

Supplementary Material

Supplementary Table S1. Two-point physical and chemical stability of the lead formulation F5 under ICH Q1A(R2) long-term conditions (25 ± 2 °C / $60 \pm 5\%$ RH, light-protected): mean $\pm$ SD ($n = 3$) at baseline (Month 0) and at the six-month endpoint (Month 6). F5 was the only composition placed on stability.

Formulation	Size, Month 0 (nm)	Size, Month 6 (nm)	Δ Size (%)	Appearance (Month 6)	Curcumin recovered (% of nominal)
F5 (lead)	34.0 ± 1.0	34.4 ± 1.1	+1.18	clear, monophasic, no phase separation	99.9

The Month-0 droplet size corresponds to the value reported in Table 5. Stability was evaluated for the lead formulation F5 only; no other composition was placed on stability, and no values are reported or estimated for the remaining formulations. Curcumin recovery is expressed as a percentage of the nominal 0.2% w/w loading, because a time-zero content assay was not performed (Sections 2.5 and 2.9).

Supplementary Table S2. Reduced models, model statistics, and lack-of-fit tests for the permeation responses. Terms not significant against the pure-error term were removed before refitting.

Response	Reduced model (coded factors)	R ²	Adj. R ²	Lack-of-fit F (df)	p (lack of fit)
Jss ($\mu\text{g}/\text{cm}^2/\text{h}$)	$J_{ss} = 5.901 - 0.596 \cdot A - 0.414 \cdot AB$	0.827	0.758	0.86 (5, 16)	0.529
D ($\times 10^{-3} \text{ cm}^2/\text{h}$)	$D = 125.25 + 21.25 \cdot C$	0.527	0.448	0.78 (6, 16)	0.598
Droplet size (nm)	saturated; all seven terms significant	1.000	–	not estimable	–
PDI	saturated; all seven terms significant	1.000	–	not estimable	–

A = oil content, B = water phase, C = Smix ratio, coded $-1/+1$. Lack of fit was tested by comparing the lack-of-fit mean square of the reduced model against the pooled pure-error mean square obtained from the triplicate measurements at each design point (16 degrees of freedom). A non-significant lack of fit ($p > 0.05$) indicates that the reduced model describes the eight design points to within measurement error.

Supplementary Table S3. Receptor-phase analysis. Terminal receptor concentration referred to the donor concentration, and the observed 24-h cumulative permeation compared with the amount predicted by extrapolating the fitted linear phase ($J_{ss} \times (24 - T_{lag})$).

Run	C _r at 24 h ($\mu\text{g}/\text{mL}$)	C _r / C ₀ (%)	Gradient retained (%)	Q ₂₄ observed ($\mu\text{g}/\text{cm}^2$)	Q ₂₄ from linear phase ($\mu\text{g}/\text{cm}^2$)	Obs./linear (%)
F1	16.90	0.85	99.15	130.93	150.15	87.2
F2	15.67	0.78	99.22	121.40	150.60	80.6
F3	14.13	0.71	99.29	109.46	130.54	83.9
F4	10.92	0.55	99.45	84.57	104.26	81.1
F5	17.14	0.86	99.14	132.73	142.79	93.0
F6	16.97	0.85	99.15	131.41	150.25	87.5
F7	15.05	0.75	99.25	116.57	141.34	82.5
F8	12.25	0.61	99.39	94.90	104.92	90.4
Comparator	1.44	0.07	99.93	11.14	14.06	79.3

C_r is the terminal receptor concentration, calculated as the cumulative amount permeated multiplied by the diffusional area (4.906 cm^2) and divided by the receptor volume (38 mL). C₀ is the donor concentration, 2000 $\mu\text{g}/\text{mL}$ for every run. The gradient retained is $100 \times (1 - C_r/C_0)$. C_r is a total concentration and is therefore an upper bound on the thermodynamically active concentration: taking the equilibrium solubility of curcumin in the receptor medium as below 1 $\mu\text{g}/\text{mL}$, the dissolved concentration corresponds to less than 0.05% of C₀ for every run (Section 2.8). Across the nine runs the Pearson correlation between C_r and the observed-to-linear ratio is $r = +0.55$ ($p = 0.13$); across the eight microemulsions alone it is $r = +0.35$ ($p = 0.39$). A negative correlation would be expected if receptor saturation limited transport. The comparator attained the lowest receptor concentration of the series yet showed the largest deviation from its linear phase, which indicates that the deviation arises from donor depletion and boundary-layer effects common to all runs rather than from loss of receptor capacity.

Supplementary Figure S1. Model diagnostics. (A) Residual versus fitted value for the reduced steady-state flux model and (B) the corresponding normal probability plot. (C) Half-normal plot of the seven factor effects on droplet size. (D) Residual versus fitted value for the reduced diffusion-coefficient model and (E) the corresponding normal probability plot. (F) Replicate standard deviation versus mean droplet size, showing the measurement precision that underlies the pure-error term.

