleukin-8 (IL-8) has been shown to be particularly important in the development of retinol-induced irritation [7].

In this study, the effect of non-encapsulated retinol and SLP-retinol on pro-inflammatory response (IL-8 release) was evaluated *in vitro* on fibroblasts and demonstrated the absence of Il-8 secretion in presence of SLP-retinol, contributing to avoid retinol induced irritation.

When having an encapsulated retinol, it is essential to determine whether the encapsulation process used ensures that retinol remains accessible to the cells in the skin and maintains its efficacy. For this purpose, we evaluated the biological efficacy of SLP-retinol *vs* non-encapsulated retinol diluted in a gel and applied on skin explants, on the stimulation of a dermal target: collagen I.

This comparative study was performed with SLP-retinol at 2% comparatively to the non-encapsulated retinol corresponding dose of 0.1%,.

With our SLP-retinol encapsulation technology, we showed an increase in collagen I equivalent to the application of a free retinol (non-encapsulated) demonstrating that our encapsulation process, in addition to strongly protect retinol from degradation, preserves its effectiveness after topical application.

5. Conclusion

In conclusion, the SLP encapsulation technology effectively addresses the main drawbacks of retinol by enhancing its stability, bioavailability, and minimizing skin irritation. This ultimate encapsulation solution enables the use of retinol without any formulation constraints. With high stability in a cosmetic formulation and no specific packaging, this technology is setting a new standard for skincare efficacy. This advancement better addresses consumer demand for effective retinol formulations that provide visible anti-aging benefits.

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