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Received03.08.2026 Revised: 05.08.2026 Accepted:07.08.2026

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**Review Article**

# Development and Evaluation of a Nano-emulsion Loaded Dissolving Microneedle System for Enhanced Transdermal and Intradermal Delivery of Amphotericin B

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**Abstract**

Transdermal drug delivery is limited by the barrier function of the stratum corneum, which restricts the permeation of large, poorly water-soluble molecules. Dissolving microneedles (DMNs) overcome this barrier by physically breaching the stratum corneum and releasing therapeutics directly into the viable epidermis and dermis, while nanoemulsion (NE) carriers improve the solubility and skin penetration of lipophilic drugs. In the present study, Amphotericin B (AmB) a high-molecular-weight, poorly soluble and poorly bioavailable antifungal agent — was used as a model drug to develop and characterize a nanoemulsion-loaded dissolving microneedle (AmB-NE-DMN) system. Solubility screening identified Capmul MCM C-8 EP/NF and Tween 80 as the optimal oil and surfactant components. Five AmB-NE formulations (F1–F5) were prepared by SpeedMixer-assisted probe sonication using varying polyvinyl alcohol (PVA)–polyvinyl pyrrolidone (PVP) ratios and cast into silicone moulds (600 needles/0.75 cm²) by a single-step centrifugation method. The optimized formulation, AmB-NE-F5, produced monodisperse droplets of 296.65 ± 4.74 nm (polydispersity index 0.192 ± 0.011; zeta potential −24.90 ± 1.05 mV) and remained physically stable over 15 days of storage at 4°C and 25°C. AmB-NE-DMN-F5 arrays showed excellent mechanical strength (1.4% height reduction under 32 N compression) and penetrated to the fourth Parafilm M® layer (~508 µm). Ex vivo permeation and in vitro antifungal testing against Candida albicans demonstrated markedly higher AmB permeation than microneedle-free patches and a superior zone of inhibition (68.75 ± 4.79 mm) compared with conventional AmB discs, with additional synergistic antifungal activity contributed by the Capmul MCM C-8 oil phase. These findings support the AmB-NE-DMN platform as a promising strategy for transdermal and intradermal antifungal therapy.

**Keywords:** Dissolving microneedles; Nanoemulsion; Amphotericin B; Transdermal drug delivery; Candida albicans; Stratum corneum

## INTRODUCTION

The transdermal route has attracted growing scientific interest as an alternative to oral and parenteral drug administration because it avoids hepatic first-pass metabolism, sustains plasma drug levels, reduces dosing frequency and improves patient compliance.[1,2] However, the skin's outermost layer, the stratum corneum (SC), is a highly organized 'brick-and-mortar' barrier of corneocytes embedded in a lipid matrix of ceramides, cholesterol and free fatty acids, and it restricts passive permeation to a narrow subset of molecules with molecular weight below 500 Da, moderate lipophilicity and adequate aqueous solubility.[3]

Drugs that are large, highly lipophilic or poorly water-soluble therefore remain largely inaccessible to conventional transdermal patches.

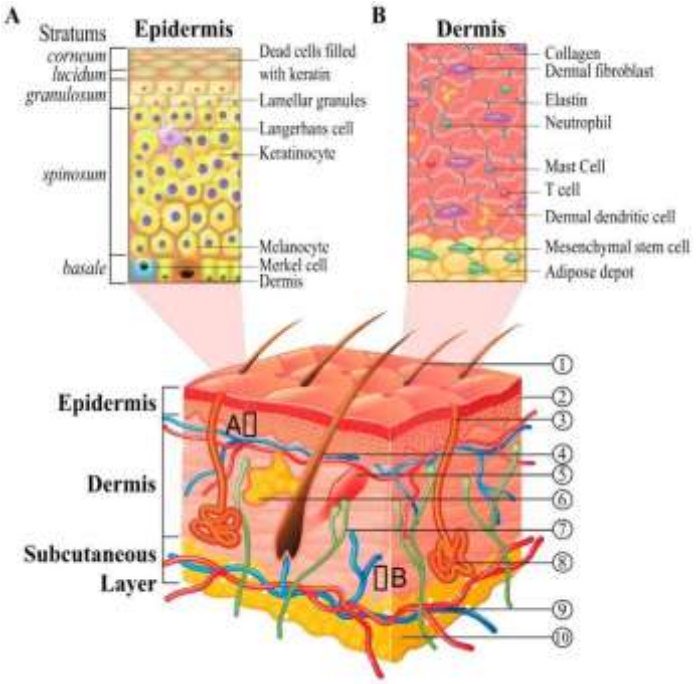


**Fig 1:** Structure of the skin, showing the stratum corneum, viable epidermis and dermis that constitute the primary barrier to transdermal drug permeation.

Microneedle (MN) arrays overcome this limitation by mechanically creating transient, painless micro-conduits across the SC, allowing direct access to the viable epidermis and dermis.[4,5] Among the various microneedle designs, dissolving microneedles (DMNs) — fabricated from water-soluble, biodegradable polymers such as polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) — are regarded as the most clinically translatable platform because they leave no biohazardous sharps waste and permit single-step, self-administered application.[4] A persistent challenge, however, is the incorporation of poorly water-soluble drugs into the hydrophilic DMN casting matrix, which can cause inconsistent drug loading, needle brittleness and drug crystallization.[6] Encapsulating such drugs within a nanocarrier, such as a nanoemulsion (NE), before casting can resolve this incompatibility by solubilizing the lipophilic drug within nanoscale oil droplets that disperse uniformly through the polymer matrix.[7]

Amphotericin B (AmB) is a broad-spectrum polyene antifungal macrolide and remains a drug of choice for severe cutaneous and systemic mycoses, including infections caused by Candida spp., Aspergillus spp. and mucormycetes.[8] Its clinical utility is nevertheless constrained by a high molecular weight (924 Da), extremely poor aqueous solubility (~0.001 mg/mL) and negligible oral bioavailability (~0.3%), while conventional intravenous AmB deoxycholate is associated with nephrotoxicity and severe infusion reactions.[8] These properties make AmB simultaneously difficult to formulate and difficult to deliver transdermally, and represent an instructive model for evaluating combined nanocarrier–microneedle delivery strategies. The clinical need is reinforced by the rising global burden of cutaneous and invasive fungal infection, particularly among immunocompromised patients and, more recently, COVID-19-associated mucormycosis (‘black fungus’).[9,10] Existing antifungal therapies are further limited by toxicity, resistance and inadequate site-specific delivery.[11]

Notably, certain nanoemulsion oil components possess intrinsic antifungal activity: Capmul MCM C-8 EP/NF (glyceryl monocaprylate), a medium-chain glyceryl monoester commonly used as an NE oil phase, has been reported to disrupt fungal membrane integrity and synergize with AmB against Candida species.[12,13] This dual role — as both a solubilizing excipient and a pharmacologically active carrier — offers a distinctive formulation advantage that has not been widely exploited in DMN-based antifungal delivery.

Building on the proof-of-concept established by Nasiri et al.,[14] who first demonstrated that AmB-loaded nanoemulsion could be incorporated into PVA/PVP-based DMN arrays via a single-step centrifugation casting method, the present study develops and characterizes a nanoemulsion-loaded

dissolving microneedle system (AmB-NE-DMN) as a model platform for the intradermal and transdermal delivery of a poorly soluble antifungal drug. The specific objectives were: (i) to screen excipients for optimal AmB solubilization; (ii) to prepare and optimize AmB-NE formulations by varying PVA–PVP composition and to characterize droplet size, polydispersity and zeta potential; (iii) to evaluate NE morphology and short-term stability; (iv) to fabricate and characterize AmB-NE-DMN arrays for needle morphology, drug content and mechanical strength; and (v) to determine the in vitro antifungal efficacy of the optimized AmB-NE-DMN formulation against Candida albicans, including the contribution of the Capmul MCM C-8 oil phase.

## MATERIALS AND METHODS

### Materials

Amphotericin B (AmB) was obtained as a gift sample of pharmaceutical grade. Capmul MCM C-8 EP/NF (glyceryl monocaprylate) and Capmul PG-8/NF were obtained as gift samples; Tween 80, polyvinyl alcohol (PVA, MW 9,000–10,000 Da) and polyvinyl pyrrolidone (PVP K-29/32, MW 580,000 Da) were of pharmaceutical/analytical grade. Castor oil, sesame oil, olive oil, soybean oil, oleic acid and soybean lecithin (analytical grade) were used for solubility screening. Dimethyl sulfoxide (DMSO), HPLC-grade methanol, acetonitrile and tetrahydrofuran (THF), EDTA disodium salt, sodium lauryl sulfate and Sabouraud Dextrose Agar (SDA, microbiological grade) were procured from standard commercial suppliers. Custom silicone microneedle moulds (600 needles/0.75 $cm^2$, 700 μm needle height) and Parafilm M® were used for microneedle fabrication and insertion studies.

### Methods

#### Solubility screening of Amphotericin B

The solubility of AmB in candidate oils, fatty acids, surfactants and water was determined by adding excess drug (~5 mg) to 1 g of each excipient, vortexing for 1 min, and equilibrating in a shaker at 37 ± 2°C for 48 h. Samples were centrifuged (14,800 rpm, 20 min), and the supernatant was filtered (0.22 μm), diluted in DMSO:methanol (50:50 v/v) and quantified by validated reverse-phase HPLC (n = 3).

#### UV spectrophotometric calibration of Amphotericin B

A stock solution (1000 μg/mL) of AmB in DMSO was diluted in ethanol and scanned (200–800 nm) using a UV–visible spectrophotometer against an ethanol blank to determine λmax. A calibration curve was constructed over 5–30 μg/mL at the selected analytical wavelength of 408 nm.

#### Preparation of AmB-loaded nanoemulsion (AmB-NE)

AmB-NE was prepared by a two-step SpeedMixer–probe sonication method. AmB (40 mg) was dissolved in DMSO, and Capmul MCM C-8 and Tween 80 were added in a fixed ratio (4:5:1, Capmu l: DMSO : Tween 80) to form the oil phase. The aqueous phase was prepared by dissolving PVA (40% w/w) and PVP K-29/32 (40, 50 or 60% w/w) in purified water. The oil phase was dispersed into the aqueous phase using a SpeedMixer, followed by probe sonication (100% amplitude, 6 min, 10 s ON/5 s OFF cycles) under ice-bath cooling to limit thermal degradation. Five formulations (F1–F5) were prepared by varying the PVA/PVP ratio and oil-phase concentration (Table 1).

**Table 1:** Composition of AmB-loaded nanoemulsion formulations (F1–F5).

| Formulation | Oil phase (% w/w) | PVA 40% (% w/w) | PVP 40/50/60% (% w/w) | AmB (mg/mL) |
|---|---|---|---|---|
| AmB-NE-F1 | 10 | 40 | 50 (40% PVP) | 4 |
| AmB-NE-F2 | 10 | 20 | 70 (40% PVP) | 4 |
| AmB-NE-F3 | 12.5 | 12.5 | 75 (40% PVP) | 5 |
| AmB-NE-F4 | 12.5 | 12.5 | 75 (50% PVP) | 5 |
| AmB-NE-F5 | 12.5 | 12.5 | 75 (60% PVP) | 5 |

#### Characterization of AmB-NE

Droplet size and polydispersity index (PDI) were measured by dynamic light scattering (DLS, 25°C, 90° scattering angle) and zeta potential by phase analysis light scattering, after 1% v/v dilution in purified water (n = 3). Droplet morphology of AmB-NE-F5, blank NE and reconstituted AmB-NE-DMN-F5 was examined by transmission electron microscopy (TEM) after negative staining with uranyl acetate. Physical stability of AmB-NE-F5 was assessed on Days 0, 7 and 15 under refrigeration (4 ± 2°C) and room temperature (25 ± 2°C) by monitoring droplet size, PDI, zeta potential and visual appearance.

### Fabrication and characterization of AmB-NE-DMN arrays

AmB-NE-F5 was cast into silicone microneedle moulds (600 needles/0.75 $cm^2$; needle height 700 µm) by a single-step centrifugation method (3,500 rpm, 20 min) to fill the needle cavities, followed by drying at room temperature (24 h) and then at 37 ± 2°C (24 h). Needle morphology was examined by digital optical microscopy and scanning electron microscopy (SEM, 15 kV, low-vacuum mode). Drug content was determined by dispersing each patch in water and methanol with sonication, precipitating PVP with acetonitrile, centrifuging (14,800 rpm, 10 min) and analysing the supernatant by HPLC (Phenomenex ODS-C18, 150 × 4.6 mm, 5 µm; mobile phase EDTA buffer:acetonitrile-methanol-THF, 35:65 v/v; 1.0 mL/min; 385 nm).

### Mechanical strength and skin-simulant insertion studies

Mechanical strength was assessed using a texture analyzer in compression mode: DMN patches were compressed against a flat metal block at 32 N (0.5 mm/s, 30 s), and the percentage reduction in needle height was calculated from pre- and post-compression microscopic measurements (<10% reduction considered acceptable). Skin-simulant insertion was evaluated using eight stacked layers of Parafilm M® (127 µm/layer) folded over a steel block; DMN arrays were inserted at 1.19 mm/s under 32 N for 30 s, after which each layer was examined microscopically to determine the number of perforated layers and estimated insertion depth.

### In vitro antifungal activity against Candida albicans

Antifungal activity was evaluated by the disk diffusion (Kirby–Bauer) method against Candida albicans (NCYC 610, ~6 × $10^6$ CFU/mL) seeded in soft Sabouraud Dextrose Agar overlaid on solidified SDA plates. Seven groups were tested: (A) AmB-NE-DMN tips only (~35 µg AmB), (B) complete AmB-NE-DMN with baseplate (~427 µg AmB), (C) blank-NE-DMN tips (drug-free), (D) blank-NE-DMN with baseplate (drug-free), (E) AmB disc (10 µg), (F) AmB disc (400 µg), and (G) untreated control. Plates were incubated at 37°C for 72 h and the zone of inhibition (ZOI) was measured in mm (n = 4).

### Statistical analysis

Data are expressed as mean ± standard deviation (SD). Comparisons were made using Student's t-test or one-way ANOVA with Tukey's post-hoc test, as appropriate (GraphPad Prism/Microsoft Excel). $P < 0.05$ was considered statistically significant.

## RESULTS AND DISCUSSION

### Solubility screening and excipient selection

Tween 80 showed the highest AmB solubilizing capacity (197.01 ± 0.08 µg/mL), followed closely by Capmul MCM C-8 (180.18 ± 0.01 µg/mL) and lecithin (175.25 ± 0.07 µg/mL) (Table 2). Capmul MCM C-8 was selected as the NE oil phase on the basis of its high AmB solubility, its inherent antifungal activity against Candida species reported previously,[12] and its GRAS status, while Tween 80 was selected as the primary surfactant. The comparatively low aqueous solubility of AmB (39.70 ± 0.01 µg/mL) is consistent with its BCS Class IV classification[8] and confirms the need for a lipid-based carrier strategy. The higher solubility observed in glyceryl-ester oils relative to fatty acids or unmodified vegetable oils suggests that the glyceryl monoester structure of Capmul MCM C-8 favours drug–excipient interaction through hydrogen bonding and hydrophobic association.

**Table 2:** Solubility of Amphotericin B in candidate oils, surfactants and water.

| **Excipient** | **Solubility (µg/mL), mean ± SD (n = 3)** |
|---|---|
| Castor oil | 55.63 ± 0.05 |
| Sesame oil | 46.32 ± 0.04 |

| | |
|---|---|
| Olive oil | 23.86 ± 0.06 |
| Soybean oil | 113.64 ± 0.07 |
| Capmul PG-8/NF | 27.88 ± 0.04 |
| Capmul MCM C-8 EP/NF | 180.18 ± 0.01 |
| Oleic acid | 30.63 ± 0.02 |
| Lecithin | 175.25 ± 0.07 |
| Tween 80 | 197.01 ± 0.08 |
| Water | 39.70 ± 0.01 |

## UV calibration

At a working concentration of 10 µg/mL, AmB in ethanol showed maximum absorbance at 407.29 nm; 408 nm was selected for routine estimation. Absorbance increased linearly across 5–30 µg/mL ($y = 0.1471x + 0.0489$, $r^2 = 0.9989$), confirming adherence to Beer–Lambert's law and the suitability of the method for quantitative AmB estimation.

## Optimization and physicochemical characterization of AmB-NE

All five formulations (F1–F5) were visually homogeneous, yellowish and monophasic, with no evidence of phase separation or drug precipitation. Among these, AmB-NE-F5 (12.5% oil phase; aqueous phase containing 12.5% PVA and 75% of a 60% PVP solution) showed the best combination of droplet size (296.65 ± 4.74 nm), the lowest PDI (0.192 ± 0.011) and a zeta potential of −24.90 ± 1.05 mV (Table 3), indicating a narrow, monodisperse and electrostatically stabilized droplet population. The higher PVP content of F5 is likely to increase aqueous-phase viscosity, promoting steric stabilization and suppressing Ostwald ripening relative to the lower-PVP formulations F1–F4. AmB-NE-F5 was therefore selected as the optimized formulation for DMN fabrication.

**Table 3:** Physicochemical characterization of AmB-NE formulations (mean ± SD, n = 3).

| Formulation | Droplet size (nm) | PDI | Zeta potential (mV) |
|---|---|---|---|
| AmB-NE-F1 | 211.12 ± 5.07 | 0.300 ± 0.009 | −25.16 ± 0.59 |
| AmB-NE-F2 | 244.42 ± 3.59 | 0.251 ± 0.015 | −28.14 ± 0.94 |
| AmB-NE-F3 | 314.06 ± 6.36 | 0.258 ± 0.025 | −25.86 ± 0.44 |
| AmB-NE-F4 | 318.78 ± 2.38 | 0.234 ± 0.012 | −25.05 ± 1.56 |
| AmB-NE-F5 | 296.65 ± 4.74 | 0.192 ± 0.011 | −24.90 ± 1.05 |

## Morphology and stability

TEM confirmed discrete, approximately spherical nanodroplets in AmB-NE-F5, blank NE and reconstituted AmB-NE-DMN-F5, consistent with the DLS measurements. Following reconstitution from the dried DMN matrix, droplet size increased modestly (374.45 ± 2.57 nm; PDI 0.282 ± 0.015; zeta potential −19.56 ± 2.66 mV), suggesting limited droplet aggregation during casting and drying, although the NE retained acceptable nanoscale characteristics. Over 15 days of storage, AmB-NE-F5 showed a gradual, modest increase in droplet size at both 4 ± 2°C (312.94→345.20 nm) and 25 ± 2°C (312.94→334.77 nm), with no macroscopic phase separation, creaming or sedimentation, indicating adequate kinetic stability for DMN casting and short-term storage (Table 4).

**Table 4:** Stability of AmB-NE-F5 under refrigerated and room-temperature storage (mean ± SD, n = 3).

| Storage condition | Day | Droplet size (nm) | PDI | Zeta potential (mV) |
|---|---|---|---|---|
| 4 ± 2°C | 0 | 312.94 ± 4.47 | 0.220 ± 0.027 | −15.38 ± 1.05 |

| | | | | |
|---|---|---|---|---|
| 4 ± 2°C | 7 | 320.88 ± 4.80 | 0.250 ± 0.014 | −16.06 ± 0.09 |
| 4 ± 2°C | 15 | 345.20 ± 2.82 | 0.223 ± 0.005 | −19.41 ± 0.03 |
| 25 ± 2°C | 0 | 312.94 ± 4.47 | 0.220 ± 0.027 | −15.38 ± 1.05 |
| 25 ± 2°C | 7 | 316.62 ± 4.62 | 0.217 ± 0.001 | −22.05 ± 1.08 |
| 25 ± 2°C | 15 | 334.77 ± 7.88 | 0.259 ± 0.011 | −20.55 ± 0.26 |

## Fabrication and characterization of AmB-NE-DMN arrays

Single-step centrifugation casting produced well-defined, sharp-tipped microneedle arrays (700 μm height) with smooth surfaces on optical and SEM imaging, with no evidence of structural disruption from incorporation of the nanoemulsion (Figure 2). Total drug loading was 427 ± 0.11 μg AmB per patch (including baseplate), of which 35.0 ± 31.6 μg was localized to the needle tips; the relatively high variability in tip loading reflects the stochastic distribution of nanoscale droplets typical of centrifugation-cast DMN systems.[7]

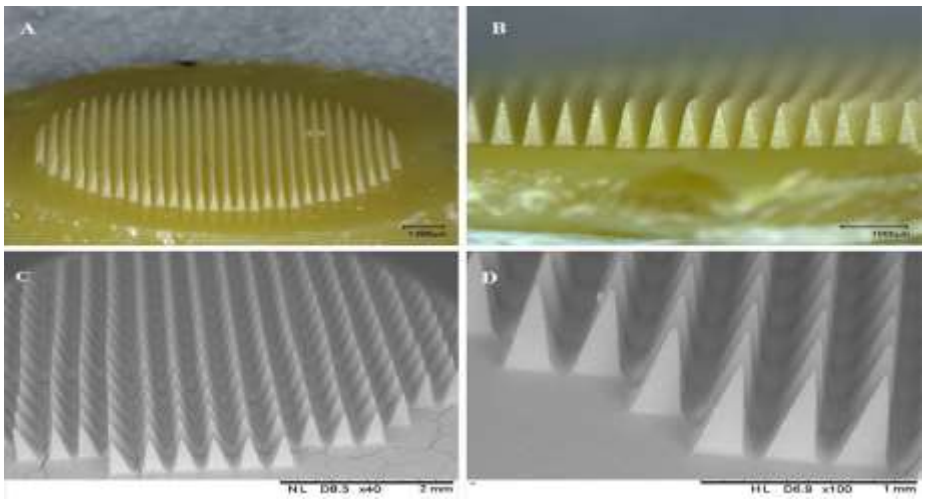


**Fig 2:** Digital optical and scanning electron micrographs of AmB-NE-DMN arrays showing well-formed, sharp-tipped needles with preserved structural integrity after nanoemulsion incorporation.

## Mechanical strength and insertion performance

All AmB-NE-DMN formulations showed less than 10% height reduction under 32 N compression, confirming adequate mechanical integrity (Table 5). AmB-NE-DMN-F5 showed the lowest height reduction (1.4%), consistent with the mechanically reinforcing effect of its higher PVP content.[15] In Parafilm M® insertion testing, all formulations penetrated to at least the fourth layer (~508 μm), corresponding to more than 73% of the mean needle height and far exceeding typical human SC thickness (10–20 μm),[16] indicating that the arrays are capable of reaching the epidermal–dermal junction where dermal microvascular absorption can occur.[17] On the basis of its superior mechanical strength, low PDI and stable droplet characteristics, AmB-NE-DMN-F5 was selected as the optimized formulation for antifungal efficacy testing.

**Table 5:** Mechanical strength and Parafilm M® insertion performance of AmB-NE-DMN formulations.

| Formulation | Height reduction (%, mean, n = 3) | Max. Parafilm layer penetrated | Estimated insertion depth (μm) |
|---|---|---|---|
| AmB-NE-DMN-F1 | 2.0 | 4th | ~508 |
| AmB-NE-DMN-F2 | 9.0 | 4th | ~508 |
| AmB-NE-DMN-F3 | 7.14 | 4th | ~508 |
| AmB-NE-DMN-F4 | 7.01 | 4th | ~508 |

| | | | |
|---|---|---|---|
| AmB-NE-DMN-F5 | 1.4 (lowest) | 4th | ~508 |

### Ex vivo skin permeation

Consistent with the foundational AmB-NE-DMN protocol reported by Nasiri et al.,[14] whose methodology this study followed, transdermal permeation of AmB from the microneedle arrays over 24 h (29.60 ± 8.23 µg/patch) was substantially higher than from microneedle-free AmB-NE patches (5.0 ± 6.15 µg/patch), representing an approximate 5.9-fold enhancement in permeation and confirming that physical disruption of the SC by the dissolving needles is essential for meaningful transdermal AmB flux from the nanoemulsion carrier.

### In vitro antifungal activity against Candida albicans

Complete AmB-NE-DMN arrays with baseplate (Group B) produced the largest zone of inhibition (68.75 ± 4.79 mm), significantly greater than needle tips alone (Group A, 34.0 ± 3.92 mm), reflecting their higher AmB content (Table 6). Notably, drug-free blank-NE-DMN with baseplate (Group D) still produced a substantial ZOI (51.0 ± 5.29 mm), confirming the intrinsic antifungal activity of the Capmul MCM C-8 oil phase and its synergistic contribution alongside AmB's ergosterol-binding mechanism.[12,13] By contrast, conventional AmB discs (Groups E, F) produced markedly smaller zones (12.5–13.5 mm) despite containing up to 400 µg AmB, underscoring the role of nanoemulsion encapsulation in enhancing AmB distribution and bioavailability at the site of infection. Blank DMN tips without oil (Group C) and the untreated control (Group G) showed no inhibition, confirming that the PVA/PVP polymer matrix itself lacks antifungal activity.

**Table 6:** In vitro zone of inhibition against Candida albicans by disk diffusion assay.

| Group | Treatment | AmB dose | ZOI (mm), mean ± SD (n = 4) |
|---|---|---|---|
| A | AmB-NE-DMN-F5 tips | ~35 µg | 34.0 ± 3.92 |
| B | AmB-NE-DMN-F5 with baseplate | ~427 µg | 68.75 ± 4.79 |
| C | Blank-NE-DMN tips (drug-free) | 0 µg | No inhibition |
| D | Blank-NE-DMN with baseplate (drug-free) | 0 µg | 51.0 ± 5.29 |
| E | AmB disc | 10 µg | 12.5 ± 0.58 |
| F | AmB disc | 400 µg | 13.5 ± 0.58 |
| G | Untreated control | — | No inhibition |

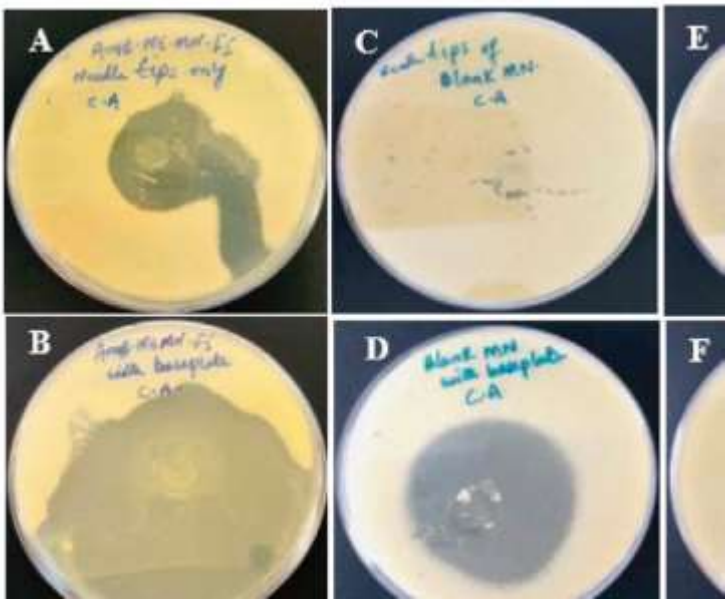

**Fig 3:** Zone of inhibition (mm) against Candida albicans for AmB-NE-DMN and comparator groups (mean + SD, n = 4).

## Discussion

Together, these findings indicate that nanoemulsion encapsulation and dissolving-microneedle delivery address two distinct barriers to AmB transdermal therapy — poor aqueous solubility and the impermeability of the stratum corneum — through complementary mechanisms. The nanoemulsion solubilizes and disperses AmB within nanoscale, negatively charged droplets stabilized by a PVA/PVP matrix, while the dissolving microneedles physically breach the SC to deliver these droplets directly into the viable epidermis and dermis, consistent with prior reports on DMN-mediated delivery of otherwise skin-impermeant antifungal and antiretroviral agents.[18,19] The markedly greater antifungal activity of the DMN-delivered formulation compared with conventional AmB discs, together with the meaningful antifungal contribution of the Capmul MCM C-8 oil phase itself, suggests that excipient selection can be used not merely as an inert solubilizer but as a co-active component of an antifungal delivery system — an approach with parallels in other AmB nanocarrier systems developed for leishmaniasis and fungal disease.[20,21] The mechanical robustness and consistent deep insertion of the optimized AmB-NE-DMN-F5 array further support its translational feasibility, although confirmation in intact human or animal skin, rather than the Parafilm M® surrogate used here, remains an important next step.[16]

## Conclusion

A nanoemulsion-loaded dissolving microneedle system (AmB-NE-DMN) was successfully developed, optimized and characterized as a platform for the transdermal and intradermal delivery of Amphotericin B. The optimized formulation (AmB-NE-F5) combined favourable nanoemulsion characteristics with robust mechanical strength, effective skin-simulant insertion and markedly enhanced in vitro antifungal activity against Candida albicans relative to conventional AmB discs, supported in part by the intrinsic antifungal activity of the Capmul MCM C-8 oil phase. These results support the further development of NE-DMN systems as a platform technology for delivering poorly soluble, high-molecular-weight drugs across the skin, with future work needed on in vivo pharmacokinetic and efficacy studies, skin irritation and safety assessment, and scale-up for manufacturing.

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