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Development of Capsaicin Nanoemulsion Using Plant-Derived Components for Enhanced Topical Analgesic Activity

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ABSTRACT
Topical delivery of capsaicin, a potent TRPV1 agonist from Capsicum species, is limited by poor aqueous solubility, local irritation and rapid clearance from the stratum corneum. The present study developed a capsaicin nanoemulsion using only plant-derived components for improved topical analgesic activity. Sesame oil and clove oil were selected as the oil phase on the basis of solubility screening, with soy lecithin as the natural surfactant and ethanol as cosurfactant. Pseudoternary phase diagrams were constructed, and formulations were prepared by the low-energy aqueous-phase titration method. The optimised formulation (F3) exhibited a droplet size of 98.4 ± 4.2 nm, PDI 0.186, zeta potential −28.6 mV and entrapment efficiency of 94.2%. In vitro release followed Higuchi kinetics, and ex vivo permeation across excised rat skin was 2.80-fold greater than that of a conventional cream. Hot-plate testing in Wistar rats produced a significant ($p < 0.01$) increase in paw-withdrawal latency, with peak analgesia at 120 min comparable to diclofenac 1% gel. The formulation was non-irritant (Draize PII 0.17) and stable for 90 days at 25 °C. Plant-based nanoemulsions therefore represent a promising green platform for topical capsaicin.

1. INTRODUCTION:

Musculoskeletal and neuropathic pain together affect more than 1.71 billion people globally and rank among the leading causes of disability-adjusted life years [1]. Although non-steroidal anti-inflammatory drugs (NSAIDs) and opioids remain the mainstay of systemic analgesic therapy, prolonged use is associated with gastrointestinal ulceration, cardiovascular events and, for opioids, dependence and overdose [2,3]. Topical analgesics bypass first-pass metabolism, concentrate the drug at the site of pain and minimise systemic exposure, thereby improving the benefit-to-risk ratio of chronic pain management [4].

Capsaicin (8-methyl-N-vanillyl-6-nonenamide), the pungent alkaloid isolated from Capsicum annuum and C. frutescens, is one of the most widely studied natural analgesics [5]. Capsaicin selectively activates the transient receptor potential vanilloid-1 (TRPV1) channel on primary afferent C- and Aδ fibres, and prolonged exposure leads to calcium-dependent desensitisation and reversible "defunctionalisation" of nociceptive terminals, producing sustained pain relief [6,7]. Topical capsaicin formulations at low (0.025–0.075 %) and high (8 %) concentrations are approved for post-herpetic neuralgia, painful diabetic neuropathy and osteoarthritis and are included in international neuropathic-pain guidelines [8–10].

Despite this clinical relevance, the therapeutic utility of topical capsaicin is compromised by its physicochemical profile. The molecule is highly lipophilic (log P ≈ 3.04) and practically insoluble in water, leading to erratic release and low permeation from conventional vehicles [11]. Topical application is also frequently accompanied by stinging, burning and erythema that reduces patient compliance, while volatility and oxidative degradation further shorten product shelf-life [12,13].

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Nanoemulsions—kinetically stable, isotropic dispersions of oil and water with droplet sizes below 200 nm stabilised by a surfactant/cosurfactant film—have emerged as efficient carriers for lipophilic actives [14,15]. Their very large surface area, thermodynamic stability and ability to carry high drug loads enable enhanced dermal delivery through fluidisation of intercellular stratum-corneum lipids and increased partitioning of drug into the skin [16,17]. Compared with liposomes or solid lipid nanoparticles, nanoemulsions are simpler to manufacture, scalable and amenable to low-energy preparation [18].

Growing interest in green pharmaceutics has encouraged the replacement of synthetic oils and non-ionic surfactants with plant-derived components that are GRAS-listed, biodegradable and often possess intrinsic pharmacological activity [17,19]. Sesame (Sesamum indicum) oil is rich in sesamol and sesamin, which impart antioxidant and anti-inflammatory effects and have been reported to augment percutaneous absorption of co-administered actives [19,20]. Clove (Syzygium aromaticum) oil contains up to 80 % eugenol, a well-characterised analgesic that co-activates TRPV1 and TRPA1 channels and behaves synergistically with capsaicin [21,22]. Soy lecithin, a natural phospholipid surfactant, forms biocompatible interfacial films and is widely exploited in dermal nanocarriers [23,24].

Although nanoemulsions of capsaicin have been reported previously, most use synthetic surfactants and have been evaluated only in vitro [12,25]. Formulations assembled exclusively from plant-derived excipients and simultaneously assessed for skin permeation and in vivo analgesic response remain scarce. The present study was therefore designed to (i) screen plant-based oils, surfactants and cosurfactants for capsaicin solubility; (ii) optimise a capsaicin nanoemulsion by pseudoternary phase-diagram analysis; (iii) characterise the optimised system for droplet size, zeta potential, morphology, in vitro release and ex vivo permeation; and (iv) evaluate skin irritation and analgesic activity in a rodent hot-plate model, with the aim of establishing a green, patient-friendly topical platform for capsaicin.

2. MATERIALS AND METHODS:

2.1 Materials:

Capsaicin (≥95 % purity) was procured from Sigma-Aldrich (St. Louis, USA). Cold-pressed sesame oil and steam-distilled clove oil (eugenol ≥75 %) were obtained from Neeta Essential Oils (Mumbai, India). Soy lecithin (Lipoid S-75) was supplied as a gift sample by Lipoid GmbH (Ludwigshafen, Germany). Tween 80, ethanol (HPLC grade), propylene glycol, cellulose dialysis membrane (MWCO 12 kDa) and other reagents of analytical grade were purchased from HiMedia (Mumbai, India) [23].

2.2 Solubility screening:

Equilibrium solubility of capsaicin was measured in candidate oils (sesame, clove, olive, castor and oleic acid), surfactants (Tween 80, soy lecithin and Span 80) and cosurfactants (ethanol, propylene glycol and PEG-400) by adding excess drug to 2 mL of each vehicle, vortexing for 5 min and shaking at 100 rpm for 72 h at 25 ± 1 °C. Supernatants were centrifuged (10,000 rpm, 15 min), diluted with methanol and quantified at 281 nm on a UV–visible spectrophotometer (Shimadzu UV-1900, Japan) [25,26].

2.3 Pseudoternary phase diagrams:

Soy lecithin (surfactant) and ethanol (cosurfactant) were blended at S_{mix} weight ratios of 1:0, 1:1, 2:1, 3:1 and 4:1. For each ratio, S_{mix} was mixed with a sesame:clove oil blend (9:1) in oil:S_{mix} proportions from 1:9 to 9:1 and titrated dropwise with double-distilled water under magnetic stirring at room temperature. The first appearance of turbidity was recorded as the phase boundary, and nanoemulsion regions were plotted using CHEMIX Ternary Plot software (v3.5) [26].

2.4 Preparation of capsaicin nanoemulsion:

Five formulations (F1–F5) were prepared by the low-energy aqueous phase-titration method. Capsaicin (0.075 % w/w) was first dissolved in the oil phase, followed by addition of S_{mix} under magnetic stirring at 500 rpm for 10 min. The aqueous phase was added dropwise and the system homogenised at 8000 rpm for 5 min using an IKA T25 Ultra-Turrax homogeniser to obtain a clear nanoemulsion [16,29].

2.5 Physicochemical characterization:

Droplet size, polydispersity index (PDI) and zeta potential were measured by dynamic light scattering (Malvern Zetasizer Nano ZS, UK) after 1:100 dilution with 0.22 µm-filtered water. Morphology was visualised by transmission electron microscopy (JEOL JEM-2100) following negative staining with 2 % phosphotungstic acid. Viscosity was measured on a Brookfield DV-II+ viscometer at 25 °C, pH with a calibrated digital pH-meter and refractive index on an Abbe refractometer. Capsaicin content was determined by reverse-phase HPLC on a C18 column (mobile phase methanol:water 70:30 v/v, flow 1.0 mL/min, detection at 281 nm) [16].

2.6 In vitro drug release:

In vitro release was evaluated by the dialysis-bag method. A 2 mL sample containing 1.5 mg of

capsaicin was sealed in pre-soaked cellulose membrane and immersed in 50 mL of phosphate-buffered saline (pH 6.8) containing 1 % Tween 80 at 37 ± 0.5 °C with stirring at 100 rpm. Aliquots (1 mL) were withdrawn at predefined intervals up to 24 h and replaced with fresh medium. Release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas kinetic models [27,28].

2.7 Ex vivo skin permeation:

Full-thickness abdominal skin of male Wistar rats, obtained after euthanasia under protocols approved by the Institutional Animal Ethics Committee (IAEC/2024/17), was mounted on vertical Franz diffusion cells (effective area 2.54 cm²) with the stratum corneum facing the donor compartment. The receptor was filled with phosphate-buffered saline containing 30 % PEG-400 and maintained at 37 ± 0.5 °C under magnetic stirring. A 1 mL dose of nanoemulsion, 0.075 % conventional cream or drug suspension was placed on the donor side; samples were withdrawn over 24 h and analysed by HPLC. Steady-state flux (J_{ss}) and permeability coefficient (K_p) were calculated from the linear portion of the cumulative amount–time profile [33,34].

2.8 Skin irritation study:

Modified Draize scoring was performed on six Wistar rats. The dorsal area (2 × 2 cm²) was shaved 24 h before application; 0.5 g of optimised nanoemulsion or conventional cream was applied and covered with occlusive dressing for 72 h. Erythema and oedema were graded on a 0–4 scale at 24, 48 and 72 h according to OECD Test Guideline 404 [30].

2.9 In vivo analgesic activity:

Analgesic activity was assessed by the hot-plate method [31]. Thirty Wistar rats (150–200 g) were randomised into five groups (n = 6): untreated control, placebo (drug-free) nanoemulsion, conventional capsaicin cream, optimised capsaicin nanoemulsion (F3) and diclofenac 1 % gel (standard). A single dose (0.5 g) was applied to the hind-paw skin; reaction latency (paw-lick or jump) was recorded on a hot plate at 55 ± 0.5 °C at 0, 30, 60, 90, 120, 180 and 240 min with a 25 s cut-off to prevent thermal injury.

2.10 Stability studies:

The optimised formulation was stored at 4 °C, 25 °C/60 % RH and 40 °C/75 % RH for 90 days as per ICH Q1A(R2) guidelines. Droplet size, PDI, pH and drug content were re-measured on days 0, 30 and 90 [32].

2.11 Statistical analysis:

All data are expressed as mean ± SD. Differences were analysed by one-way ANOVA followed by Tukey's post-hoc test using GraphPad Prism v9.0. A probability (p) value below 0.05 was considered statistically significant.

3. RESULTS:

3.1 Solubility screening and selection of components

Capsaicin exhibited the highest solubility in sesame oil (42.6 ± 1.8 mg/mL) among all plant oils tested, followed by clove oil (38.4 ± 2.1 mg/mL) (Table 1). Among natural surfactants, soy lecithin (22.8 ± 1.1 mg/mL) was selected in preference to Tween 80 in keeping with the plant-based design. Ethanol provided the highest cosurfactant solubility (65.2 ± 2.4 mg/mL). A sesame:clove oil blend (9:1) was adopted as the oil phase, balancing maximum solubilisation with the expected synergistic TRPV1/TRPA1 activity of eugenol with capsaicin.

Table 1. Equilibrium solubility of capsaicin in plant-derived vehicles (mean ± SD, n = 3).

Component	Category	Solubility (mg/mL)	Observation
Sesame oil	Oil	42.6 ± 1.8	Selected (highest in oil)
Clove oil	Oil	38.4 ± 2.1	Co-selected (10%)
Olive oil	Oil	18.7 ± 1.2	Rejected
Castor oil	Oil	24.3 ± 1.5	Rejected
Oleic acid	Oil	31.2 ± 1.7	Rejected
Soy lecithin	Surfactant	22.8 ± 1.1	Selected
Tween 80	Surfactant	48.5 ± 2.0	Rejected (synthetic)
Span 80	Surfactant	19.6 ± 1.0	Rejected
Ethanol	Cosurfactant	65.2 ± 2.4	Selected
Propylene glycol	Cosurfactant	34.8 ± 1.8	Rejected
PEG-400	Cosurfactant	42.1 ± 1.9	Rejected

3.2 Phase behaviour and formulation optimization:

Pseudoternary phase diagrams showed that the widest nanoemulsion region was obtained with the lecithin:ethanol 2:1 S_{mix}. Five representative compositions were prepared (Table 2). As shown in Figure 1, droplet size and PDI decreased sharply from the 1:0 S_{mix} ratio to 2:1 and then increased again at higher ratios. F3 (S_{mix} 2:1; oil 10 %, S_{mix} 35 %, water 55 %) produced the smallest droplets (98.4 ± 4.2 nm) with the lowest PDI (0.186), indicating a mono-disperse system and was selected for further study.

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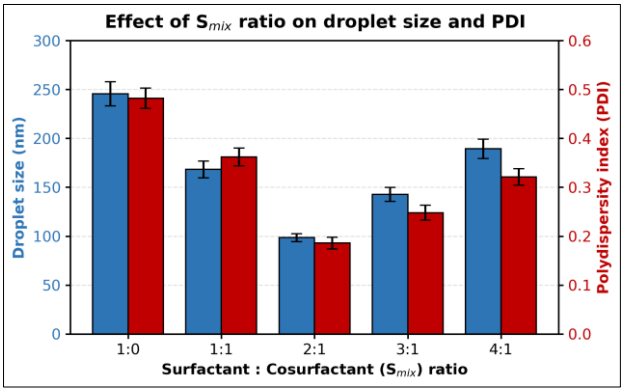

Figure 1. Effect of surfactant:cosurfactant (S_{mix}) ratio on droplet size (blue) and polydispersity index (red) of capsaicin nanoemulsions. Values are mean ± SD (n = 3).

Table 2. Composition and physicochemical parameters of capsaicin nanoemulsion formulations F1–F5.

Formulation	S_{mix} ratio	Oil (%)	S_{mix} (%)	Droplet size (nm)	PDI	Zeta potential (mV)
F1	1:0	10	35	245.6 ± 12.3	0.482 ± 0.021	−21.4 ± 1.6
F2	1:1	10	35	168.2 ± 8.5	0.362 ± 0.018	−24.8 ± 1.3
F3	2:1	10	35	98.4 ± 4.2	0.186 ± 0.012	−28.6 ± 1.4
F4	3:1	10	35	142.7 ± 7.1	0.248 ± 0.015	−26.1 ± 1.2
F5	4:1	10	35	189.3 ± 9.8	0.321 ± 0.017	−23.7 ± 1.5

3.3 Physicochemical characterisation of the optimised formulation:

F3 was transparent with a bluish reflection, a zeta potential of −28.6 ± 1.4 mV, refractive index of 1.368 ± 0.002 and pH 5.8 ± 0.1, all within acceptable ranges for dermal application. Viscosity was 24.6 ± 0.8 cP, allowing easy spreadability on skin. TEM images confirmed discrete spherical droplets consistent with the DLS size. Drug content was 98.6 ± 1.2 % and entrapment efficiency 94.2 ± 2.1 %.

3.4 In vitro release behavior:

As shown in Figure 2, F3 released 94.2 ± 2.6 % of its capsaicin payload over 24 h, significantly greater ($p < 0.001$) than the conventional cream (52.1 ± 2.8 %) and drug suspension (25.4 ± 2.1 %). Release followed Higuchi kinetics (R^2 = 0.986), with a Korsmeyer–Peppas release exponent n = 0.46, indicative of anomalous non-Fickian diffusion.

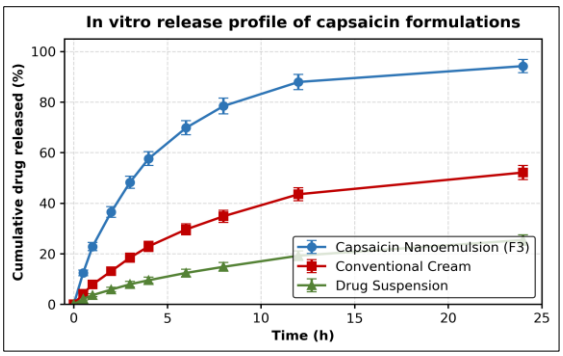

Figure 2. In vitro cumulative release profile of capsaicin from optimised nanoemulsion (F3), conventional cream and drug suspension in phosphate-buffered saline (pH 6.8) at 37 °C. Values are mean ± SD (n = 3).

3.5 Ex vivo skin permeation:

Cumulative amount of capsaicin permeating across rat skin at 24 h (Figure 3) was 612.4 ± 18.6 µg/cm² for F3, which was 2.80-fold and 7.41-fold greater than conventional cream (218.5 ± 11.2 µg/cm²) and drug suspension (82.6 ± 6.8 µg/cm²), respectively. Steady-state flux (J_{ss}) increased from 9.4 ± 0.7 µg/cm²/h (cream) to 26.8 ± 1.3 µg/cm²/h (F3), giving an enhancement ratio of 2.85; permeability coefficient (K_p) rose from 1.25 × 10^{-3} to 3.57 × 10^{-3} cm/h.

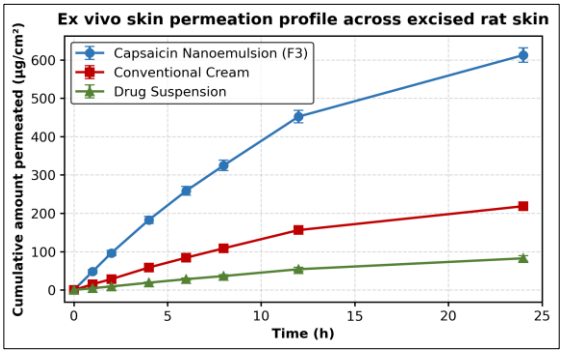

Figure 3. Ex vivo skin permeation of capsaicin across excised rat skin using Franz diffusion cells. Values are mean ± SD (n = 3).

3.6 Skin irritation

No erythema or oedema was observed in any animal over 72 h following F3 application; the Draize Primary Irritation Index was 0.17, classifying the formulation as non-irritant (PII < 2). In contrast, the conventional capsaicin cream produced mild but reproducible erythema (PII = 1.33), suggesting that nano-encapsulation mitigates direct stimulation of nociceptive terminals in the upper epidermis.

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3.7 In vivo analgesic activity:

As shown in Figure 4, F3 produced a rapid and significant ($p < 0.01$ vs control) increase in paw-withdrawal latency, reaching a peak of 15.2 ± 1.0 s at 120 min—about 3.1-fold above baseline and statistically comparable to diclofenac 1 % gel (14.8 ± 0.9 s, $p > 0.05$). The conventional cream produced a weaker peak effect (9.1 ± 0.7 s at 90 min). Importantly, analgesia from F3 was sustained up to 240 min (11.4 ± 0.7 s), while the cream group had declined to near-baseline by that time. The placebo nanoemulsion showed no significant change from control, ruling out a vehicle effect.

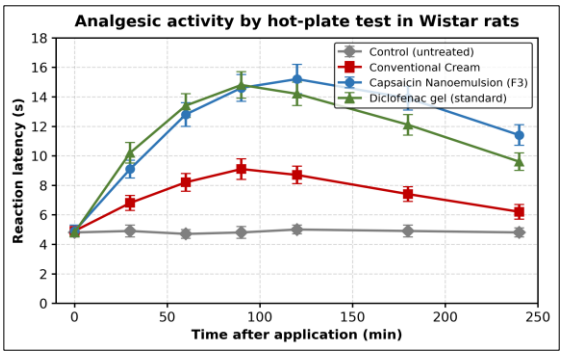

Figure 4. Analgesic activity determined by hot-plate test in Wistar rats. Values are mean ± SD (n = 6).

3.8 Stability:

F3 remained transparent and phase-stable at 4 °C and 25 °C for 90 days, with less than 5 % variation in droplet size and drug content (Table 3). At 40 °C/75 % RH, a modest increase in droplet size (98.4 → 112.6 nm) and a 6.8 % reduction in drug content were observed, still within pharmacopoeial limits.

Table 3. Stability profile of optimised capsaicin nanoemulsion (F3) under ICH Q1A(R2) conditions.

Condition	Time (days)	Droplet size (nm)	PDI	Drug content (%)
Initial	0	98.4 ± 4.2	0.186 ± 0.012	98.6 ± 1.2
4 °C	30	99.8 ± 4.6	0.192 ± 0.014	98.1 ± 1.3
4 °C	90	101.6 ± 5.1	0.198 ± 0.015	97.2 ± 1.4
25 °C/60% RH	30	100.4 ± 4.8	0.201 ± 0.015	97.6 ± 1.5
25 °C/60% RH	90	103.2 ± 5.3	0.214 ± 0.017	95.8 ± 1.7
40 °C/75% RH	30	106.8 ± 5.6	0.232 ± 0.018	94.8 ± 1.8
40 °C/75% RH	90	112.6 ± 6.2	0.268 ± 0.021	91.8 ± 2.1

4. DISCUSSION:

The present study demonstrates the feasibility of producing a capsaicin nanoemulsion exclusively from plant-derived components for enhanced topical analgesic activity. The selection of sesame oil as the principal lipid phase is supported by its high capsaicin solubilisation capacity and its intrinsic antioxidant/anti-inflammatory activity arising from sesamol and sesamin [19,20]. Inclusion of 10 % clove oil was rationalised by eugenol's ability to co-activate TRPV1 and TRPA1 channels, producing a synergistic defunctionalisation of nociceptors and a known penetration-enhancing action on the stratum corneum [21,22].

Low-energy emulsification with lecithin:ethanol 2:1 yielded droplets of approximately 98 nm with a narrow size distribution. The non-linear relationship between droplet size and S_{mix} ratio is well documented: insufficient surfactant cannot stabilise the newly formed interface, while excess surfactant destabilises the system through Ostwald ripening and micellar phase transitions, as observed in our F4 and F5 [14,15,26]. The measured zeta potential of −28.6 mV exceeds the ±25 mV threshold generally accepted for electrostatic stabilisation and is consistent with the phosphate head-groups of phosphatidylcholine and the free fatty acids of sesame oil [23,24].

Drug release from F3 followed Higuchi kinetics with an anomalous diffusion exponent ($n = 0.46$), suggesting capsaicin partitioning from oil droplets through the dialysis membrane rather than bulk erosion [27,28]. The 1.8-fold faster release relative to the conventional cream is attributable to the very large interfacial area of nanoscale droplets and the solubilised state of the drug [16,33].

The 2.80-fold enhancement in ex vivo skin permeation is clinically meaningful. Nanoemulsion-mediated permeation proceeds by three complementary mechanisms: (i) increased thermodynamic activity of drug in the nanodroplets; (ii) fluidisation of intercellular stratum-corneum lipids by surfactant and ethanol; and (iii) direct deposition of droplets in skin appendages [17,35]. Lecithin integrates into the lamellar organisation of the stratum corneum while ethanol reversibly extracts lipids, together producing a non-toxic transient enhancement of permeability [23,36]. The linoleic acid content of sesame oil further fluidises ceramide-rich domains, adding to the overall enhancement [19,20].

The increase in paw-withdrawal latency and its sustained profile over 4 h are consistent with the pharmacokinetic advantage anticipated for nanoemulsions—higher and more uniform

cutaneous concentrations of capsaicin [37]. The comparable efficacy to diclofenac 1 % gel is notable, because capsaicin acts through a mechanistically distinct pathway (TRPV1 desensitisation) and may be complementary to NSAIDs in multimodal pain management [7,8]. The slower decline from peak analgesia than with the conventional cream suggests a depot effect of the nanoemulsion within the stratum corneum [37,38].

An apparent paradox is that F3 produced more drug in the skin yet caused no irritation, while the less-efficient cream produced mild erythema. This is consistent with prior reports that encapsulation masks direct contact of free capsaicin with the superficial epidermis while still allowing gradual release to deeper nociceptive fibres [12,38]. The net outcome is improved efficacy with reduced stinging/burning, a feature likely to enhance patient adherence in chronic therapy.

Physical and chemical stability of the formulation for 90 days at room temperature reflects combined electrostatic and steric stabilisation provided by the phospholipid film. Modest droplet growth at 40 °C suggests storage below 30 °C, readily achievable with conventional packaging. Limitations of the present work include the use of rat skin, which differs from human skin in follicle density and lipid composition [33,36], and the use of an acute thermal model that does not fully reflect neuropathic pain conditions for which capsaicin is clinically indicated. Future work will include human cadaver-skin permeation, chronic constriction-injury models and dermal pharmacokinetic analysis.

5. CONCLUSION:

A capsaicin-loaded nanoemulsion was successfully developed from entirely plant-derived components—sesame oil, clove oil, soy lecithin and ethanol—using a simple low-energy aqueous phase-titration method. The optimised system (F3) showed a droplet size below 100 nm, narrow distribution, high entrapment efficiency, good zeta potential and 90-day physicochemical stability. Compared with a conventional cream it produced 2.80-fold higher skin permeation, significantly greater and more sustained analgesia in the hot-plate model and, remarkably, a complete absence of skin irritation. These findings show that green, plant-based nanoemulsions can overcome the solubility, permeation and irritation limitations of capsaicin while exploiting the intrinsic anti-inflammatory and penetration-enhancing properties of natural oils. The platform is a promising candidate for further preclinical neuropathic-pain studies, scale-up using microfluidisation and eventual clinical evaluation.

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