

BULETINUL INSTITUTULUI POLITEHNIC DIN IAȘI

Publicat de

Universitatea Tehnică „Gheorghe Asachi” din Iași

Volumul 72 (76), Numărul 3, 2026

Secția

CHIMIE și INGINERIE CHIMICĂ

DOI: 10.5281/zenodo.23061145

DEVELOPMENT AND PRELIMINARY PHYSICAL STABILITY ASSESSMENT OF ANHYDROUS KOJIC ACID– TETRAHEXYLDECYL ASCORBATE SYSTEMS

BY

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Received: June 15, 2026

Accepted for publication: September 18, 2026

Abstract. Kojic acid and vitamin C are widely used depigmenting actives whose therapeutic potential is limited by pronounced instability in aqueous media. This study developed and characterized anhydrous suspensions designed to co-stabilize both compounds within a minimalist squalane-beeswax matrix. Four formulations (F1-F4), varying in active composition, were evaluated immediately after preparation, at 48 hours and after four months of storage, using electrical resistivity, optical microscopy, centrifugation and vortex testing. All suspensions displayed infinite resistivity, suggesting a water-free, non-polar system, and maintained homogeneous active dispersion without agglomeration. Centrifugation revealed composition-dependent stability, with the balanced kojic acid-tetrahexyldecyl ascorbate (THDA) ratio (F3) showing the greatest resistance to phase separation, while higher THDA loading reduced mechanical robustness. No yellowing, sedimentation or textural change occurred over four months, consistent with a sustained chemical protection. These findings validate anhydrous

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suspension as an effective, technologically simple strategy for stabilizing photosensitive depigmenting actives in dermatocosmetic formulations.

Keywords: kojic acid, tetrahexyldecyl ascorbate (THDA), anhydrous suspension, hyperpigmentation, physical stability

1. Introduction

The skin, the largest organ of the human body, performs functions that go far beyond a simple mechanical boundary between the internal and external environments. Within epidermis, its outermost compartment, keratinocytes make up more than 80% of the resident cell population and organize into five morphologically distinct layers with successive stages of differentiation (Bento-Lopes *et al.*, 2023). Interspersed among these keratinocytes, melanocytes confer upon the skin its pigmentary identity and its capacity to buffer damages induced by UV rays (Wang *et al.*, 2024; Abbas *et al.*, 2025).

Pigment production becomes excessive and spatially uneven, resulting in hyperpigmentation, when melanogenesis is disturbed by chronic oxidative stress, hormonal fluctuations, inflammation or other extrinsic and intrinsic triggers. Conditions such as melasma, post-inflammatory hyperpigmentation and solar lentigines illustrate the diversity of this presentation, frequently undermining patients' self-esteem and quality of life (Nautiyal and Wairkar, 2021).

Current first-line strategies, hydroquinone and retinoids, are associated with irritation, excessive dryness and, paradoxically, secondary hypopigmentation. Given the chronic, relapsing nature of these disorders, treatment courses often extend over months or years, eroding adherence and satisfaction (Nautiyal and Wairkar, 2021; Moolla and Miller-Monthrope, 2022), which has fuelled interest in better-tolerated actives that interrupt melanogenesis through complementary mechanisms.

Kojic acid (5-hydroxy-2-hydroxymethyl-4H-pyran-4-one), a fungal metabolite obtained mainly from *Aspergillus* and *Penicillium* species, is among the most extensively studied tyrosinase inhibitors (Wang *et al.*, 2024; Zilles *et al.*, 2022). It offers a comparatively favorable safety profile relative to hydroquinone (Khadivi *et al.*, 2024). Its main formulation constraint is physicochemical: as a hydrophilic crystalline solid it penetrates the lipophilic stratum corneum poorly and is highly sensitive to pH, heat, UV-driven oxidation and iron complexation, the latter producing an undesirable reddish discoloration (Phasha *et al.*, 2022; Kang *et al.*, 2024).

Ascorbic acid, the biologically active form of vitamin C, complements kojic acid through an independent but convergent mechanism (Sanadi and Deshmukh, 2020; Martínez-Valverde *et al.*, 2022). As a weak acid with a reactive ene-diol moiety, it degrades readily with water, oxygen, light, heat and metal ions, oxidizing first to dehydroascorbic acid before further, irreversible decomposition (yellow aspect of the finished product) (Njus *et al.*, 2020; Caritá *et al.*, 2020).

The combination of kojic acid and vitamin C is pharmacologically attractive precisely because their mechanisms are complementary. Both molecules are equally unstable in aqueous environments, where hydrolysis, photo-oxidation and metal-catalyzed degradation combine to diminish their potency.

Anhydrous delivery systems offer a rational solution to this formulation challenge. By excluding the continuous aqueous phase, these vehicles suppress the hydrolytic and oxidative pathways that principally govern the instability of both actives, while simultaneously conferring intrinsic microbiological robustness and enabling the incorporation of poorly water-soluble excipients (Sheraz *et al.*, 2015; Banov *et al.*, 2023). Anhydrous suspensions allow both kojic acid and ascorbic acid to be dispersed in their solid, undissociated state, thereby maximizing shelf-life stability while raising distinct technological challenges related to particle sedimentation, rheological control and consumer-acceptable sensory attributes (Lukic and Krajisnik, 2024; Alves *et al.*, 2020).

Previously reported anhydrous vehicles for kojic acid and vitamin C rely on more complex delivery architectures: nanoemulsions (Yun *et al.*, 2021), silicone- and polyol-based anhydrous emulsions built around free ascorbic acid (Caritá *et al.*, 2020; Martínez-Valverde *et al.*, 2022) or address a single active in isolation.

We hypothesized that co-dispersing kojic acid and Tetrahexyldecyl Ascorbate (THDA) within a minimalist squalane–beeswax anhydrous matrix would produce a formulation whose physical stability—assessed *via* vortex, centrifugation, microscopic and conductivity testing, would be maintained without the need for additional stabilizing excipients.

2. Materials and methods

All raw materials used in the preparation of the topical formulation were supplied by Ellemental (Romania), selected on the basis of pharmaceutical-grade purity, complete and rigorously documented technical specifications (Table 1).

2.1. Materials

Table 1
Raw materials used in the formulation of the anhydrous suspensions

Material	INCI name / CAS no.	Key physicochemical specifications	Functional role
Kojic acid	Kojic Acid; CAS 501-30-4	White crystalline powder, >99% purity, M = 142.11 g/mol, m.p. 152–156 °C, LOD <0.5%, heavy metals <0.001%	Primary depigmenting active; hydrophilic solid phase dispersed within the anhydrous matrix

Vitamin C (THDA)	Tetrahexyldecyl Ascorbate; CAS 183476-82-6	Pale-yellow oily liquid, >95% purity, M = 1129.76 g/mol, refractive index 1.459–1.465, sp. gravity 0.930–0.943 g/mL, LOD <0.5%	Lipophilic, thermally/oxidatively stable ascorbic acid ester suited to anhydrous systems
Olive-derived squalane	Squalane; CAS 111-01-3	Colorless, odorless liquid, min. 92% squalane, refractive index 1.450–1.454, acid value ≤ 0.2 , iodine value ≤ 4.0	Principal vehicle and emollient; biomimetic carrier enhancing epidermal delivery of the actives
Beeswax	Cera Alba; CAS 8012-89-3	m.p. 61–66°C, relative density 0.96 (20°C), saponification value 87–104 mg KOH/g, acid value 17–24 mg KOH/g	Structuring/consistency agent; forms the crystalline network that suspends and stabilizes the actives

2.2. Methods

Formulation was carried out following the physicochemical characteristics specified in each raw material's technical data sheet, with particular attention to ensuring compatibility between squalane and beeswax and to achieving optimal, agglomerate-free dispersion of the kojic acid powder within the lipophilic matrix.

Process optimization at laboratory scale relied on careful control of working times for each stage and on establishing the most suitable sequence of technical steps. Three process parameters were treated as critical and calibrated accordingly: the melting and mixing **temperature**, kept high enough to ensure adequate wax fluidity yet low enough to prevent thermal degradation of squalane and of the active ingredients (wax melting was carried out in a water bath maintained at a hotplate setpoint of 90°C); the **stirring speed**, optimized to promote homogeneous dispersion while avoiding aggregate formation (homogenization of each suspension was performed for a fixed duration of 15 minutes on the same magnetic hotplate stirrer, with the STIR function engaged continuously throughout at the 7 level of 15); the **cooling rate** of the suspensions, held constant to ensure controlled, uniform solidification without compromising the stability of the incorporated actives.

This stepwise approach was essential to achieving the desired texture and stability of the final preparations, converting a small set of simple raw materials into a complex, dermatocosmetically functional anhydrous suspension. Suspension integrity was subsequently verified through vortex and centrifugation

testing, microscopic examination and electrical conductivity measurement, complemented by an assessment of suspension behavior under conditions simulating real-world use.

The investigations were conducted in real-use conditions: storage at ambient room temperature (22°C), protected from direct light and moisture, over a four-month period, with periodic handling and container opening intended to approximate typical patient storage and use, rather than a formal, chamber-controlled stability protocol.

3. Preparation of the anhydrous dermatocosmetic suspensions

All glassware was UVC-irradiated for 20 minutes prior to formulation, for disinfection.

The actives were incorporated gradually. Kojic acid, being a fine powder, required slow stirring to prevent air entrapment while still ensuring uniform particle dispersion;

Mixing was continued until an opaque suspension free of visible agglomerates was reached. Wax melting was performed separately, in a water bath heated to 90°C and temperature and mixing times were tightly controlled throughout to prevent premature wax solidification (Fig. 1).

Four test formulations were prepared to compare stabilization efficacy and to evaluate the kojic acid– THDA synergism, differing in active-ingredient composition while the squalane-to-beeswax ratio was kept proportionally consistent:

- F1 contained kojic acid only;
- F2 contained THDA only;
- F3 combined both actives at a lower THDA level (10%);
- F4 combined both actives at a higher THDA level (20%).

The exact quantities used for each suspension are summarized in Table 2.

Table 2
Quantitative composition of the kojic acid and THDA suspensions

Suspension	Kojic acid (wt.%)	THDA (wt.%)	Squalane (wt.%)	Beeswax (wt.%)	Total (g)
F1	0.95	–	93.5	5.57	37.72
F2	–	8.62	86.21	5.17	17.40
F3	0.85	8.55	85.47	5.13	17.55
F4	0.79	15.75	78.74	4.72	19.05

For F1, the weighed kojic acid was first pre-dispersed in a small aliquot of squalane before being combined with the molten wax–squalane base and homogenized on the magnetic hotplate for 15 minutes. F2 followed the same base protocol, with THDA added directly and gently to the wax–squalane system in

place of kojic acid. F3 combined both actives, pre-mixing the kojic acid and THDA in a small squalane aliquot before incorporation into the anhydrous base, again with 15 minutes of homogenization. F4 replicated the F3 protocol with the THDA quantity doubled (3 g), requiring closer monitoring of stirring and heating to prevent kojic acid sedimentation.

Immediately after preparation, each suspension underwent organoleptic evaluation. Physical stability was further assessed via centrifugation and vortex testing, electrical conductivity measurement (to indicate the absence of residual water) and optical microscopy (to evaluate textural homogeneity).

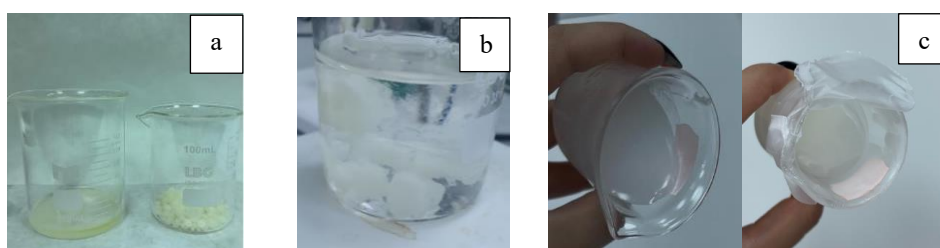


Fig. 1 – Difference between molten wax (left) and unmelted wax (right) (a.), Wax solidified within the squalane kept at room temperature (b.), Suspensions F2 and F4 at 48 hours after preparation (c).

4. Stability evaluation and physical characterization of the anhydrous suspensions

Initial characterization

Immediately after manufacture, the anhydrous matrix was validated through electrical resistivity measurement, used as an indirect marker of conductivity and, by extension, of the system's non-polar, water-free nature. The multimeter used was a Multicomp Pro MP730026 digital multimeter. Thin films of each sample were spread on microscope slides and probed with a digital multimeter; because anhydrous media are excellent electrical insulators, a high resistivity value indicates the absence of a free aqueous phase and of mobile ions, a property essential for shielding L-ascorbic acid and kojic acid from hydrolytic and oxidative degradation. Two oil-in-water (O/W) emulsions were included as comparative references.

Optical microscopy with Leica DM IL LED, brightfield illumination, objective magnification of 40x for the objective and 10x for the eyepiece, complemented this assessment by suggesting that both actives persisted as discrete solid particles embedded in the wax crystalline network, rather than dissolving into the continuous phase, and that their distribution throughout the product mass was homogeneous. Beeswax was expected to counteract

sedimentation by raising the matrix's viscosity at rest, while the absence of visible aggregates was taken as evidence of accurate, reproducible dosing and acceptable sensory quality (Fig. 2).

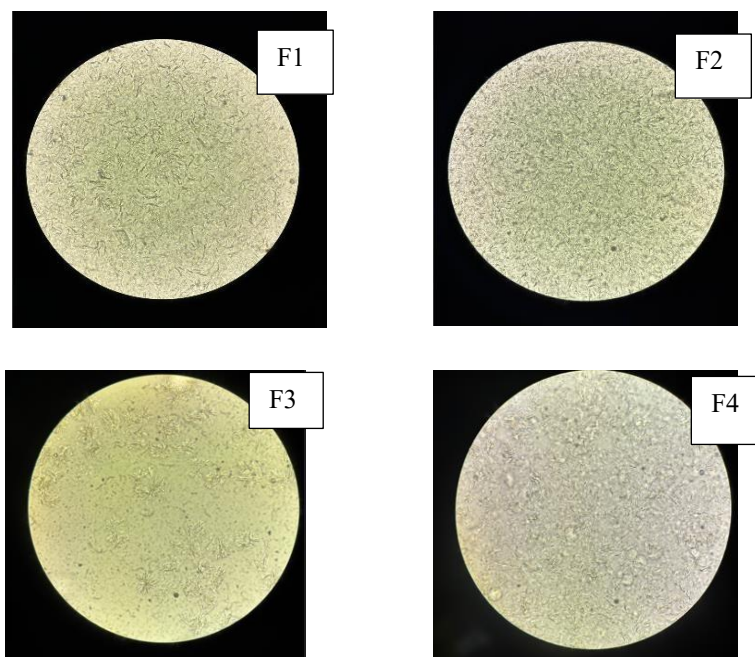


Fig. 2 – Microscopic aspect of suspensions.

Accelerated stability testing

To anticipate long-term behavior, the formulations were subjected to mechanical and thermal stress designed to simulate extreme handling and storage conditions. Samples were first held at a constant 22°C to verify that the wax crystalline network preserved its structure and viscosity, without phase separation, under standard use temperatures.

Resistance to strong gravitational forces was then examined by centrifugation: 5 g aliquots were loaded into diametrically opposed tubes to balance the rotor and centrifuged at 3000 rpm for 30 minutes at room temperature, with a stable sample expected to show neither surface oil separation nor irreversible sedimentation of the actives. Resistance to high-frequency mechanical agitation was assessed separately via a 15-second vortex test, intended to confirm that the wax network was robust enough to withstand rapid shear without excessive fluidization or particle aggregation; visual homogeneity after this test would indicate adequate cohesion between the solid (powdered actives) and continuous phases.

Four-month characterization

A final evaluation was performed four months after preparation, under controlled storage (22°C, protected from light). Unlike the immediate mechanical stress tests, this longer-term assessment was designed to capture the suspensions' real-world storage behavior, focusing on whether the squalane–beeswax matrix continued to protect kojic acid and THDA from physical or chemical degradation - evaluated through the presence or absence of sediment, the persistence of homogeneous active dispersion and any change in color.

5. Results and discussion

Immediately after preparation, all four suspensions shared a common baseline profile on organoleptic evaluation: a whitish, translucent appearance, an extremely fine and homogeneous texture, a faint beeswax-derived odor, good skin penetrability and high spreadability, with a small volume sufficient to cover a large skin area and leaving only a thin, short-lived film. The formulations differed mainly in flow resistance and its evolution over the following 48 hours, together with their behavior under centrifugal stress, summarized in Table 3.

Table 3
Comparative organoleptic and centrifugation behavior of suspensions F1–F4

Sample	Composition	Flow resistance (immediate)	Change at 48 h	Centrifugation outcome
F1	Kojic acid only	High	Color and firmness intensified, converging toward F3	Mild phase separation
F2	THDA only	Lowest (most fluid)	Unchanged	Pronounced separation compared to F1
F3	Kojic acid + 10% THDA	Highest of the series	Unchanged	No separation (most stable)
F4	Kojic acid + 20% THDA	Intermediate	Slight viscosity increase; remained less firm than F3	Pronounced separation compared to F1

Microscopic examination at 48 hours displayed a fine, uniform dispersion of the solid phase in all four suspensions, with no aggregate formation: kojic acid remained finely and homogeneously distributed in F1, F3 and F4 regardless of THDA concentration, while F2 showed evenly dispersed THDA crystals - a form the ester can adopt on cooling below its transition point within an anhydrous vehicle. This persistence of fine dispersion after 48 hours indicates

that the cooling and solidification process was optimal, preventing uncontrolled recrystallization.

Vortex testing showed no macroscopic signs of instability in any of the four formulations, indicating adequate cohesion between the solid and continuous phases irrespective of composition, in contrast to the compositionally dependent behavior observed under centrifugation, where higher THDA loading (F2, F4) consistently correlated with greater phase separation relative to F1, and F3 emerged as the most centrifugation-stable formulation overall.

Electrical resistivity measurements suggested the anhydrous, non-polar character of all four suspensions, each of which exceeded the multimeter's upper detection limit and returned an overload ("OL") reading - behavior consistent with an ideal electrical insulator. This contrasted sharply with the two O/W reference emulsions, E1 (2.48 mega Ω) and E2 (4.557 mega Ω) which returned finite resistivity values owing to their aqueous phase, experimentally substantiating the water-free nature of the anhydrous matrices and their capacity to protect kojic acid and THDA from hydrolytic degradation.

After four months of storage, all suspensions retained the macroscopic characteristics recorded at 48 hours, with no sedimentation, phase separation or firmness loss in any sample. Notably, the vitamin-C-containing suspensions (F2, F3, F4) showed no yellowing, indicating that the anhydrous matrix had effectively excluded moisture and atmospheric oxygen and thereby prevented oxidative degradation of the vitamin - an outcome supporting both the long-term chemical stability of the actives and the suspensions' continued suitability for easy, uniform application to the skin.



Fig. 3 – Suspension after centrifugation (a) and vortex (b).

6. Conclusions

The present study is proposed as a formulation-screening, proof-of-concept investigation. Each formulation was prepared and characterized as a single batch, with physical stability assessed through a single round of measurements per endpoint. Within this scope, the results are presented as an

initial, exploratory signal to identify a promising formulation strategy and a preferred active ratio. Future work should build directly on these findings by preparing at least three independently manufactured batches per formulation, with replicate physicochemical measurements (resistivity, centrifugation, vortex and microscopic analysis) to allow variability to be assessed statistically, alongside Franz cell diffusion studies to characterize the release and permeation behavior of kojic acid and THDA from the anhydrous matrix under controlled *in vitro* conditions. We present this work as a preliminary, encouraging investigation of a research direction we consider worth pursuing further.

This work synthesizes the following core findings:

- **Anhydrous formulation is an effective stabilization strategy:** eliminating water from the vehicle proved sufficient to protect both kojic acid and THDA from hydrolytic and oxidative degradation, as suggested by the infinite resistivity recorded across all samples.
- **A minimalist two-excipient matrix could be technologically sufficient:** squalane and purified beeswax alone provided the structural network needed to disperse and physically stabilize both actives, without requiring additional stabilizers or complex delivery systems.
- **Process parameters are critical success factors:** outcomes were governed primarily by tight control of melting temperature and stirring rate, indicating that reproducibility depends more on manufacturing discipline than on ingredient count.
- **Composition ratio directly governs mechanical robustness:** higher THDA loading (F2, F4) consistently correlated with reduced resistance to centrifugal stress, whereas the balanced kojic acid– THDA ratio in F3 delivered the best overall stability, pointing to an optimal active ratio rather than a simple additive effect.
- **Physical and chemical stability were sustained over time:** four months of storage produced no sedimentation, phase separation, or discoloration, predicting a long-term shelf stability for this system.
- **The system offers a favorable safety and sensory profile:** fine texture, rapid penetration and minimal dosing volume, without caking, support both patient comfort and gentle application on vulnerable hyperpigmented skin.

Collectively, these findings validate this minimalist anhydrous suspension as a technologically robust, dermatocosmetically viable platform, and support its further development toward safer topical treatments for melasma and other chronic pigmentary disorders.

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DEZVOLTAREA UNOR SISTEME ANHIDRE ACID KOJIC-ASCORBAT DE
TETRAHEXILDECIL ȘI EVALUAREA PRELIMINARĂ A STABILITĂȚII LOR
FIZICE

(Rezumat)

Acidul kojic și vitamina C sunt agenți depigmentanți cu utilizare largă, al căror potențial terapeutic este limitat de instabilitatea în mediile apoase. Acest studiu a dezvoltat suspensii anhidre pentru co-stabilizarea celor doi compuși într-o matrice minimalistă de squalan și ceară de albine. Patru formulări (F1-F4), cu compoziții diferite, au fost evaluate imediat după preparare, la 48 de ore și după patru luni, prin rezistivitate electrică, microscopie optică, centrifugare și vortex. Toate suspensiile au prezentat rezistivitate infinită, indicând un sistem anhidru, nepolar, cu dispersie omogenă a activelor, fără aglomerări. Centrifugarea a evidențiat o stabilitate dependentă de compoziție, raportul echilibrat acid kojic- ascorbat de tetrahexildecil (THDA) (F3) prezentând cea mai mare rezistență la separare, în timp ce o concentrație mai mare de THDA a redus robustețea mecanică. Nu s-au observat viraj cromatic, sedimentare sau modificări texturale timp de patru luni. Rezultatele validează suspensia anhidră ca strategie eficientă pentru stabilizarea activelor depigmentante fotosensibile.