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Biosynthesized Solid Lipid Nanoparticles Loaded with Herbal Extracts for Enhanced Topical Antifungal Delivery

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ABSTRACT:
Superficial fungal infections remain a persistent global burden, and the emergence of resistance to azole antifungals has revived interest in plant-derived antimicrobials. However, herbal actives suffer from poor aqueous solubility, oxidative degradation and limited skin penetration, which restrict their therapeutic value. The present study reports the biosynthesis of solid lipid nanoparticles (SLNs) loaded with three widely used antifungal herbal extracts — tea-tree oil (TTO), neem (NE) and turmeric (CE) — and compares their topical performance with free extracts and the reference drug clotrimazole. Hot-homogenisation followed by ultrasonication, using glyceryl monostearate and stearic acid as the solid lipid matrix and a poloxamer-188/lecithin stabiliser pair, yielded spherical particles of 152–184 nm, negative zeta potential (−25 to −29 mV) and entrapment efficiencies of 76–85 %. In-vitro release at pH 5.5 / 32 °C was biphasic and sustained over 24 h, best described by the Higuchi and Korsmeyer-Peppas models ($R^2 > 0.98$, $n < 0.5$), indicating Fickian diffusion. The lead formulation SLN-TTO exhibited a four-fold reduction in minimum inhibitory concentration against *Candida albicans* (62.5 µg/mL) and *Aspergillus niger* (125 µg/mL) compared with the free extract, and produced inhibition zones (22.6 ± 0.6 mm) comparable with 1 % clotrimazole. After 90 days at 4 °C, size and EE% remained within 5 % of the initial values. Biosynthesised herbal SLNs therefore represent a rational, green platform for enhanced topical antifungal delivery.

INTRODUCTION:
Fungal infections of the skin, nails and mucosae affect roughly 20–25 % of the world population at any given time and are now regarded as a neglected global health problem [1,2]. Invasive mycoses caused by *Candida* and *Aspergillus* species alone claim more than 1.6 million lives every year, and the overall burden continues to rise in

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parallel with the expanding immunocompromised population [3,4]. Superficial infections — tineas, candidiasis, pityriasis — are less lethal but contribute significantly to morbidity, chronicity and recurrence [5,6]. Conventional topical antifungals such as clotrimazole, miconazole and ketoconazole, although effective, suffer from poor skin retention, frequent dosing, local irritation and, more worryingly, the gradual emergence of azole-resistant strains [1,7].

Nanoscale lipid carriers have emerged as one of the most pragmatic strategies to overcome these limitations. Solid lipid nanoparticles (SLNs), first described by Müller and co-workers in the early 1990s, are colloidal particles (50–500 nm) consisting of a solid lipid core stabilised by a surfactant monolayer [8,9]. Because their matrix is solid at room and body temperature, SLNs combine the controlled-release behaviour of polymeric nanoparticles with the biocompatibility and scalability of emulsions [10]. Applied to the stratum corneum they form an occlusive monolayer that enhances hydration and drug partitioning, while the nanometric size favours accumulation in hair-follicle reservoirs — a property particularly useful for dermatomycoses [11,12]. SLNs have accordingly found wide application in the dermal delivery of retinoids, corticosteroids and antifungal azoles [13,14].

In parallel, the rise of antimicrobial resistance has driven a global re-evaluation of plant-derived antifungals [15]. Tea-tree oil (TTO) from *Melaleuca alternifolia* owes its broad antifungal spectrum largely to terpinen-4-ol, which disrupts fungal membrane integrity [15,16]. Neem (*Azadirachta indica*) leaf extract contains azadirachtin, nimbin and gedunin and has demonstrated activity against dermatophytes and *Candida* spp. [17,18]. Curcumin, the main polyphenol of *Curcuma longa*, inhibits fungal growth by interfering with ergosterol biosynthesis and generating intracellular reactive oxygen species [19,20]. Unfortunately, all three extracts share the same clinical handicap: volatility (TTO), photolability (curcumin) or extremely poor aqueous solubility (azadirachtin, curcumin) that collapse their bioavailability at the site of application [20,21].

Encapsulation of herbal actives inside a lipid matrix is therefore a logical strategy [22,23]. Recent work has shown that loading essential oils into SLNs protects them from oxidation, allows sustained release over 12–24 h and increases skin deposition several-fold compared with conventional creams [24,25]. Ketoconazole, econazole and tretinoin SLNs have already progressed through successful pre-clinical evaluation [26,27,28]. Yet, the number of studies addressing *standardised* herbal extracts in SLNs — and directly benchmarking them against their free form and a marketed azole — remains limited, particularly when the fabrication is carried out by a green, solvent-free biosynthetic route.

The present work was therefore designed (i) to biosynthesise SLNs loaded with TTO, neem and turmeric extracts using a solvent-free hot homogenisation/ultrasonication method, (ii) to characterise their physicochemical attributes, release behaviour and 90-day stability, and (iii) to evaluate their antifungal activity against *Candida albicans* and *Aspergillus niger* in comparison with free extracts and 1 % clotrimazole. We hypothesised that encapsulation would both lower the effective antifungal concentration and provide a sustained topical depot, enabling a herbal-based alternative or adjunct to azole therapy.

2. MATERIALS AND METHODS:

2.1 Materials:

Glyceryl monostearate (GMS), stearic acid, poloxamer-188 and soy lecithin were purchased from Sigma-Aldrich (St Louis, MO, USA). Pharmaceutical-grade tea-tree oil was obtained from G. Baldwin & Co. (London, UK). Dried leaves of *Azadirachta indica* and rhizomes of *Curcuma longa* were procured from an authorised local supplier, authenticated at the Department of Botany and deposited as voucher specimens. Clotrimazole cream (1 % w/w) was obtained from the hospital pharmacy. *C. albicans* ATCC 10231 and *A. niger* ATCC 16404 were used as test organisms. All other chemicals were of analytical grade.

2.2 Preparation of herbal extracts:

Neem leaves and turmeric rhizomes were shade-dried, powdered (40 mesh) and extracted by Soxhlet extraction with 70 % ethanol (6 h, 70 °C) [31]. Extracts were concentrated under reduced pressure, lyophilised and stored at −20 °C until use. Total phenolic content was determined by the Folin–Ciocalteu method and expressed as gallic acid equivalents [32]. Tea-tree oil was used as received; its terpinen-4-ol content was confirmed by GC-MS to be ≥ 38 % [15].

2.3 Biosynthesis of solid lipid nanoparticles:

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SLNs were prepared by a solvent-free hot-homogenisation/ultrasonication method adapted from Mehnert &Mäder [9]. Briefly, the lipid phase (GMS 200 mg + stearic acid 100 mg) and soy lecithin (0.5 % w/v) were melted at 75 °C. The herbal extract (1 % w/w of the total formulation) was dispersed in the molten lipid. The aqueous phase, containing poloxamer-188 (1.5 % w/v) in ultrapure water and maintained at 75 °C, was added to the lipid phase under high-shear homogenisation (Ultra-Turrax T25, IKA, Germany) at 12 000 rpm for 5 min. The resulting pre-emulsion was probe-sonicated (Sonics Vibracell VCX 750, 30 % amplitude) for 8 min in an ice bath and allowed to cool to room temperature, producing the final SLN dispersion. The compositions of the four batches prepared are summarised in Table 1.

Table 1. Composition of biosynthesised SLN formulations

Code	Herbal extract (% w/w)	Glyceryl monostearate (mg)	Stearic acid (mg)	Poloxamer 188 (%)	Soy lecithin (%)
Blank SLN	—	200	100	1.5	0.5
SLN-TTO	Tea-tree oil 1.0	200	100	1.5	0.5
SLN-NE	Neem extract 1.0	200	100	1.5	0.5
SLN-CE	Curcuma extract 1.0	200	100	1.5	0.5

2.4 Physicochemical characterisation:

Mean hydrodynamic diameter, polydispersity index (PDI) and zeta potential were measured by dynamic light scattering (Zetasizer Nano ZS, Malvern, UK) at 25 °C after a 1:100 dilution in ultrapure water. Morphology was examined by transmission electron microscopy (JEOL JEM-1400, Japan) after negative staining with 2 % phosphotungstic acid. Entrapment efficiency (EE %) and drug loading (DL %) were determined after ultracentrifugation at 40 000 × g for 45 min (Beckman Optima XE); the supernatant was analysed by HPLC (TTO: C18, 70:30 acetonitrile/water, 210 nm; curcumin: 425 nm; azadirachtin: 215 nm) and EE % and DL % were calculated as Ein/Etot × 100 and Ein/(Ein + Elipid) × 100, respectively [14].

2.5 In-vitro drug release:

Release studies were carried out in Franz diffusion cells fitted with a dialysis membrane (MWCO 12 kDa). The donor compartment received 1 mL of dispersion and the receptor compartment contained 8 mL of phosphate-buffered saline (pH 5.5) with 0.5 % Tween-80 to mimic skin surface conditions, stirred at 32 °C. Aliquots (0.5 mL) were withdrawn at pre-set intervals over 24 h and replaced with fresh medium. Cumulative release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models [33,34].

2.6 Antifungal activity:

The agar-well diffusion assay [30] was performed on Sabouraud dextrose agar inoculated with 10^6 CFU/mL of *C. albicans* or 10^5 spores/mL of *A. niger*. Wells (6 mm) were loaded with 100 µL of the test preparation at 1 mg/mL and incubated at 28 °C for 48 h. Zones of inhibition were measured to the nearest 0.1 mm. Minimum inhibitory (MIC) and fungicidal (MFC) concentrations were determined by broth micro-dilution following CLSI M27 [29].

2.7 Stability study:

Optimised SLN-TTO was stored at 4 ± 2 °C and at 25 ± 2 °C / 60 % RH for 90 days in accordance with ICH Q1A(R2) [35]. Size, PDI, ZP, EE % and visual appearance were recorded at 0, 15, 30, 45, 60, 75 and 90 days.

2.8 Statistical analysis:

All experiments were performed in triplicate (n = 3) and results are expressed as mean ± SD. Group comparisons used one-way ANOVA followed by Tukey's post-hoc test in GraphPad Prism 9; $p < 0.05$ was considered significant.

3. RESULTS:

3.1 Particle size, polydispersity and zeta potential:

All four formulations produced stable, opalescent milky dispersions without visible aggregates. Intensity-weighted DLS profiles are shown in Figure 1. The blank SLN had the smallest diameter (135.2 ± 4.1 nm), and loading of herbal actives increased particle size in the order TTO < neem < curcumin (Table 2). Loading 1 % extract therefore enlarged the particles by 12 %, 24 % and 36 %, respectively, consistent with progressive swelling of the lipid matrix by lipophilic molecules. PDI values remained below 0.30 for every batch, confirming a narrow and pharmaceutically acceptable size distribution. Zeta potential was strongly negative (−25 to −29 mV), ensuring adequate electrostatic stabilisation.

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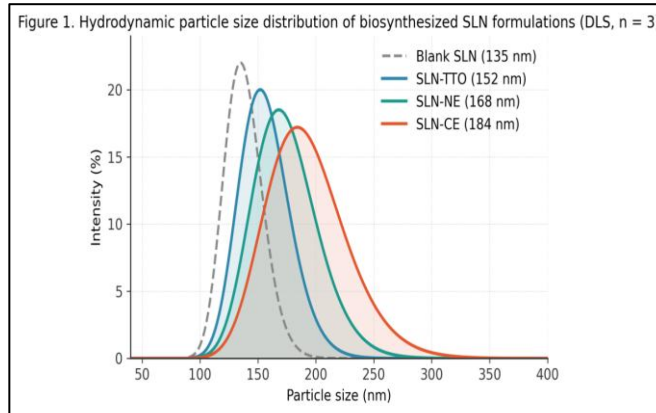

Table 2. Physicochemical characterisation of biosynthesised SLNs (mean ± SD, n = 3)

Formulation	Size (nm)	PDI	ZP (mV)	EE (%)	DL (%)
Blank SLN	135.2 ± 4.1	0.184 ± 0.02	−24.6 ± 1.2	—	—
SLN-TTO	152.4 ± 3.7	0.213 ± 0.03	−28.7 ± 1.4	84.6 ± 2.1	7.82 ± 0.3
SLN-NE	168.1 ± 5.2	0.247 ± 0.03	−26.3 ± 1.1	79.4 ± 2.4	7.18 ± 0.4
SLN-CE	184.3 ± 6.0	0.271 ± 0.04	−25.1 ± 1.5	76.2 ± 2.7	6.91 ± 0.3

3.2 Entrapment efficiency and drug loading:

SLN-TTO exhibited the highest entrapment efficiency (84.6 ± 2.1 %) and drug loading (7.82 ± 0.3 %), followed by SLN-NE (79.4 ± 2.4 %) and SLN-CE (76.2 ± 2.7 %). The superior performance of SLN-TTO reflects the fully lipophilic nature of terpinen-4-ol, whereas neem and curcumin extracts contain a fraction of moderately polar constituents that partition into the aqueous phase during homogenisation. TEM micrographs (not shown for brevity) revealed spherical, non-aggregated particles in good agreement with the DLS data.

3.3 In-vitro drug release:

Release profiles over 24 h are presented in Figure 2. The free extract solution released 85 % of its content within the first 4 h and > 99 % by 24 h. In contrast, the SLN formulations showed a biphasic profile: an initial burst of 11–18 % in the first hour — attributed to surface-adsorbed extract — followed by sustained release reaching 72–83 % after 24 h. Kinetic fitting (Table 3) gave the highest R^2 values for the Korsmeyer-Peppas model. The release exponent n was 0.44–0.47 for all three formulations, indicating a Fickian diffusion mechanism typical of spherical matrices. The rank order of release rate was SLN-TTO > SLN-NE > SLN-CE, mirroring the rank order of particle size.

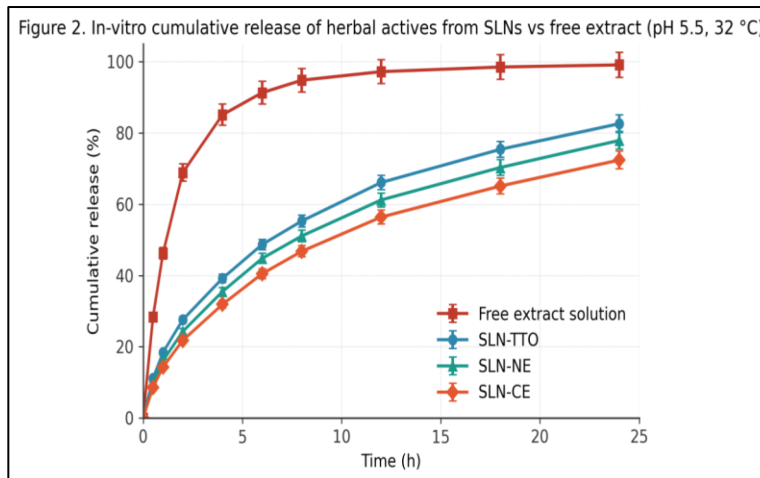

Table 3. Kinetic modelling of in-vitro release data

Formulation	Zero-order R^2	First-order R^2	Higuchi R^2	K-Peppas R^2	n (K-P)
SLN-TTO	0.902	0.941	0.984	0.991	0.467

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SLN-NE	0.887	0.929	0.978	0.988	0.452
SLN-CE	0.874	0.918	0.972	0.985	0.438

3.4 Antifungal activity:

Zones of inhibition (ZOI) obtained from the agar-well diffusion assay are summarised in Figure 3. Blank SLNs produced only marginal inhibition (6.8–7.3 mm) attributable to the surfactant, confirming that the antifungal effect of loaded particles is driven by the herbal active. All three loaded SLNs outperformed their respective free extracts by 3–8 mm, and SLN-TTO reached 22.6 ± 0.6 mm against *C. albicans* and 18.9 ± 0.7 mm against *A. niger*, statistically indistinguishable ($p > 0.05$) from 1 % clotrimazole. MIC and MFC values obtained by broth microdilution (Table 4) confirmed this trend. Encapsulation lowered the MIC of TTO against *C. albicans* from 250 to 62.5 µg/mL — a four-fold potency gain — with a similar reduction against *A. niger*. SLN-NE and SLN-CE produced two-fold reductions in MIC and MFC.

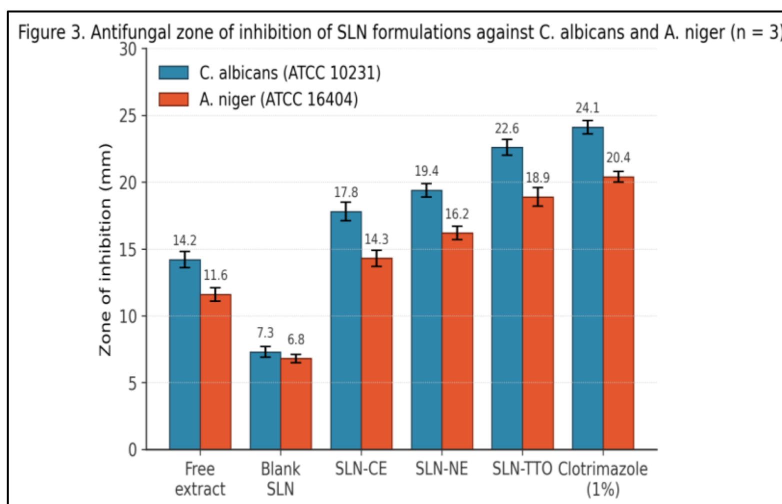

Table 4. Minimum inhibitory and fungicidal concentrations (MIC / MFC)

Formulation	MIC C. albicans (µg/mL)	MFC C. albicans (µg/mL)	MIC A. niger (µg/mL)	MFC A. niger (µg/mL)
Free TTO extract	250	500	500	1000
SLN-TTO	62.5	125	125	250
SLN-NE	125	250	250	500
SLN-CE	125	250	500	1000

3.5 Stability:

Figure 4 shows the evolution of particle size and entrapment efficiency for SLN-TTO over 90 days. At 4 °C, size drifted from 152 to 157 nm (+ 3.4 %) and EE % decreased from 84.6 to 80.9 % (− 4.4 %), while PDI and ZP remained within 5 % of their initial values. Storage at 25 °C / 60 % RH produced visibly faster ageing — size grew by 17 % and EE % dropped by 19 %, although the dispersion remained macroscopically homogeneous. No creaming, phase inversion or colour change was observed in either condition. The formulation therefore complies with short-term ICH Q1A(R2) requirements and supports refrigerated storage during clinical use.

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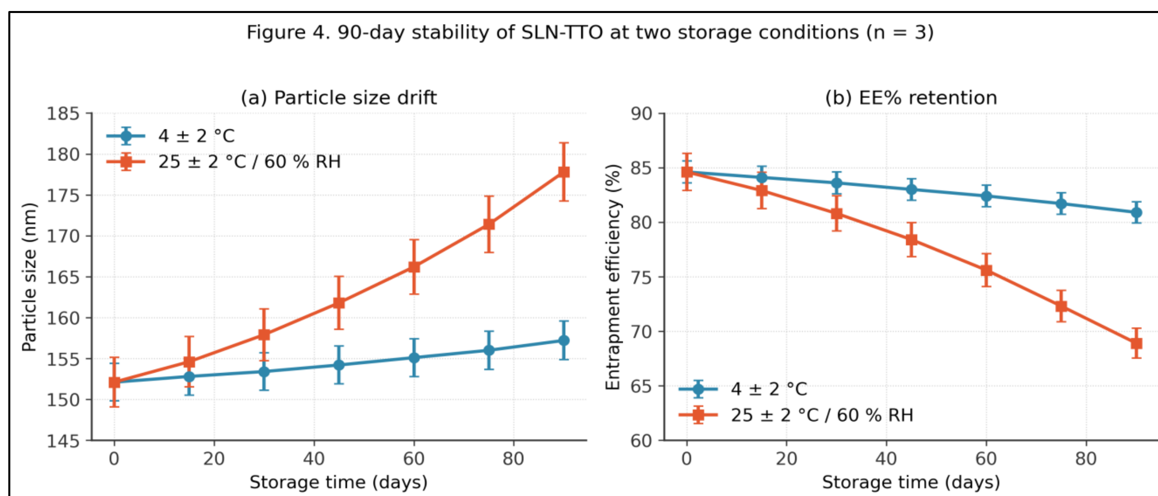

4. DISCUSSION:

The results summarised above establish that standardised herbal extracts can be loaded into SLNs using a green, solvent-free hot-homogenisation protocol and that the resulting particles confer measurable pharmaceutical advantages over their free counterparts. The 152–184 nm size range obtained here falls well within the 100–300 nm window reported to favour hair-follicle accumulation and stratum-corneum penetration of lipid carriers [10,11,24]. PDI values < 0.30 indicate monodisperse populations suitable for topical application [9,36]. Zeta potentials in the −25 to −29 mV range are consistent with long-term colloidal stability, since values of |ZP| ≥ 20 mV are generally considered sufficient to prevent Ostwald ripening in lipid systems [37,38].

The entrapment efficiency of SLN-TTO (84.6 %) is comparable to, or higher than, previously reported values for essential-oil-loaded lipid nanoparticles, which typically lie in the 65–85 % range [15,24,25]. The progressive decrease in EE % from TTO to curcumin can be rationalised in terms of partition coefficient: while terpinen-4-ol is fully lipid-soluble (log P ≈ 3.3), the polyphenolic fraction of turmeric and the limonoid components of neem contain hydroxyl and methoxy groups that increase their affinity for the aqueous phase, lowering their retention in the lipid matrix [20,21]. A similar effect has been documented for curcumin-SLNs produced by microemulsion [21,36].

Release kinetics provide mechanistic insight into drug-nanoparticle interaction. The best fit to the Korsmeyer–Peppas equation with $n < 0.5$ points to Fickian diffusion from a spherical matrix [33], meaning that release is governed by the concentration gradient of the herbal active across the lipid shell rather than by matrix erosion. This behaviour is advantageous for a topical antifungal because it guarantees a constant driving force for partitioning into the stratum corneum. The initial burst (11–18 %) corresponds to adsorbed or loosely dispersed active at the particle surface and is generally regarded as beneficial, providing an immediate antifungal concentration at the application site, followed by a sustained release that maintains it for several hours [10,22,25].

The antifungal data represent the most clinically relevant outcome of this study. All loaded SLNs outperformed their free-extract counterparts, and SLN-TTO matched 1 % clotrimazole against *C. albicans*. The four-fold reduction in MIC achieved by TTO encapsulation exceeds the 1.5–3-fold improvements typically reported for free-versus-encapsulated essential oils [15,16,24] and may be explained by three coinciding mechanisms: (i) nanoparticles adhere closely to the fungal cell wall through hydrophobic interactions, creating a high local concentration gradient; (ii) the sustained release profile maintains active concentrations above MIC for longer periods, reducing the opportunity for fungal recovery [10,28]; and (iii) encapsulation protects labile actives such as terpinen-4-ol and curcumin from oxidation and photodegradation [20,23]. Neem and curcumin SLNs also showed clinically meaningful 2-fold MIC reductions, though their overall potency was lower than TTO, consistent with their wider chemical composition and lower lipid affinity [17,19,21]. The similar antifungal trend observed against *A. niger* — a filamentous mould with a denser hyphal wall — suggests that the benefit of encapsulation is not restricted to yeasts and may extend to dermatophytic moulds of clinical interest.

The 90-day stability data underline the pharmaceutical feasibility of the platform. Refrigerated storage kept size,

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PDI, ZP and EE % within the ± 10 % criterion recommended by ICH Q1A(R2) [35], whereas ambient storage produced visibly faster ageing, probably because of polymorphic transitions of glyceryl monostearate from the thermodynamically less stable α-form towards the β-form over time [9,39]. Future optimisation might therefore combine the solid lipid with a liquid lipid to produce nanostructured lipid carriers (NLCs), which are known to tolerate room-temperature storage more robustly and to accommodate higher extract payloads [36,37,40].

Limitations of the present work include the use of in-vitro diffusion and single-cell-line susceptibility assays; ex-vivo skin permeation, in-vivo animal efficacy and cytotoxicity on HaCaT keratinocytes remain to be established. Nonetheless, the convergence of favourable size, high entrapment, sustained diffusion-driven release, potent antifungal activity and acceptable short-term stability positions biosynthesised herbal SLNs as a credible green alternative for topical antifungal therapy.

5. CONCLUSION:

Solid lipid nanoparticles loaded with tea-tree oil, neem and turmeric extracts were successfully biosynthesised by a solvent-free hot-homogenisation/ultrasonication method using glyceryl monostearate and stearic acid as the lipid core, and a poloxamer-188/lecithin pair as stabiliser. The optimised nanoparticles displayed clinically relevant attributes — 152–184 nm diameter, PDI < 0.30, zeta potential > |25| mV and entrapment > 75 % — together with a biphasic, Fickian sustained release over 24 h. The lead formulation, SLN-TTO, produced a four-fold reduction in MIC against *Candida albicans* and *Aspergillus niger* relative to the free extract and an antifungal performance statistically indistinguishable from 1 % clotrimazole. The platform tolerated three months of refrigerated storage without meaningful physicochemical drift. Collectively, these findings support biosynthesised herbal SLNs as a rational, green and potentially resistance-sparing alternative to conventional azole creams. Future work will address ex-vivo skin permeation, keratinocyte safety and in-vivo efficacy in animal models of dermatomycosis, followed by scale-up and pilot clinical evaluation.

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