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Research Article

D-Optimal Mixture Design Optimization of Curcumin SNEDDS and Its Development into an Antioxidant Gel

Emmellia Yunitha[1*], Ilham Kuncahyo[2], Nuraini Harmastuti[3]

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Curcumin is a natural polyphenol with high antioxidant capacity, but its topical use is restricted by poor aqueous solubility, low stability and limited skin permeability. This study developed a curcumin self-nanoemulsifying drug delivery system (SNEDDS), optimised its composition with a D-optimal mixture design, and incorporated the optimum system into a hydrogel. Isopropyl myristate (IPM, 10–20%), Cremophor RH 40 (40–70%) and Transcutol P (10–40%) served as the oil, surfactant and co-surfactant. Sixteen design runs were characterised for droplet size, emulsification time, transmittance, drug loading, polydispersity index and zeta potential; models were fitted in Design-Expert 13 and the optimum composition was selected using the desirability function. All six response models were significant ($p<0.05$) with a non-significant lack of fit ($p>0.05$). The optimum composition was IPM 19.91%, Cremophor RH 40 70.00% and Transcutol P 10.08% (desirability 0.777), giving a droplet size of 44.25 nm, an emulsification time of 32.64 s, a transmittance of 93.20%, a drug loading of 22.84 mg/mL and a zeta potential of −12.66 mV, with no significant difference from the predicted values ($p>0.05$). The resulting gel was homogeneous, with pH 5.14±0.02, viscosity 26,330±1.54 cP, adhesion 5.95±0.47 s and spreadability 5.66±0.03 cm, and remained stable over six freeze–thaw cycles. DPPH assay gave an IC_{50} of 8.73±0.004 µg/mL (AAI 4.52) for the SNEDDS gel versus 12.62±0.033 µg/mL (AAI 3.13) for the conventional gel. Franz diffusion showed a 49.1% higher flux and 79.3% higher cumulative diffusion at 120 min for the SNEDDS gel.

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The skin is the largest organ of the human body and the first barrier against mechanical injury, pathogens and chemicals. Because it is directly exposed to sunlight, the skin is continuously challenged by ultraviolet radiation (UVR), of which roughly 95% is UVA and 5% is UVB. Chronic exposure induces a spectrum of dermatological consequences ranging from hyperpigmentation and erythema to malignant melanoma and accelerated photoaging [1].

Photoaging is driven largely by the accumulation of reactive oxygen species (ROS), which produce oxidative stress that damages cutaneous DNA, lipids and proteins [2]. ROS generated after UV exposure activate matrix metalloproteinases that degrade collagen and elastin [3, 4], while cellular senescence contributes further to loss of elasticity

[1,2,3] Master Programme in Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Setia Budi, Surakarta, Central Java, Indonesia

*Corresponding author: r272410385@mhs.setiabudi.ac.id

and hydration; clinically this is expressed as skin thinning, wrinkling and reduced glandular function [5]. Antioxidant compounds, which inactivate free radicals and interrupt oxidative chain reactions, are therefore a rational active ingredient class for protecting the skin against premature ageing [6].

Curcumin, the principal curcuminoid of Curcuma longa rhizomes, is a hydrophobic polyphenol (diferuloylmethane) with a well-documented safety profile and a broad bioactivity spectrum that includes anti-inflammatory, antimicrobial and anticancer effects. Its antioxidant action operates through two complementary routes: direct scavenging of free radicals and modulation of cell-signalling pathways that upregulate endogenous antioxidant enzymes such as glutathione S-transferase and heme oxygenase-1 [7]. Despite this potential, the therapeutic use of curcumin is constrained by very low aqueous solubility and poor permeability, so that only a small fraction of an applied dose reaches its site of action [8]. Topical formulations therefore need a carrier that keeps curcumin in a dissolved, permeation-ready state; clay-based hydrogels [9] and self-nanoemulsifying systems [10] have both been proposed for this purpose.

A self-nanoemulsifying drug delivery system (SNEDDS) is an anhydrous isotropic mixture of oil, surfactant and co-surfactant that emulsifies spontaneously into an oil-in-water nanoemulsion on contact with an aqueous medium, producing droplets of roughly 20–200 nm [11, 12]. The very large interfacial area of these droplets increases the dissolved fraction of a lipophilic drug and shortens the diffusion path, while several excipients act simultaneously as penetration enhancers. Isopropyl myristate (IPM) was selected as the oil phase because its polarity gives a high curcumin solubilising capacity and its low viscosity favours spontaneous emulsification [13, 14]. Cremophor RH 40 was chosen as surfactant for its high hydrophilic–lipophilic balance (14–16), which suits the formation of clear, thermodynamically stable o/w nanoemulsions [15, 16]. Transcutol P was used as co-surfactant because it inserts into the interfacial film, increases its fluidity and additionally enhances membrane permeability [17, 18].

The performance of a SNEDDS depends critically on the ratio between these three components, and one-factor-at-a-time screening cannot resolve their interactions. A Quality-by-Design approach based on the D-optimal mixture design is therefore preferred: unlike a simplex-lattice or factorial design, the D-optimal algorithm places experimental points inside an irregular, constrained design space and maximises the determinant of the information matrix, so that accurate polynomial models are obtained from a minimal number of runs [19, 20]. The approach has been applied successfully to curcumin and to other poorly soluble actives [21, 22, 23].

Although several curcumin SNEDDS have been reported, most were developed for oral delivery, and studies that carry an optimised SNEDDS forward into a finished topical gel and then compare it head-to-head with a conventional gel for both radical-scavenging capacity and in vitro release remain scarce. The present work therefore had three aims: to model the effect of the IPM–Cremophor RH 40–Transcutol P ratio on six critical quality attributes of curcumin SNEDDS using a D-optimal mixture design; to determine and verify the optimum composition through the desirability function; and to evaluate the physical quality, DPPH antioxidant activity and Franz-cell diffusion profile of the gel prepared from that optimum system relative to a conventional curcumin gel.

Results and Discussion

Identity of the curcumin raw material and validation of the analytical method

Fourier-transform infrared spectroscopy was used to confirm the identity of the curcumin raw material before formulation. The spectrum showed a broad band at 3510.00 cm^{-1} assigned to hydrogen-bonded phenolic O–H stretching, an intense band at 1627.92 cm^{-1} corresponding to the conjugated carbonyl of the characteristic keto–enol tautomer,

and aromatic and aliphatic C=C stretching at 1573.91 and 1512.25 cm^{-1}. In the fingerprint region, C–H bending and in-plane phenolic O–H vibrations appeared at 1456.26 and 1377.17 cm^{-1}, aromatic C–O and C–O–C stretching at 1273.00 and 1116.78 cm^{-1}, and the out-of-plane C–H bending of the trans-alkene bridge at 962.48 cm^{-1}. This pattern is consistent with the phenol, β-diketone and aromatic functionalities expected for curcumin and confirms the identity of the material used.

The analytical method used throughout the study was validated beforehand. Curcumin in methanol p.a. showed an absorption maximum at 421 nm with no interference from the solvent, and absorbance became constant between 50 and 60 min after dilution, which was adopted as the operating time. Calibration over 2–10 µg/mL was linear with a correlation coefficient of 0.9999 [24]. Recovery at three concentration levels averaged 99.65%, within the 98–102% acceptance range, and the relative standard deviation of six replicate measurements was 0.3%, below the 2% limit. The limit of detection and limit of quantification were 0.115 and 0.347 µg/mL respectively, with a V_{x0} of 1.91% [25]. The method was therefore specific, linear, accurate and precise enough to support the quantitative work reported below.

Effect of the component ratio on SNEDDS characteristics

Sixteen SNEDDS were prepared according to the D-optimal mixture design and characterised for six responses (Table 1). Droplet size varied over almost two orders of magnitude, from 76.57 nm (run 13) to 2,719.67 nm (run 1), emulsification time from 9.00 to 48.00 s, transmittance from 58.40 to 95.41%, drug loading from 18.20 to 23.58 mg/mL, polydispersity index from 0.1947 to 0.3180, and zeta potential from −6.68 to −13.48 mV. This wide spread confirms that the ratio of oil, surfactant and co-surfactant, rather than their absolute amounts, governs the quality of the nanoemulsion that forms on dilution.

Each response was fitted in Design-Expert 13. Droplet size required a full cubic model, whereas the remaining five responses were adequately described by linear mixture models. The fit statistics are summarised in Table 2 and the corresponding equations, in which A, B and C denote the proportions of IPM, Cremophor RH 40 and Transcutol P respectively, are given below:

Y_1 (droplet size, nm) = $1.240\times10^6A - 7{,}804.97B + 3{,}894.94C - 2.104\times10^6AB - 2.141\times10^6AC + 12{,}568.55BC + 1.867\times10^6ABC - 9.633\times10^5AB(A-B) - 9.434\times10^5AC(A-C) + 28{,}040.60BC(B-C)$

Y_2 (emulsification time, s) = $92.37A + 12.96B - 22.26C$

Y_3 (transmittance, %) = $130.96A + 80.84B + 69.14C$

Y_4 (drug loading, mg/mL) = $38.0792A + 19.9305B + 13.4627C$

Y_5 (polydispersity index) = $0.6644A + 0.2345B + 0.1425C$

Y_6 (zeta potential, mV) = $-25.9702A - 10.8894B + 0.7924C$

All six models were statistically significant ($p<0.05$) and none showed a significant lack of fit ($p>0.05$), indicating that the fitted surfaces describe the experimental data without systematic deviation. The droplet-size model was by far the strongest ($F = 10.66$; $p = 0.0047$; $R^2 = 0.9412$), and every binary and ternary interaction term in it was significant, which demonstrates that droplet formation is governed by the combined behaviour of the three components rather than by any of them alone [26]. The gap between adjusted and predicted R^2 exceeded 0.20 for this response, so its predictive capability should be interpreted with care; the adequate-precision value of 12.5352, however, is well above the threshold of 4 and confirms a sufficient signal-to-noise ratio for navigating the design space

Table 1. Composition of the sixteen D-optimal mixture design runs and the resulting SNEDDS responses

Run	IPM (%)	Cremophor RH 40 (%)	Transcutol P (%)	Droplet size (nm)	Emulsification time (s)	Transmittance (%)	Drug loading (mg/mL)	PDI	Zeta potential (mV)
1	12.50	63.75	23.75	2,719.67	34.23	83.35	21.40	0.2778	−11.81
2	20.00	55.00	25.00	566.87	41.19	80.23	20.03	0.2674	−12.01
3	10.00	70.00	20.00	169.83	12.00	82.92	21.10	0.2764	−13.48
4	17.50	63.75	18.75	96.93	40.27	82.48	20.90	0.2749	−11.14
5	20.00	40.00	40.00	98.44	35.00	81.12	20.51	0.2764	−8.67
6	20.00	40.00	40.00	183.47	36.00	81.14	20.61	0.2705	−8.58
7	10.00	50.00	40.00	285.70	14.00	80.44	20.13	0.2681	−7.61
8	20.00	70.00	10.00	182.27	15.00	95.41	23.58	0.3180	−13.48
9	20.00	70.00	10.00	154.10	38.82	95.00	22.90	0.3167	−8.77
10	15.00	70.00	15.00	119.03	12.50	94.97	22.70	0.3166	−9.11
11	20.00	55.00	25.00	403.53	48.00	95.05	23.21	0.3168	−13.48
12	15.00	51.25	33.75	141.63	21.76	95.03	23.18	0.3168	−13.44
13	10.00	70.00	20.00	76.57	9.00	58.40	18.20	0.1947	−6.68
14	15.00	45.00	40.00	77.50	33.50	72.12	19.10	0.2404	−7.45
15	10.00	50.00	40.00	1,148.80	11.00	73.01	19.21	0.2436	−7.88
16	10.00	60.00	30.00	1,103.47	36.89	69.93	18.70	0.2331	−7.20

For the five linear responses the explanatory power was more modest (R^2 between 0.3701 and 0.4541), but all adequate-precision values exceeded 4 and, except for droplet size, the difference between adjusted and predicted R^2 remained below or close to 0.20. The coefficients of variation were low for transmittance (10.80%), polydispersity index (10.73%) and drug loading (6.56%), and higher for emulsification time (39.90%) and zeta potential (21.70%). The elevated coefficient of variation for zeta potential is largely an artefact of its small mean value (−10.05 mV), which inflates the ratio of standard deviation to mean even when the absolute scatter is modest; for emulsification time it reflects genuine run-to-run variability in a manually timed endpoint. Model evaluation was therefore based on the combination of analysis of variance, lack of fit, the three R^2 statistics and adequate precision rather than on any single parameter.

Table 2. Fit statistics of the mixture models for the six SNEDDS responses

Response	Model	F-value	p-value	Lack of fit (p)	R^2	Adj. R^2	Pred. R^2	Adeq. precision	CV (%)
Droplet size	Full cubic	10.66	0.0047	0.5900	0.9412	0.8529	0.5695	12.5352	nd
Emulsification time	Linear	4.54	0.0320	0.1687	0.4112	0.3206	0.1157	5.1683	39.90
Transmittance	Linear	4.48	0.0331	0.6032	0.4080	0.3170	0.1318	5.5218	10.80
Drug loading	Linear	5.41	0.0195	0.5636	0.4541	0.3702	0.2374	6.3097	6.56
Polydispersity index	Linear	4.57	0.0315	0.6126	0.4126	0.3223	0.1398	5.5156	10.73
Zeta potential	Linear	3.82	0.0496	0.6370	0.3701	0.2732	0.1021	5.3076	21.70

nd = not reported. A model is significant at $p<0.05$; a lack of fit is acceptable at $p>0.05$; adequate precision should exceed 4.

The signs of the model coefficients are mechanistically coherent. IPM carried a large positive coefficient for droplet size and the dominant positive coefficient for emulsification time (+92.37), because a larger oil fraction presents more interfacial area that must be covered by surfactant; if the surfactant supply is not increased in proportion, coarser droplets form and dispersion takes longer [18]. Cremophor RH 40 carried a negative coefficient for droplet size, consistent with its role in lowering oil–water interfacial tension and making droplet break-up more efficient. Transcutol P shortened the emulsification time (−22.26), which is attributable to its insertion into the interfacial film and the resulting increase in film fluidity [21]. All three components raised transmittance and drug loading, IPM most

strongly, reflecting the high solubilising capacity of the oil phase for curcumin and the greater optical clarity of systems that disperse into small droplets [27]. Both IPM and Cremophor RH 40 shifted the zeta potential in the negative direction, which for a non-ionic surfactant system is normally ascribed to adsorption of hydroxyl ions and free fatty acid residues at the droplet interface [28].

The contour plots in Figure 1 present these relationships graphically. In Figure 1a the blue region, corresponding to the smallest droplets, occupies the part of the design space where oil, surfactant and co-surfactant are balanced, whereas the yellow-to-red region of coarse droplets lies where the composition is unbalanced. Figure 1b shows emulsification times shortening as the IPM proportion falls and the combined Cremophor RH 40 and Transcutol P proportion rises. Figure 1c shows transmittance increasing towards the higher-IPM corner, in agreement with the positive coefficients of Y_3. Figure 1d overlays all six responses through the desirability function.

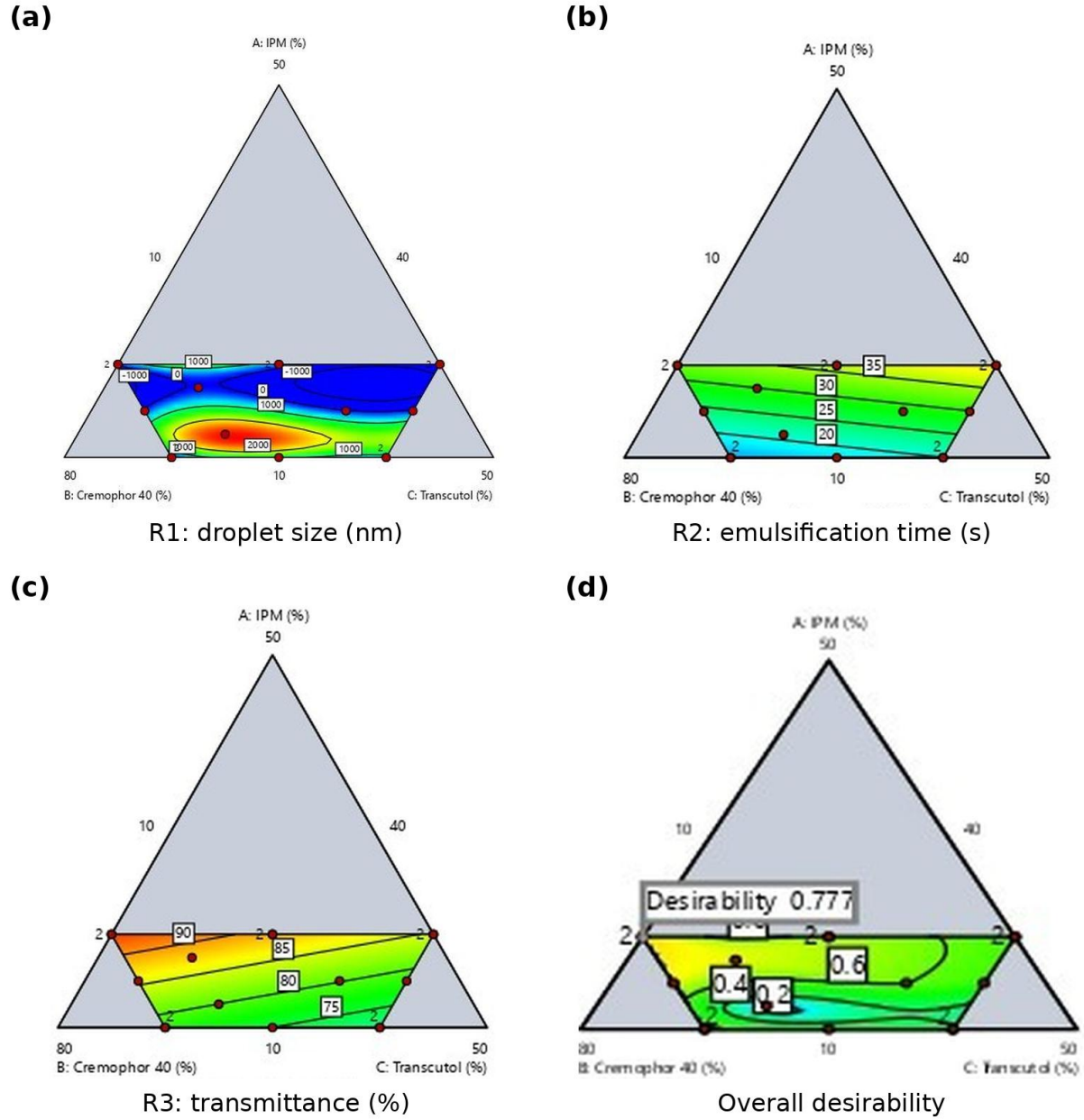


Figure 1. Contour plots of the D-optimal mixture design for (a) droplet size, (b) emulsification time, (c) percentage transmittance and (d) the overall desirability function. A = isopropyl myristate, B = Cremophor RH 40, C = Transcutol P.

Determination and verification of the optimum formulation

Numerical optimisation was set to minimise droplet size, emulsification time and polydispersity index while maximising transmittance and drug loading and driving the zeta potential away from neutrality. The desirability function condenses these competing targets into a single value between 0 and 1, and the best compromise reached a desirability of 0.777 (Figure 1d), which is high enough to treat the corresponding composition as the optimum for experimental verification [29].

The optimum composition consisted of IPM 19.91%, Cremophor RH 40 70.00% and Transcutol P 10.08%. This lies at the surfactant-rich boundary of the design space, which is consistent with the models: a high Cremophor RH 40 proportion minimises droplet size and maximises both transmittance and drug loading, while the IPM proportion is held near its upper bound to sustain curcumin solubility without allowing droplet size and emulsification time to rise excessively. The formulation was reproduced in triplicate and re-characterised (Table 3). It gave a droplet size of 44.25 nm, well within the nanoemulsion range and smaller than any individual design run, an emulsification time of 32.64 s, a transmittance of 93.20%, a drug loading of 22.84 mg/mL and a zeta potential of −12.66 mV. No phase separation or drug precipitation was observed, and the observed values did not differ significantly from those predicted by the models ($p>0.05$), confirming the validity of the design.

The polydispersity index of the optimum system was consistent with the narrow size distribution expected of a system in this droplet-size range, and the moderately negative zeta potential indicates electrostatic repulsion sufficient to retard coalescence in a non-ionic surfactant system, where steric stabilisation by the polyoxyethylene chains of Cremophor RH 40 provides the dominant stabilising mechanism [30, 31].

Table 3. Composition and measured characteristics of the optimum curcumin SNEDDS

Parameter	Optimum formulation
IPM (%)	19.91
Cremophor RH 40 (%)	70.00
Transcutol P (%)	10.08
Desirability	0.777
Droplet size (nm)	44.25
Emulsification time (s)	32.64
Transmittance (%)	93.20
Drug loading (mg/mL)	22.84
Zeta potential (mV)	−12.66

Physical quality of the gels

The optimum SNEDDS was incorporated into an HPMC-based hydrogel and compared with a conventional gel containing the same nominal amount of unformulated curcumin (Table 4). Both gels were orange with the characteristic odour of curcumin and a semisolid consistency, indicating that neither the nanoemulsifying system nor the polymer matrix disturbed the conjugated chromophore of the curcuminoid structure.

The two preparations differed clearly in homogeneity. The SNEDDS gel was homogeneous, whereas the conventional gel was not. Curcumin added directly to a hydrophilic gel base cannot dissolve in it and aggregates into coarse crystalline particles that disperse unevenly through the polymer network. In the SNEDDS gel the drug is already dissolved in the oil core of droplets stabilised by surfactant and co-surfactant, and at the nanometre scale Brownian motion prevents coalescence and phase separation, so the droplets remain uniformly distributed. Homogeneity is not a cosmetic detail: it determines content uniformity and therefore the consistency of the delivered dose, and a poorly homogeneous gel risks dose variability and local irritation from aggregated crystals.

Both gels had a pH within the 4.5–6.5 range specified for topical preparations (SNI 06-2588), at 5.14±0.02 for the SNEDDS gel and 5.41±0.31 for the conventional gel, with no significant difference between them ($p>0.05$). Viscosity was higher for the SNEDDS gel (26,330±1.54 cP versus 24,460±0.60 cP),

which is attributable to the dispersed lipid and surfactant components increasing the structural density and flow resistance of the matrix. The adhesion time of both gels exceeded the 4 s minimum, the SNEDDS gel adhering longer (5.95±0.47 s versus 5.35±0.05 s) and therefore offering a longer contact time for permeation. Under a 150 g load both gels spread within the ideal 5–7 cm range, at 5.66±0.03 cm and 5.51±0.02 cm respectively [32].

Over six freeze–thaw cycles between 4 °C and 40 °C, neither preparation showed phase separation, and pH and viscosity were essentially unchanged — pH moved from 4.93±0.39 to 5.14±0.02 for the SNEDDS gel and from 5.13±0.10 to 5.05±0.19 for the conventional gel, while viscosity remained at approximately 26,300 cP for both. The formulations were therefore physically and chemically stable under accelerated thermal cycling [33].

Table 4. Physical quality of the curcumin SNEDDS gel and the conventional curcumin gel

Parameter	SNEDDS gel	Conventional gel
Appearance	Orange, characteristic odour, semisolid	Orange, characteristic odour, semisolid
Homogeneity	Homogeneous	Not homogeneous
pH	5.14±0.02	5.41±0.31
Viscosity (cP)	26,330±1.54	24,460±0.60
Adhesion (s)	5.95±0.47	5.35±0.05
Spread, 50 g (cm)	3.23±0.25	4.00±0.02
Spread, 100 g (cm)	4.30±0.25	4.02±0.02
Spread, 150 g (cm)	5.66±0.03	5.51±0.02

Antioxidant activity

Radical-scavenging capacity was assessed with the DPPH assay and expressed both as IC_{50} and as the antioxidant activity index (AAI), the latter being the ratio of the DPPH concentration in the assay (39.5 µg/mL) to the IC_{50} [34]. The results are shown in Table 5. The gel base alone was almost inactive (IC_{50} 114.19±8.45 µg/mL; AAI 0.35), confirming that the activity measured in the medicated gels originates from curcumin rather than from the excipients.

The curcumin SNEDDS gel was the more potent preparation, with an IC_{50} of 8.73±0.004 µg/mL against 12.62±0.033 µg/mL for the conventional gel, a 30.8% reduction in the concentration required to quench half the radical population. Both values fall below 50 µg/mL and both AAI values exceed 2.0, so both gels are classified as very strong antioxidants; the SNEDDS gel nonetheless ranks higher on both scales (AAI 4.52 versus 3.13). The improvement is attributable to solubilisation: curcumin dispersed molecularly within nanometre-scale droplets is available to react with the DPPH radical, whereas a substantial fraction of the drug in the conventional gel remains as undissolved crystals whose reactive phenolic hydroxyl groups are inaccessible in the reaction medium [35].

Table 5. DPPH radical-scavenging activity of the gel base and the two medicated gels

Sample	IC_{50} (µg/mL)	AAI	Category
Gel base	114.19±8.454	0.35	Weak
Conventional curcumin gel	12.62±0.033	3.13	Very strong
Curcumin SNEDDS gel	8.73±0.004	4.52	Very strong

AAI = antioxidant activity index, calculated as the DPPH concentration in the assay (39.5 µg/mL) divided by the IC_{50}. AAI >2.0 is classified as very strong

In vitro release across a synthetic membrane

In vitro release was studied in a Franz diffusion cell across an HT-Tuffryn synthetic membrane with phosphate buffer pH 7.4 as receptor medium at 37±1 °C (Figure 2). Cumulative diffusion increased with time for both preparations, but the SNEDDS gel released curcumin faster and to a greater extent throughout the two-hour experiment.

The flux, taken as the slope of the linear portion of the profile, was 0.0445 µg/cm²/min for the

SNEDDS gel against 0.0299 µg/cm²/min for the conventional gel, an increase of 49.1%. At 120 min, cumulative diffusion reached 5.88% for the SNEDDS gel and 3.28% for the conventional gel, a difference of 79.3%. An independent-samples t-test on the 120-min values gave p = 0.000, and a Mann–Whitney U test on the flux values gave p = 0.043, so both differences are statistically significant.

The shape of the two profiles is also informative. The conventional gel plateaued after about 60 min at roughly 3.3%, which is consistent with depletion of the dissolved drug fraction and the inability of the remaining crystalline curcumin to redissolve fast enough to sustain the concentration gradient. The SNEDDS gel continued to release drug up to 120 min, because the nanoemulsion droplets act as a reservoir that keeps replenishing dissolved curcumin at the membrane surface. The combination of a very large interfacial area, the maintenance of curcumin in a dissolved state and the penetration-enhancing action of Transcutol P and IPM accounts for the improvement [36, 37]. Comparable enhancements have been reported for curcumin SNEDDS-loaded topical systems elsewhere [10, 38].

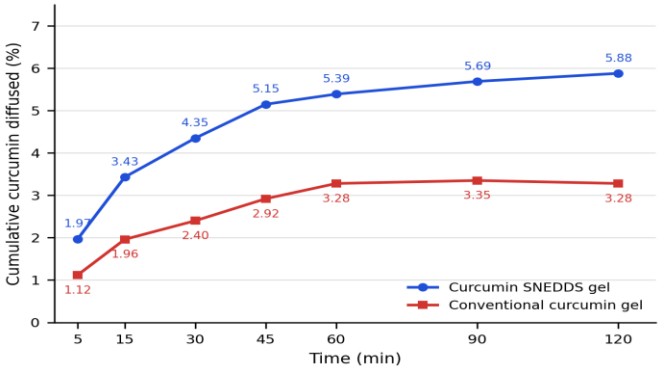


Figure 2. Cumulative percentage of curcumin diffused from the SNEDDS gel and the conventional gel across an HT-Tuffryn membrane into phosphate buffer pH 7.4 at 37±1 °C.

Conclusion

Varying the proportions of IPM, Cremophor RH 40 and Transcutol P significantly affected all six critical quality attributes of curcumin SNEDDS, and the D-optimal mixture design produced significant models with non-significant lack of fit for each of them. The optimum composition, IPM 19.91%, Cremophor RH 40 70.00% and Transcutol P 10.08% at a desirability of 0.777, yielded a droplet size of 44.25 nm, an emulsification time of 32.64 s, a transmittance of 93.20%, a drug loading of 22.84 mg/mL and a zeta potential of −12.66 mV, with no significant difference between predicted and observed values (p>0.05). Incorporating this system into an HPMC gel gave a homogeneous, skin-compatible preparation that remained stable through six freeze–thaw cycles, and that outperformed a conventional curcumin gel both in radical-scavenging capacity (IC_{50} 8.73 versus 12.62 µg/mL; AAI 4.52 versus 3.13) and in membrane transport (49.1% higher flux and 79.3% higher cumulative diffusion at 120 min). The curcumin SNEDDS gel is therefore a promising topical antioxidant candidate, and *in vivo* permeation, irritation and efficacy studies together with ICH-compliant long-term stability testing are the logical next steps.

Materials and Methods

Materials and instruments

Curcumin, isopropyl myristate, Cremophor RH 40 (PEG-40 hydrogenated castor oil), Transcutol P, 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydroxypropyl methylcellulose (HPMC), propylene glycol, glycerin, methyl paraben, propyl paraben, potassium bromide, analytical-grade methanol and ethanol, and distilled water were used. Instrumentation comprised a Fourier-transform infrared spectrophotometer, a Shimadzu UV-1800 UV-Vis spectrophotometer, a HORIBA Nano Partica SZ-100 particle size and zeta potential analyser, a magnetic stirrer, a vortex mixer, an ultrasonicator, a centrifuge, a Mettler Toledo XS205 analytical balance, a Starter 3100 OHAUS pH meter, a Brookfield viscometer, adhesion and spreadability testers, and a Franz diffusion cell. The study used no human or animal subjects and therefore required no ethical approval.

Identification of curcumin by infrared spectroscopy

Curcumin (5 mg) was triturated with potassium bromide (500 mg) and compressed into a transparent pellet. The infrared spectrum was recorded over 500–4000 cm^{-1} and the absorption bands were interpreted against reference spectra to confirm the functional groups of curcumin.

Calibration curve and validation of the analytical method

A 100 µg/mL stock solution of curcumin in methanol p.a. was scanned over 400–800 nm to establish the absorption maximum, and absorbance was followed from 0 to 60 min after dilution to define the operating time. Calibration standards of 2, 4, 6, 8 and 10 µg/mL were prepared from the stock and measured at the absorption maximum to construct the linear regression equation. The method was validated for specificity, linearity, accuracy (percentage recovery at 4, 6 and 8 µg/mL, three replicates each), precision (six replicates at 2 µg/mL, expressed as relative standard deviation), and limit of detection and quantification, calculated from the standard deviation of the intercept and the slope of the calibration curve.

Experimental design

The composition of the SNEDDS was optimised with a D-optimal mixture design in Design-Expert 13 under the constraints IPM 10–20%, Cremophor RH 40 40–70% and Transcutol P 10–40%, with the three proportions summing to 100%. The algorithm generated sixteen runs, including replicated points for the estimation of pure error. Six responses were modelled: droplet size, emulsification time, percentage transmittance, drug loading, polydispersity index and zeta potential.

Preparation of the curcumin SNEDDS

For each run, IPM, Cremophor RH 40 and Transcutol P were combined in the prescribed proportions and stirred on a magnetic stirrer at room temperature for 2 min until an isotropic mixture formed. Curcumin was then added in small portions until saturation, indicated by persistent turbidity, and the mixture was left for 24 h. The saturated system was centrifuged and the clear supernatant transferred to a vial for characterisation.

Characterisation of the SNEDDS

Emulsification time was determined by pipetting 100 µL of SNEDDS into 10 mL of distilled water under stirring at 100 rpm and recording the time required to form a homogeneous dispersion. The resulting dispersion was stirred at 500 rpm for 5 min and its transmittance read against water at 650 nm. Droplet size, polydispersity index and zeta potential were measured by dynamic light scattering after diluting 1 mL of SNEDDS to 100 mL with distilled water. For drug loading, 100 µL of SNEDDS was diluted to 5 mL with ethanol, 1 mL of this solution was further diluted to 10 mL, and the curcumin content was quantified spectrophotometrically at the absorption maximum.

Determination and verification of the optimum formulation

The optimum composition was selected using the desirability function, which combines the six responses into a single index between 0 and 1. Droplet size, emulsification time and polydispersity index were set to be minimised, transmittance and drug loading to be maximised, and the zeta potential to be driven away from neutrality. The predicted optimum was prepared in triplicate by combining the three excipients in a vial, adding curcumin to saturation, homogenising at 300 rpm for 10 min and centrifuging at 12,000 rpm for 45 min; the supernatant was retained as the optimum SNEDDS. All six responses were re-measured and compared with the model predictions.

Preparation of the gels

Two gels were prepared, both containing 0.2% active (optimum SNEDDS or unformulated curcumin), 3% HPMC, 5% glycerin, 10% propylene glycol, 0.18% methyl paraben, 0.01% propyl paraben and distilled water to 100%. HPMC was dispersed in hot water at

80–90 °C and stirred at 300 rpm (mixture A). Separately, methyl and propyl paraben were dissolved in propylene glycol, glycerin was added, and the active was incorporated and homogenised (mixture B). Mixture B was then stirred slowly into mixture A until a homogeneous gel of uniform consistency was obtained.

Evaluation of the physical quality of the gels

Organoleptic properties were assessed by direct observation of colour, odour and consistency, and homogeneity by spreading the gel on a glass slide and inspecting for undispersed particles. The pH was measured with a calibrated pH meter and evaluated against the 4.5–6.5 range of SNI 06-2588. Viscosity was determined with a Brookfield viscometer. Adhesion was measured by pressing 0.5 g of gel between two object glasses under a 1 kg load for 5 min and recording the time to separation. Spreadability was measured by placing 0.5 g of gel between glass plates for 1 min under successive loads of 50, 100 and 150 g and recording the mean spread diameter. Stability was assessed over six freeze–thaw cycles alternating 24 h at 4 °C with 24 h at 40 °C, monitoring organoleptic properties, phase separation, pH and viscosity.

DPPH radical-scavenging assay

A 0.2 mM DPPH solution was prepared by dissolving 19.7 mg of DPPH in methanol p.a. to 250 mL and stored protected from light. Sample stock solutions of 100 µg/mL were prepared in methanol p.a., methanol being used to break the SNEDDS structure and allow complete dispersion, and diluted to give working concentrations of 2, 4, 6, 8 and 10 µg/mL. One millilitre of each working solution was mixed with 1 mL of DPPH solution, made up to volume with methanol, and incubated in the dark for 30 min before measuring absorbance at 516 nm. Percentage inhibition was calculated as the difference between control and sample absorbance divided by control absorbance, IC_{50} was obtained from the linear regression of percentage inhibition against concentration, and the antioxidant activity index was calculated as the DPPH concentration in the assay divided by the IC_{50}. Each determination was performed in triplicate.

In vitro release using a Franz diffusion cell

In vitro release was determined with a Franz diffusion cell fitted with an HT-Tuffryn synthetic membrane. The receptor compartment held 25 mL of phosphate buffer pH 7.4 and was maintained at 37±1 °C. A 0.5 g sample of each gel was spread evenly on the membrane, and aliquots were withdrawn at 5, 15, 30, 45, 60, 90 and 120 min and replaced with fresh buffer. Curcumin was quantified spectrophotometrically at 421 nm against a calibration curve prepared in the same buffer over 2–10 µg/mL. Flux was calculated as the slope of the linear portion of the cumulative amount against time.

Data analysis

Mixture models were fitted and the optimum determined in Design-Expert 13, with model adequacy judged from analysis of variance, lack of fit, R^2, adjusted R^2, predicted R^2, adequate precision and the coefficient of variation. Comparisons between the two gels were performed in SPSS using the Wilcoxon test for pH, the independent-samples t-test for cumulative diffusion and the Mann–Whitney U test for flux, according to the distribution of the data. A p-value below 0.05 was considered statistically significant.

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