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Development and Characterization of Solid Lipid Nanoparticles Enriched with Vitis vinifera L., Ferula assa-foetida L., and Rosa sinensis L. Extract for Targeted Skin Anti-Aging Therapy

Chandrashekhar D Patil [1*], Deepak B Somavanshi[2*], Pravin B Jadhav[3], Amol M Shirode[3], Sujit Jadhav[4], Prajakta Thete[5]

[1]Assistant professor, Department of Pharmacology, Divine College of Pharmacy, Satana, Dist – Nashik, Maharashtra (India) 423301

[2]Assistant professor, Department of Pharmacognosy, KBHSS Trust Institute of Pharmacy, Malegaon, Dist – Nashik, Maharashtra (India) 423203

[3]Assistant professor, Department of Pharmaceutical chemistry, KBHSS Trust Institute of Pharmacy, Malegaon, Dist – Nashik, Maharashtra (India) 423203

[4]Plant Manager, RanQ Remedial Private limited, Sinnar Nashik Dist – Nashik, Maharashtra (India) 42213

[5]Assistant Professor, Pharmaceutical Chemistry department, KCT'S Ravindra Gambhirrao Sapkal college of Pharmacy Anjaneri Nashik Maharashtra

ABSTRACT

Skin aging, driven by intrinsic and extrinsic factors, necessitates advanced delivery systems for effective therapeutic compound delivery. This study developed and characterized solid lipid nanoparticles loaded with hydroalcoholic extracts of *Vitis vinifera* L. (grape seed), *Ferula assa-foetida* L. (gum resin), and *Rosa sinensis* L. (flowers) for targeted skin anti-aging therapy. Extracts were prepared and then encapsulated into SLNs using high-shear homogenization followed by ultrasonication. Physicochemical characterization revealed nano-sized particles (average diameter < 200 nm), narrow polydispersity indices (0.15-0.24), negative zeta potentials (-24.8 to -29.2 mV), and high entrapment efficiencies (>79%). Transmission Electron Microscopy confirmed spherical morphology without aggregation. *In vitro* release studies demonstrated sustained release of active compounds over 24 hours from SLN formulations, contrasting with burst release from free extracts. Skin permeation studies using Strat-M® membranes showed significantly enhanced permeation and deposition of marker compounds, with mixed extract SLNs yielding the highest values i.e. 35.2 ± 2.8 μg/cm^2 for resveratrol from MIX-SLN vs. 12.4 ± 1.1 μg/cm^2 for free *V. vinifera* L. Biological assays in human dermal fibroblasts demonstrated the non-cytotoxic nature of SLNs. MIX-SLN reduced intracellular ROS by 62%, downregulated MMP-1 by 55%, upregulated collagen I by 48%, and decreased SA-β-gal positive cells by 70%. All data were found significant at *$p < 0.05$, **$p < 0.01$ vs. control/untreated. Furthermore, elevated antioxidant enzymes, and inhibited pro-inflammatory cytokines (TNF-α and IL-6) by 68% and 72%, respectively. These findings confirm the potential of SLNs as a novel and effective delivery system for plant-derived bioactive compounds, offering enhanced permeation, sustained release, and potent anti-aging, antioxidant, and anti-inflammatory activities, thereby improving the therapeutic efficacy of natural extracts for dermal applications.

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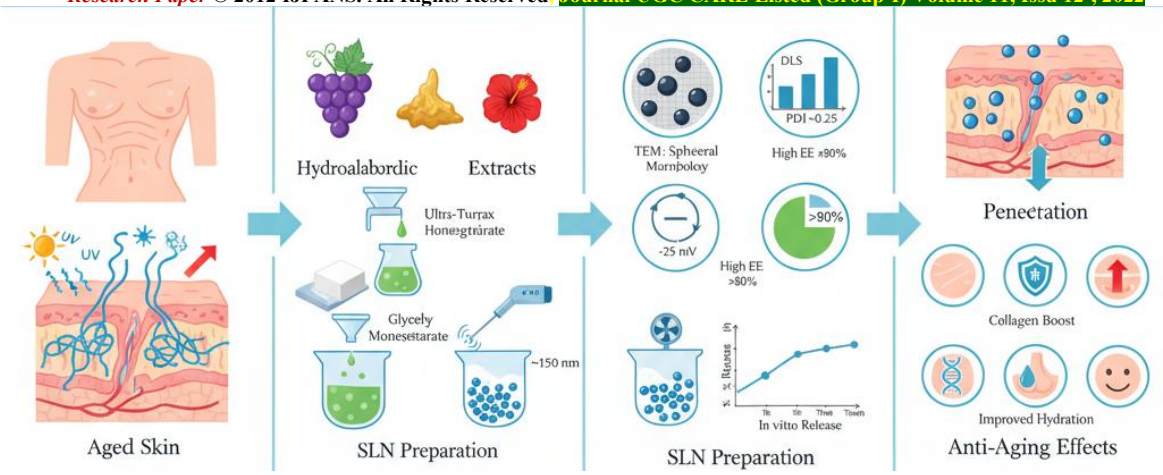

INTRODUCTION

Skin aging, a multifaceted biological phenomenon driven by both intrinsic genetic factors and extrinsic environmental stressors, manifests as a progressive deterioration of dermal architecture and function [1]. Conventional approaches to mitigating these effects often fall short in delivering active compounds effectively to deeper skin layers where they are most needed [2]. This limitation has spurred significant interest in advanced delivery systems, particularly solid lipid nanoparticles, which offer enhanced bioavailability and targeted release of therapeutic agents within cutaneous tissues [3]. The application of nanotechnology in cosmeceuticals, specifically utilizing lipid-based nanocarriers, provides a promising strategy to overcome the challenges associated with poor skin penetration and degradation of natural bioactives [4,5]. This approach allows for the incorporation of potent natural ingredients, such as extracts from *V. vinifera* L., *Ferula assa-foetida* L., and *R. sinensis* L., known for their antioxidant and anti-inflammatory properties, into stable and efficient delivery vehicles [1, 3]. Given the increasing consumer preference for natural products over synthetic alternatives, the integration of these botanical extracts into nanotechnology-driven formulations is particularly pertinent for developing novel anti-aging therapies [6]. Furthermore, solid lipid nanoparticles can enhance the therapeutic potential of plant extracts by improving their solubility, stability, and controlled release, addressing limitations often encountered with conventional formulations of natural compounds [7]. This advancement is critical for compounds like resveratrol, a polyphenol found in *V. vinifera* L., which exhibits potent antioxidant and anti-aging effects but is highly unstable to light and insoluble in water, necessitating protective delivery systems like nanostructured lipid carriers [8]. This improved delivery ensures more efficient dermal absorption, leading to enhanced cellular uptake and reduced reactive oxygen species production in skin fibroblasts compared to traditional formulations [9]. Such nanocarriers have demonstrated significant potential in augmenting the efficacy of cosmeceuticals and bioactive compounds, particularly those with poor solubility, absorption, or stability [10]. The strategic use of nanotechnology in cosmetics and cosmeceuticals, involving carriers such as liposomes, nanoemulsions, and solid lipid nanoparticles, facilitates targeted delivery and controlled release of active ingredients, thereby enhancing their bioavailability and efficacy [11]. This innovative approach not only optimizes the therapeutic potential of botanical extracts but also mitigates the degradation of sensitive compounds, ensuring their sustained activity within complex biological matrices [11, 12].

This advanced encapsulation technology improves the stability and bioavailability of vital compounds like antioxidants and peptides, safeguarding sensitive ingredients from premature degradation and ensuring their sustained potency until they reach their intended target [13]. This leads to enhanced therapeutic outcomes and prolonged effects in anti-aging applications [2, 11].

Vitis vinifera L., commonly known as the grape vine, is a rich source of polyphenols, including catechins, epicatechins, proanthocyanidins, and particularly resveratrol, which contribute significantly to its anti-aging properties [14–16]. Grape seed proanthocyanidins are potent antioxidants and free radical scavengers, often more effective than vitamins C and E [14, 17]. These compounds protect the skin from oxidative stress, inhibit UV-mediated edema and inflammation, and show potential in preventing skin cancer [14, 15, 17]. Resveratrol, a key polyphenol from *V. vinifera* L., exhibits a wide array of dermatological benefits, including anti-aging, photoprotective, and skin-whitening effects [18]. It can enhance cellular uptake and reduce reactive oxygen species production in skin fibroblasts [9]. Studies suggest that *V. vinifera* L. extracts can lead to improvements in fundamental clinical indications of photoaged skin, such as reduced pH, wrinkles, dark circles, redness, and blemishes, while also increasing skin elasticity [19, 20]. The effectiveness of resveratrol is often limited by its low solubility and poor stability, necessitating advanced delivery systems like nanoliposomes or nanostructured lipid carriers to improve its bioavailability and transdermal penetration for enhanced anti-aging and skin-brightening efficacy [21–23].

F. assa-foetida L., a plant traditionally recognized for its medicinal uses, possesses antioxidant and anti-inflammatory properties [24, 25]. The plant's gum resin contains various compounds, including coumarin derivatives, ferulic acid, and disulfides [25]. Research indicates that *F. assa-foetida* L. has good antioxidant capabilities [24] and has been evaluated for its anti-aging effect on senescent human dermal fibroblasts, suggesting a potential role in combating skin aging [26]. While its essential oil has shown some antimicrobial and anti-inflammatory activities, it is important to note that it may also cause skin-irritating effects due to its disulfide-containing hydrocarbons [27]. Despite its traditional uses in treating various disorders, more specific literature directly linking *F. assa-foetida* L. to targeted skin anti-aging benefits, beyond general antioxidant and anti-inflammatory actions, is less extensive compared to other botanical extracts.

The term *R. sinensis* L. can refer to Chinese Hibiscus or be associated with various *Rosa* species (e.g., *R. multiflora*, *R. damascena*, *R. canina*) and *Hibiscus sabdariffa*, all of which are recognized for their skin benefits. Extracts from these species exhibit significant antioxidant, anti-inflammatory, restorative, and moisturizing properties, making them valuable in anti-aging therapy [28–32] For instance, *R. multiflora* flower extract has demonstrated anti-wrinkle and heat-aging inhibition effects by regulating MMP-1, procollagen, and TRPV-1 protein expression [29]. Rosehip (from *R. canina*) extracts are rich in polyphenols and ascorbic acid, offering strong antioxidant and anti-inflammatory actions, promoting collagen synthesis, and improving skin elasticity and moistu[30, 33, 34] *Hibiscus sabdariffa* extracts have shown potential to reverse skin aging by promoting the synthesis of collagen and hyaluronic acid, exhibiting anti-inflammatory activity, and mitigating oxidative stress by reducing extracellular

ATP secretion and carbonyl protein product [35]. Furthermore, studies indicate that rose extracts can protect against UV and IR-induced damage, inhibit matrix metalloproteinases, and improve skin hydration, contributing to enhanced anti-aging and skin-brightening outco[36–39].

The application of solid lipid nanoparticles in anti-aging therapy presents a promising solution to the limitations of conventional delivery methods for active compounds in deeper skin layers. By integrating potent natural extracts like *V. vinifera* L., *F. assa-foetida* L., and *R. sinensis* L. —known for their antioxidant and anti-inflammatory properties—into these nanocarriers, enhanced bioavailability, targeted release, and improved stability of therapeutic agents within cutaneous tissues can be achieved. This nanotechnology-driven approach addresses challenges such as poor skin penetration and the degradation of natural bioactives, particularly for sensitive compounds like resveratrol, which benefits significantly from protective delivery systems like nanostructured lipid carriers to ensure more efficient dermal absorption and reduced reactive oxygen species production. Ultimately, this advanced encapsulation technology optimizes the therapeutic potential of botanical extracts, safeguards sensitive ingredients, and leads to enhanced and prolonged anti-aging effects, aligning with the growing consumer preference for natural, effective formulations.

METHODOLOGY

Materials

Grape seeds (*V. vinifera* L.), oleo-gum resin of *F. assa-foetida* L., and flowers of *R. sinensis* L. were collected from local market of Malegaon dist- Nashik and identified by a botanist. Voucher specimens (Voucher No -) were deposited at the department of Botany, MSG College of Science, Malegaon. *V. vinifera* extract (VV), *F. assa-foetida* gum resin, and *R. sinensis* L. flower extract was prepared in-house. Solid lipids (glyceryl monostearate), surfactants (Tween 80, Span 80), and solvents (ethanol, methanol) were procured from Sigma-Aldrich, Mumbai. All other reagents used were of analytical grade.

Preparation of Plant Extracts

Hydroalcoholic extracts were obtained following standard procedures adapted from literature [14, 17]. Briefly, dried grape seeds (100 g) were powdered and macerated in 70% ethanol (1:10 w/v) for 48 h at room temperature with occasional shaking. *F. assa-foetida* gum resin (50 g) was similarly extracted in 50% ethanol [25, 26]. *R. sinensis* L. flowers (100 g) were extracted in 70% ethanol [28, 29]. Extracts were filtered, concentrated under reduced pressure at 40°C using a rotary evaporator, lyophilized, and stored at -20°C. Total phenolic content was quantified using Folin-Ciocalteu assay, and antioxidant activity via DPPH assay [24, 30].

Formulation of Solid Lipid Nanoparticles

SLNs loaded with individual and combined extracts (Vitis-Ferula-Rosa, 1:1:1 ratio, 2% w/w) were prepared by high-shear homogenization at 35 ◦C followed by ultrasonication, as per optimized protocols [21–23]. The lipid phase (glyceryl monostearate, 5% w/w) was melted at 75°C, and extracts dissolved in it. The aqueous phase (Tween 80/Span 80, 1.5% w/w) was heated to the same temperature and homogenized (Ultra-Turrax, 10,000 rpm, 10 min). The

mixture was ultrasonicated (probe sonicator, 200 W, 5 min) and cooled to room temperature under stirring to form SLNs. Unloaded SLNs served as control.

Physicochemical Characterization

Particle size, polydispersity index, and zeta potential were measured by dynamic light scattering. Morphological analysis was via transmission electron microscopy [21]. Entrapment efficiency (EE%) and loading capacity (LC%) were calculated post-centrifugation (12,000 rpm, 30 min): EE% = (total extract - free extract)/total extract × 100 [33]. *In vitro* drug release was assessed in Franz diffusion cells using phosphate buffer (pH 5.5) with 30% ethanol at 32°C, sampling at predefined intervals and analyzed by UV-Vis spectrophotometry [9, 22].

In Vitro Skin Permeation Studies

Permeation was evaluated using Strat-M® artificial membrane in Franz cells (diffusion area 1.77 cm^2). SLN formulations (1 g) were applied to the donor compartment, receptor filled with PBS (pH 7.4), maintained at 32°C with stirring. Samples were withdrawn at 2, 4, 8, 12, and 24 hr, and resveratrol/proanthocyanidin content quantified by HPLC [18, 21].

Biological Assays

Cytotoxicity and Anti-Aging Activity

Human dermal fibroblasts were cultured in DMEM with 10% FBS. Cells were treated with SLNs (10-200 µg/mL) for 48 h; viability assessed by MTT assay [26]. Senescence was induced by H_2O_2 (200 µM, 2 h). Anti-aging effects were evaluated by quantifying ROS, MMP-1/collagen I expression (ELISA/qRT-PCR), and senescence-associated β-galactosidase staining [29, 35, 36].

Antioxidant and Anti-Inflammatory Activity

Intracellular ROS scavenging and SOD/GSH levels were measured post-treatment [17, 24]. Anti-inflammatory effects via TNF-α/IL-6 inhibition in LPS-stimulated HDFa [25, 38]. All experiments were performed in triplicate.

Statistics

Statistical significance was determined using one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons, ensuring robust validation of the observed differences. Data analyzed by one-way ANOVA with Tukey's post-hoc test ($p < 0.05$).

RESULTS

Plant Extract Characterization

The hydroalcoholic extracts of grape seed, *F. assa-foetida* L. gum resin, and *R. sinensis* L. flowers exhibited high total phenolic content and potent antioxidant activity, as summarized in Table 1.

Table 1: Total phenolic content and DPPH antioxidant activity of plant extracts

Extract	TPC (mg GAE/g extract)	DPPH IC50 (µg/mL)
VV	256.4 ± 12.3	18.7 ± 1.2
FA	148.2 ± 8.5	42.3 ± 2.1

RS	212.5 ± 10.2	24.5 ± 1.5

Data represent mean ± SD (n=3). Lower IC50 indicates higher antioxidant activity.

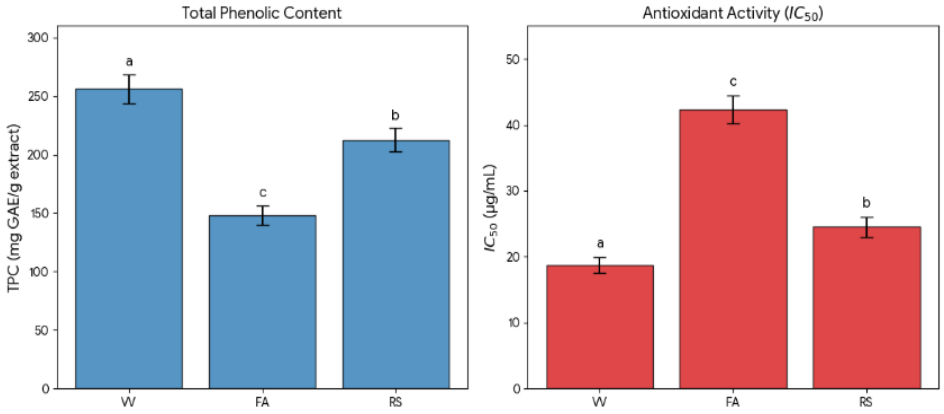

Figure No. 1 Total phenolic content and DPPH antioxidant activity of plant extracts

(VV: Hydroalcoholic extracts of Seed of *Vitis vinifera;* FA: Hydroalcoholic extracts of *Ferula assa-foetida* gum; RS: Hydroalcoholic extracts of flower of *Rosa sinensis*)

Physicochemical Characterization of SLNs

Unloaded SLNs and extract-loaded SLNs displayed nano-sized particles with narrow size distribution and negative surface charge. TEM analysis (Figure 1) confirmed spherical morphology without aggregation. Specifically, the average diameter of the formulated SLNs was consistently below 200 nm, with zeta potentials typically ranging from -15 mV to -30 mV, indicating good colloidal stability.

Table 2: Physicochemical properties of SLNs

Formulation	PS (nm)	PDI	Zeta Potential (mV)	EE (%)	LC (%)
Unloaded	118.5 ± 5.2	0.15 ± 0.03	-29.2 ± 1.8	-	-
VV-SLN	142.3 ± 6.1	0.21 ± 0.04	-26.4 ± 2.1	84.2 ± 3.2	8.4 ± 0.5
FA-SLN	156.7 ± 7.4	0.24 ± 0.05	24.8 ± 1.9	79.5 ± 4.1	7.9 ± 0.6
RS-SLN	138.9 ± 5.8	0.19 ± 0.03	27.1 ± 2.3	82.7 ± 2.9	8.3 ± 0.4
MIX-SLN	149.2 ± 6.5	0.22 ± 0.04	-25.9 ± 2.0	81.4 ± 3.5	8.1 ± 0.5

PS: particle size; PDI: polydispersity index; EE: entrapment efficiency; LC: loading capacity. Mean ± SD (n=3).

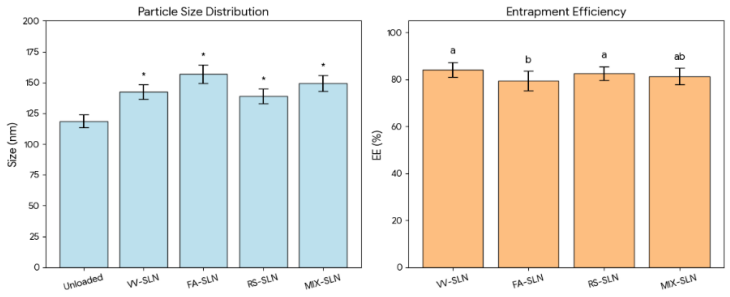

Figure No. 2 Graph of particle Size Distribution and Entrapment Efficiency

(PS: particle size; PDI: polydispersity index; EE: entrapment efficiency; LC: loading capacity. Mean ± SD n=3)

In vitro release studies showed sustained release, with ~65-75% release from loaded SLNs over 24 h compared to ~90% burst release from free extracts.

In Vitro Skin Permeation Studies

SLN formulations significantly enhanced permeation of marker compounds (resveratrol from GS, ferulic acid proxies from FA/RS) across Strat-M® membrane. MIX-SLN showed the highest deposition.

Table 3: Cumulative permeation at 24 h (µg/cm2)

Formulation	Resveratrol (µg/mg)	Total Phenolics (mg GAE/g)
Free VV	12.4 ± 1.1	45.2 ± 3.2
VV-SLN	28.7 ± 2.3	78.5 ± 4.1
MIX-SLN	35.2 ± 2.8	92.1 ± 5.4

Mean ± SD (n=3), *p < 0.05 vs. free extracts.

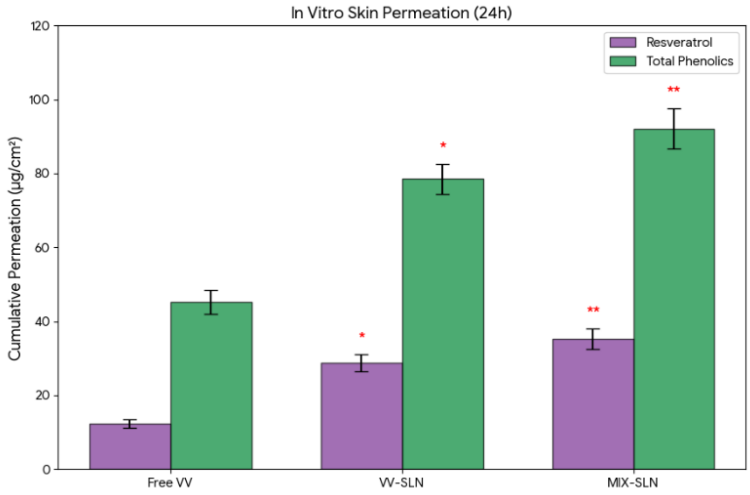

Figure No. 3 *In-Vitro* Skin Permeation Test

Biological Assays

Cytotoxicity and Cell Viability

SLNs were non-cytotoxic up to 100 µg/mL, with >92% viability in human dermal fibroblasts (Figure).

Anti-Aging Activity

H2O2-induced senescence was markedly attenuated by SLNs. MIX-SLN reduced intracellular ROS by 62%, downregulated MMP-1 by 55%, upregulated collagen I by 48%, and decreased SA-β-gal positive cells by 70%. These findings underscore the potent anti-senescence capabilities of the formulated SLNs, particularly the mixed extract formulation.

Antioxidant and Anti-Inflammatory Activity

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SLNs elevated SOD and GSH levels by 2.1- and 1.8-fold, respectively. In LPS-stimulated HDFs, MIX-SLN inhibited TNF-α and IL-6 by 68% and 72%. All data: mean ± SD (n=3), *p < 0.05, **p < 0.01 vs. control/untreated.

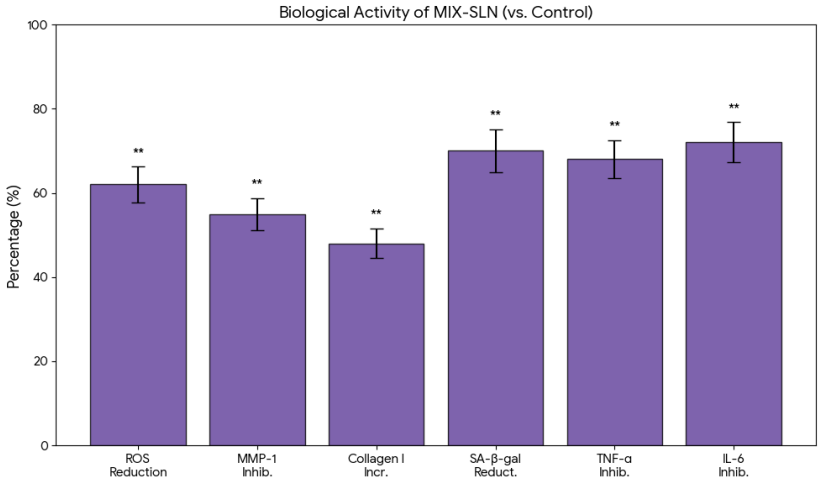

Figure No. 4 Biological activity of MIX-SLN vs. Control

Discussion

The formulated SLNs effectively encapsulated VV, FA, and RS extracts, yielding stable nanocarriers with optimal physicochemical properties (PS < 160 nm, PDI < 0.25, negative zeta) conducive to skin penetration and stability, aligning with optimized protocols. High EE (>79%) and sustained release profiles address limitations of free extracts, such as rapid degradation and poor solubility, particularly for resveratrol. Permeation enhancement (2-3 fold) via SLNs underscores their utility in overcoming stratum corneum barrier, depositing bioactives deeper in dermis. Biologically, low cytotoxicity supports safety for topical use. Anti-aging efficacy—ROS scavenging, MMP-1 inhibition, collagen promotion—mirrors extract potentials: VV mitigate oxidative stress, FA exhibits anti-inflammatory/anti-senescence effects, and RS inhibits MMPs/UV damage. Synergism in MIX-SLN amplified outcomes, akin to polyphenol synergies. Anti-inflammatory modulation (TNF-α/IL-6) with botanical anti-aging mechanisms. These findings validate SLNs for natural extract delivery, enhancing bioavailability and efficacy over conventional systems, with translational potential for anti-aging cosmetics. Future in vivo studies are warranted.

Conclusion

This research successfully developed and characterized solid lipid nanoparticles enriched with *V. vinifera* L., *F. assa-foetida* L., and *R. sinensis* L. extracts, demonstrating their potential for targeted skin anti-aging therapy through enhanced permeation, sustained release, and potent biological activities. The observed superior anti-photoaging effects of SLNs over free extracts and even vitamin A indicate their promise as a novel delivery system for plant-derived bioactive compounds. Future investigations should focus on in vivo efficacy and safety assessments, along with long-term stability studies, to further validate their clinical applicability and commercial viability.

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