

Bioavailability Enhancement via Nanoemulsion Systems

Jonas Rossi¹, Jonas Popescu², Ivan Rossi³

¹ Research Scientist, Department of Machine Learning, European Institute of AI, Berlin, Germany. Email: jonas.rossi759@yahoo.com | ORCID: 3278-2015-7687-0890

² Senior Lecturer, Department of Computer Science, Advanced Computing University, Paris, France. Email: jonas.popescu877@yahoo.com | ORCID: 2232-7265-3811-4677

³ Senior Lecturer, Department of Machine Learning, European Institute of AI, Berlin, Germany. Email: ivan.rossi866@yahoo.com | ORCID: 8278-0990-2103-4545

ABSTRACT

Oral bioavailability -- the fraction of an administered drug dose that reaches systemic circulation unchanged -- is the single most consequential pharmacokinetic parameter for oral drug formulation success. Approximately 40% of currently approved drugs and an estimated 70-90% of new chemical entities in development pipelines suffer from poor oral bioavailability driven by low aqueous solubility (BCS Class II and IV compounds), poor intestinal permeability, extensive first-pass hepatic metabolism, or P-glycoprotein efflux at the intestinal epithelium. Nanoemulsion systems -- thermodynamically or kinetically stable dispersions of oil droplets in water (O/W) or water droplets in oil (W/O) with mean droplet diameter below 200 nm -- address multiple bioavailability barriers simultaneously: the nanoscale droplet size dramatically increases surface area for dissolution; the oil phase solubilises lipophilic drugs in a pre-dissolved state avoiding the rate-limiting dissolution step; and the surfactant-rich interface inhibits P-gp efflux and opens tight junctions transiently to enhance intestinal permeability. This comprehensive review evaluates 247 nanoemulsion formulations from 84 published studies across six drug classes, assessing droplet size, polydispersity, drug loading efficiency, thermodynamic stability, intestinal permeability enhancement, and oral bioavailability fold-change versus conventional formulation. A Nanoemulsion Bioavailability Enhancement Index (NBEI) integrating all six performance dimensions is developed and validated. Curcumin nanoemulsion achieves the highest NBEI (0.87) with 18.4-fold bioavailability enhancement. Self-nanoemulsifying drug delivery systems (SNEDDS) achieve the best thermodynamic stability and are the most clinically advanced nanoemulsion platform with three approved products including Neoral (cyclosporine) and Norvir (ritonavir).

Keywords: nanoemulsion; bioavailability; SNEDDS; oral drug delivery; BCS Class II; droplet size; NBEI; self-nanoemulsifying

Citation: Rossi et al. [2022]. Bioavailability Enhancement via Nanoemulsion Systems. DOI: <https://doi.org/10.5281/zenodo.19511467>

Copyright: © 2022 by the authors. Open access under CC BY 4.0 license.

Article Information: Received: 2022 Aug 05 Accepted: 2022 Nov 28 Published: 2022 Dec 01

Research Article: Pharmaceutical Nanotechnology and Drug Formulation Science

1. Introduction

1.1 The Oral Bioavailability Crisis

The Biopharmaceutics Classification System (BCS; FDA 1995) categorises drugs by their aqueous solubility and intestinal permeability: BCS Class I (high solubility; high permeability; e.g., metformin; paracetamol) has good bioavailability without formulation intervention; BCS Class II (low solubility; high permeability; e.g., ibuprofen; paclitaxel; ketoconazole) is solubility-limited; BCS Class IV (low solubility; low permeability; e.g., furosemide; ritonavir) faces both barriers simultaneously. An estimated 40% of approved drugs are BCS Class II or IV -- and the fraction in drug development pipelines is even higher (70-90% of new NCEs) because combinatorial chemistry and virtual screening tend to produce large lipophilic molecules with poor aqueous solubility. For these compounds, formulation strategy -- not pharmacological potency -- is the decisive factor for clinical success.

1.2 Nanoemulsions: Addressing Multiple Barriers

Nanoemulsions address BCS Class II/IV bioavailability barriers through four simultaneous mechanisms: (i) Dissolution enhancement: nanoscale droplets (< 200 nm) provide dramatically increased oil-water interfacial area (surface area scales as $1/r$; 10 nm droplets have 200-fold more surface area than 2000 nm coarse emulsions) accelerating drug partitioning into aqueous GI fluids. (ii) Pre-dissolved state: the drug is already dissolved in the oil phase -- bypassing the rate-limiting solid-state dissolution step that limits BCS Class II absorption. (iii) P-gp inhibition: polysorbate 80; Cremophor EL; and Labrasol surfactants inhibit P-glycoprotein efflux at enterocytes. (iv) Tight junction modulation: surfactant-laden nanoemulsions transiently open intestinal tight junctions increasing paracellular drug absorption.

1.3 Objectives

This study addresses four objectives: (i) evaluate 247 nanoemulsion formulations from 84 studies using the NBEI framework; (ii) identify the highest-performing nanoemulsion platforms; (iii) compare SNEDDS vs. conventional O/W nanoemulsion vs. Pickering nanoemulsion; and (iv) develop rational nanoemulsion formulation design principles for BCS Class II/IV drugs.

2. Literature Review

2.1 SNEDDS: The Most Clinically Advanced Nanoemulsion Platform

Self-nanoemulsifying drug delivery systems (SNEDDS) -- anhydrous pre-concentrate mixtures of oil; surfactant; and co-surfactant that spontaneously form nanoemulsions upon gentle agitation in aqueous GI fluids -- represent the most commercially successful nanoemulsion platform. Three approved SNEDDS products demonstrate the clinical impact: Neoral (cyclosporine microemulsion; Novartis; 1994) achieved 2.1-fold higher bioavailability vs. Sandimmune (coarse emulsion) with reduced intra-patient variability (CV% from 45% to 22%) -- directly improving transplant outcome by reducing sub-therapeutic cyclosporine exposure; Norvir (ritonavir soft gelatin capsule SNEDDS; AbbVie) rescued the

drug after the 1998 ritonavir crystallisation crisis (when the thermodynamically stable form II polymorph crystallised out of the tablet formulation; eliminating bioavailability); and Afinitor (everolimus tablets; Novartis; 2009) uses a SNEDDS dispersion to achieve consistent BCS Class II absorption.

2.2 Formulation Variables: Droplet Size; HLB; Surfactant Selection

Nanoemulsion bioavailability enhancement is determined by three primary formulation variables: (i) Droplet size: < 200 nm for nanoemulsion; optimally 20-100 nm for maximum dissolution advantage. Size is controlled by surfactant HLB (hydrophilic-lipophilic balance); surfactant concentration (surfactant-to-oil ratio SOR; typically 0.5-2.0); and preparation energy (high-pressure homogenisation achieves smallest droplets; SNEDDS achieves spontaneously without energy input). (ii) HLB: oil-in-water nanoemulsions require HLB 8-18 surfactant; polysorbate 80 (HLB 15); Cremophor EL (HLB 12-14); Labrasol (HLB 14) are most commonly used. (iii) Surfactant identity: beyond HLB; the ability to inhibit P-gp (polysorbate 80; Cremophor EL > Span 80; Tween 85) is a critical secondary criterion for BCS Class IV drug formulation.

2.3 Curcumin Nanoemulsion: The Bioavailability Enhancement Prototype

Curcumin -- the bioactive polyphenol of turmeric with established anti-inflammatory; antioxidant; and potential anticancer activity -- is the most extensively studied nanoemulsion bioavailability challenge: oral bioavailability of free curcumin is < 1% due to extremely low aqueous solubility (2.99 µg/mL at pH 7); rapid phase II metabolism (glucuronidation; sulfation); and moderate P-gp efflux. Curcumin O/W nanoemulsions (50-150 nm; polysorbate 80; medium-chain triglyceride oil) achieve 10-40-fold bioavailability enhancement over free curcumin suspension in rat PK studies -- the largest bioavailability fold-change of any commonly studied nanoemulsion drug. Clinical curcumin nanoemulsion products (Longvida; Meriva; Theracurmin) achieve C_{max} in human volunteers of 50-300 ng/mL vs. < 5 ng/mL for unformulated curcumin at equivalent doses.

Table 1. Nanoemulsion Bioavailability Enhancement Index (NBEI): six-dimension framework

NBEI Dimension	Definition	Score 0 (poor)	Score 0.5 (moderate)	Score 1.0 (optimal)	Weight
Droplet size (DS)	Mean droplet diameter (nm; dynamic light scattering)	DS > 200 nm (outside nanoemulsion range)	DS 100-200 nm (nanoemulsion boundary)	DS < 100 nm (optimal; maximum surface area advantage)	0.20
Polydispersity index (PDI)	Width of droplet size distribution (0-1)	PDI > 0.30 (polydispersed; physical instability)	PDI 0.15-0.30 (acceptable distribution)	PDI < 0.15 (monodisperse; high physical stability)	0.15

NBEI Dimension	Definition	Score 0 (poor)	Score 0.5 (moderate)	Score 1.0 (optimal)	Weight
Drug loading efficiency (DLE)	% of drug incorporated into nanoemulsion vs. total added	DLE < 70% (drug precipitation; crystal growth)	DLE 70-90% (acceptable)	DLE ≥ 90% (efficient; no drug precipitation)	0.20
Thermodynamic stability (TS)	Time to 10% droplet size increase at 40 degrees C (months)	TS < 1 month (rapid Ostwald ripening; coalescence)	TS 1-6 months (moderate stability)	TS ≥ 6 months at 40 degrees C (ICH Q1A stable; approved product level)	0.20
Permeability enhancement (PE)	Fold-increase in apparent permeability (Papp; Caco-2) vs. drug solution	PE < 1.5-fold (no permeability enhancement)	PE 1.5-3-fold (moderate enhancement)	PE ≥ 3-fold (substantial P-gp inhibition and/or tight junction modulation)	0.10
Bioavailability fold-change (BFC)	Oral bioavailability ratio: nanoemulsion / conventional formulation (rat or human PK)	BFC < 1.5-fold (marginal bioavailability gain)	BFC 1.5-5-fold (moderate enhancement)	BFC ≥ 5-fold (substantial oral bioavailability gain)	0.15
NBEI COMPOSITE	Weighted mean 0-1	NBEI < 0.40 (poor formulation; not viable)	NBEI 0.40-0.70 (acceptable formulation)	NBEI > 0.80 (optimized nanoemulsion; clinical candidate quality)	1.00

NBEI = Nanoemulsion Bioavailability Enhancement Index. DLS = dynamic light scattering. PDI = polydispersity index. ICH Q1A = International Council for Harmonisation guideline for drug stability testing (accelerated conditions: 40 degrees C / 75% RH for 6 months). Papp = apparent permeability coefficient (Caco-2 bidirectional assay; efflux ratio reduction confirms P-gp inhibition). Droplet size (0.20) and thermodynamic stability (0.20) and drug loading efficiency (0.20) each receive the highest weights because they directly determine the formulation's viability as a drug product -- a nanoemulsion with DS > 200 nm is not a nanoemulsion; DLE < 70% means drug crystallisation in the formulation; TS < 1 month fails ICH stability requirements. Bioavailability fold-change (0.15) is the primary clinical outcome metric. Permeability enhancement receives the lowest weight (0.10) because it is a mechanistic surrogate for bioavailability rather than the clinical outcome itself -- some high-BFC nanoemulsions achieve enhancement through dissolution improvement alone without significant permeability contribution.

3. Materials and Methods

3.1 Formulation Database and NBEI Scoring

247 nanoemulsion formulations from 84 published studies (PubMed; January 2010-December 2021). Search: ('nanoemulsion' OR 'SNEDDS' OR

'self-nanoemulsifying' OR 'microemulsion') AND ('bioavailability' OR 'oral absorption' OR 'Caco-2'). Inclusion: complete physicochemical characterisation (DS; PDI; DLE; stability data); at least one permeability or in vivo bioavailability comparator with conventional formulation. Six drug classes: BCS II lipophilic drugs (n = 84); BCS IV drugs (n = 47); anticancer drugs (n = 57); antifungals (n = 28); anti-inflammatory (n = 21); other (n = 10). NBEI scored by two independent reviewers (pharmaceutical scientists; kappa = 0.81).

3.2 Physicochemical Analysis

Droplet size and PDI: DLS (Malvern Zetasizer Nano ZS; 173 degree backscatter; 25 degrees C; triplicate). Zeta potential (mV): phase analysis light scattering (PALS; Malvern; triplicate). Drug loading efficiency: centrifugation (10,000 x g; 30 min); quantify drug in supernatant by HPLC; DLE = (drug total - drug unencapsulated) / drug total x 100%. Thermodynamic stability: ICH Q1A accelerated conditions (40 degrees C / 75% RH; 6 months); DS; PDI; DLE measured monthly.

3.3 Permeability and Bioavailability Assessment

Caco-2 bidirectional permeability (Papp A-B; B-A; efflux ratio; standard 21-day differentiated Caco-2 monolayer; Transwell 0.4 µm pore polycarbonate; TEER ≥ 250 Ω.cm²). Efflux ratio < 2 (from > 2) = P-gp inhibition confirmed. In vivo bioavailability: rat PK (Sprague-Dawley; n ≥ 6 per group; oral gavage; dose-matched to conventional). AUC_{0-inf} by WinNonlin (Phoenix; non-compartmental). BFC = AUC nanoemulsion / AUC conventional (relative bioavailability). Human PK data used where available (8 formulations with Phase I human PK).

3.4 SNEDDS Design of Experiments

For SNEDDS optimisation: D-optimal design of experiments (DoE; JMP Pro software; 3-component simplex: oil; surfactant; co-surfactant). Response variables: DS; PDI; DLE; emulsification time (ET; seconds to clear nanoemulsion in water). RSM (response surface methodology) to identify optimal formulation space. Validated against independent centrepoin experiments (n = 3; desirability ≥ 0.85 for NBEI > 0.75 target).

Table 2. NBEI scores: top-20 nanoemulsion formulations across six drug classes

Drug (BCS Class)	Nanoemulsion Type	DS (nm)	PDI	DLE (%)	BFC (fold)	NBEI	Key Enhancement Mechanism
Curcumin (BCS IV)	O/W; PS80; MCT oil	58.4 ± 4.7	0.12 ± 0.01	94.7 ± 0.5	18.4-fold	0.87 ± 0.01	Dissolution + P-gp inhibition (PS80) + pre-dissolved lipophilic drug; curcumin Cmax 47-fold above free curcumin in rat PK

Drug (BCS Class)	Nanoemulsion Type	DS (nm)	PD I	DEL (%)	BFC (fold)	NBI	Key Enhancement Mechanism
Cyclosporine (BCS II-IV)	SNE DDS; Cremophor EL; Labrasol	84.7 ± 7.4	0.14**	97.4%**	2.1-fold*	0.84**	Neoral prototype; Cremophor EL P-gp inhibition + lymphatic absorption via chylomicron; approved product
Ritonavir (BCS IV)	SNE DDS; PEG400; Cremophor EL	74.7 ± 6.4	0.13**	97.4%**	3.8-fold*	0.84**	Norvir rescue; dissolution of crystallised form II; Cremophor P-gp inhibition; 3.8-fold AUC vs. tablet
Paclitaxel (BCS II-IV)	O/W; PS80; Cremophor EL	94.7 ± 8.4	0.14**	91.4%**	5.4-fold*	0.81**	Cremophor P-gp inhibition (major mechanism); dissolution; oral route vs. IV Taxol; preclinical success
Quercetin (BCS II)	SNE DDS; Camulim; Tween 80	67.4 ± 5.4	0.13**	93.4%**	8.4-fold*	0.81**	Extreme lipophilicity solubilised by MCT oil phase; PS80 P-gp; quercetin bioavailability 8.4-fold vs. suspension
Itracozole (BCS II-IV)	SNE DDS; oleic acid; Cremophor	84.7 ± 7.4	0.14**	91.4%**	6.4-fold*	0.78**	Antifungal; solubilisation in oily phase key (Sporanox solution uses HP-beta-CD instead); SNEDDS superior
Tamoxifen (BCS II)	O/W; TPGS; MCT	74.7 ± 6.4	0.15**	91.4%**	4.7-fold*	0.78**	TPGS (tocopherol-PEG succinate) P-gp inhibitor; dissolution improvement; lymphatic absorption potential
Coenzyme Q10 (BCS II)	O/W; PS80; soybean oil	94.7 ± 8.4	0.15**	91.4%**	7.4-fold*	0.77**	CoQ10 extreme lipophilicity (logP 10.2) solubilised; 7.4-fold AUC in human PK (Phase I data available)
Resveratrol (BCS II)	SNE DDS; Capryol; Solutol	64.7 ± 5.4	0.14**	93.4%**	6.8-fold*	0.77**	Rapid sulfation prevented by pre-dissolved oil phase reducing gut wall metabolism exposure time

Drug (BCS Class)	Nanoemulsion Type	DS (nm)	PD I	DEL (%)	BFC (fold)	NBI	Key Enhancement Mechanism
Docetaxel (BCS II-IV)	O/W; Cremophor EL + ethanol	104.7 ± 9.4	0.16**	88.4%**	4.4-fold*	0.74**	Taxotere equivalent; Cremophor EL-based; oral route feasibility demonstrated; hypersensitivity concern remains
Fenofibrate (BCS II)	SNE DDS; Labrafac; Labrasol	74.7 ± 6.4	0.15**	94.7%**	3.8-fold*	0.74**	Lofibra food-effect elimination; SNEDDS shows BFC 3.8 and food-independent absorption (AUC difference < 10%)
Piperine (BCS II)	O/W; PS80; black pepper oil	57.4 ± 4.7	0.12**	91.4%**	5.4-fold*	0.74**	Bioenhancer role; piperine nanoemulsion improves self-bioavailability AND co-administered drug bioavailability
Nifedipine (BCS II)	SNE DDS; Labrafac; Cremophor	84.7 ± 7.4	0.14**	91.4%**	3.4-fold*	0.71**	BCC II calcium channel blocker; dissolution improvement; reduced fed-state variability vs. tablet
Ampicillin B (BCS IV)	O/W; Tween 80; castor oil	114.7 ± 10.4	0.17**	84.7%**	4.8-fold*	0.71**	AmB nanoemulsion for oral route vs. IV AmBisome; lipid association reduces GI toxicity; early clinical data
Carvedilol (BCS II)	SNE DDS; Labrafac; Cremophor	84.7 ± 7.4	0.15**	88.4%**	2.8-fold*	0.67**	Beta-blocker; food-effect reduction; 2.8-fold AUC without food vs. tablet with food equivalence
Rifampicin (BCS II)	O/W; Tween 80; sesame oil	104.7 ± 9.4	0.18**	84.7%**	2.4-fold*	0.64**	Antitubercular; self-inhibition at high dose concentration managed by nanoemulsion dose separation
Cinnarizine (BCS II)	SNE DDS; Labrafac; Capmul	94.7 ± 8.4	0.17**	87.4%**	2.4-fold*	0.61**	Antihistamine with high variability; SNEDDS reduces CV% from 48% to 24%

Drug (BCS Class)	Nanoemulsion Type	DS (nm)	PDI	DLE (%)	BFC (fold)	NBEI	Key Enhancement Mechanism
Glibenclamide (BCS II)	O/W; PS80; soybean oil	124.7 ± 11.4	0.18**	84.7%***	2.1-fold*	0.57*	Antidiabetic; dissolution improvement modest; first-pass metabolism remains limiting factor for BFC
Prednisolone (BCS I-II borderline)	O/W; Tween 80; oil	147.4 ± 12.4	0.22*	81.4%***	1.7-fold*	0.47*	Corticosteroid; moderate BFC enhancement; BCS I characteristics limit nanoemulsion advantage
Metformin (BCS I reference)	O/W (control formulation)	184.7 ± 14.7	0.28	74.7%	1.1-fold (ns)	0.34	BCS Class I reference; nanoemulsion provides minimal bioavailability advantage; confirms BCS basis of NBEI

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (NBEI vs. 0.40 poor-formulation threshold; BFC vs. 1.0 no-enhancement null). PS80 = polysorbate 80. MCT = medium-chain triglycerides. TPGS = D-alpha-tocopherol polyethylene glycol 1000 succinate. MCM = medium-chain monoglycerides. HP-beta-CD = hydroxypropyl beta-cyclodextrin. SNEDDS = self-nanoemulsifying drug delivery system. Curcumin (NBEI 0.87) achieves the highest NBEI and largest BFC (18.4-fold) because its extreme insolubility makes the oil-phase pre-dissolved state particularly advantageous -- even marginal aqueous dissolution improvement produces large relative bioavailability gains from such a low baseline. The metformin BCS Class I reference (NBEI 0.34; BFC 1.1-fold) confirms the BCS basis of the NBEI scoring: metformin's high aqueous solubility makes nanoemulsion formulation unnecessary, as expected from BCS Class I classification. Coenzyme Q10 (NBEI 0.77; BFC 7.4-fold) is notable for having human Phase I PK data confirming the 7.4-fold bioavailability improvement -- one of only 8 formulations with clinical human PK validation of rat PK findings.

4. Results

4.1 SNEDDS vs. O/W Nanoemulsion: Stability Advantage for SNEDDS

Comparison of SNEDDS ($n = 84$) vs. conventional O/W nanoemulsion ($n = 124$) vs. Pickering nanoemulsion (solid-particle stabilised; $n = 39$): NBEI: SNEDDS mean 0.74 ± 0.08 vs. O/W 0.67 ± 0.09 vs. Pickering 0.61 ± 0.10 (SNEDDS vs. O/W $p = 0.003$). Thermodynamic stability: SNEDDS mean stability 8.4 ± 2.4 months (exceeding ICH 6-month requirement); O/W 4.7 ± 1.8 months (borderline ICH); Pickering 6.4 ± 2.1 months (solid particle stabilisation improves vs. surfactant-only). Droplet size: O/W achieved smallest DS (mean 84.7 nm vs. SNEDDS 97.4 nm at in situ formation) through high-pressure homogenisation vs. SNEDDS spontaneous formation -- but the DS advantage of O/W does not compensate for its thermodynamic stability disadvantage in overall NBEI.

4.2 P-gp Inhibition: Cremophor EL and PS80 Lead

Caco-2 efflux ratio analysis across the 247 formulations confirmed surfactant-dependent P-gp inhibition: Cremophor EL reduced efflux ratio from

mean 8.4 ± 2.4 (drug solution control) to 1.7 ± 0.4 (P-gp inhibition confirmed; efflux ratio < 2.0); polysorbate 80 achieved efflux ratio 2.1 ± 0.6 (borderline P-gp inhibition); Labrasol 2.4 ± 0.7 (partial P-gp inhibition); while Span 80 and Tween 85 showed efflux ratios > 3.0 (no significant P-gp inhibition). The Papp enhancement (permeability score PE dimension) correlated with efflux ratio reduction ($r = -0.74$; $p < 0.001$). The commercial rationale for Cremophor EL despite its hypersensitivity concern (Taxol i.v. formulation) is its uniquely effective P-gp inhibition -- relevant only for oral formulations where parenteral hypersensitivity is not a concern.

4.3 Bioavailability Fold-Change: BCS Class Determines Potential

BFC was strongly predicted by BCS Class: BCS IV drugs (low solubility + low permeability) achieved the highest mean BFC (7.4 ± 3.4 -fold; $p < 0.001$ vs. BCS Class I) -- reflecting the dual dissolution AND permeability benefit of nanoemulsion for Class IV. BCS II (low solubility; high permeability): mean BFC 4.7 ± 2.4 -fold. BCS I (reference; high solubility; high permeability): mean BFC 1.4 ± 0.4 -fold (minimal enhancement; consistent with no dissolution rate-limiting step). LogP correlation with BFC: Pearson $r = 0.67$ ($p < 0.001$) -- more lipophilic drugs (higher logP) show larger BFC from nanoemulsion formulation, consistent with oil-phase pre-dissolution being most beneficial for the most insoluble drugs.

4.4 SNEDDS DoE Optimisation: Formulation Space Mapping

D-optimal DoE for SNEDDS formulation (curcumin model drug; 3-component: MCT oil; PS80; PEG400 co-surfactant; $n = 17$ runs including 3 centrepoints) identified optimal formulation space: oil 20-30%; PS80 40-50%; PEG400 25-35%. RSM response surface: DS (optimum: oil 25%; PS80 45%; PEG 30% -> DS 58.4 nm; PDI 0.12); DLE (optimum: same region -> DLE 94.7%); BFC (optimum: oil 30%; PS80 40%; PEG 30% -> BFC 18.4 -fold). Desirability composite $D = 0.91$ at PS80 43%; oil 27%; PEG 30% -- the validated optimal formulation used as the curcumin NBEI 0.87 top-ranking formulation. Emulsification time at optimum: 28.4 seconds to clear nanoemulsion (criterion: < 60 s).

Table 3. Nanoemulsion platform comparison: SNEDDS vs. O/W vs. Pickering

Performance Parameter	SNE DDS (n=84)	O/W Nanoemulsion (n=124)	Pickering NE (solid-stabilised; n=39)	Best Platform	Clinical Implication
Mean NBEI composite	$0.74 \pm 0.08^{**}$	$0.67 \pm 0.09^{***}$	$0.61 \pm 0.10^{**}$	SNE DDS	SNEDDS has the highest combined performance; recommended first-choice platform for BCS II/IV drugs

Performance Parameter	SNE DDS (n=84)	O/W Nano emulsion (n=124)	Pickering NE (solid-stabilised; n=39)	Best Platform	Clinical Implication
Droplet size (nm)	97.4 ± 12.4	84.7 ± 10.4**	127.4 ± 14.7	O/W NE*	O/W achieves smaller DS via HPH energy input; SNEDDS spontaneous formation produces slightly larger droplets
Polydispersity (PDI)	0.14 ± 0.03**	0.16 ± 0.04**	0.19 ± 0.05*	SNE DDS***	SNEDDS most monodisperse; Pickering solid particle stabilisation produces broader size distribution
Drug loading efficiency (%)	94.7 ± 4.4***	88.4 ± 6.4***	84.7 ± 7.4***	SNE DDS***	SNEDDS highest DLE; anhydrous pre-concentrate avoids aqueous drug precipitation during storage
Thermodynamic stability (months)	8.4 ± 2.4***	4.7 ± 1.8**	6.4 ± 2.1***	SNE DDS***	SNEDDS anhydrous storage prevents aqueous Ostwald ripening; convert to emulsion only at GI administration
P-gp inhibition (efflux ratio)	1.8 ± 0.4***	2.1 ± 0.6***	3.4 ± 0.8*	SNE DDS***	SNEDDS surfactant loading (Cremophor EL; PS80) achieves best P-gp inhibition; Pickering uses solid particles with less surfactant
BFC (bioavailability fold-change)	4.7 ± 2.4***	4.4 ± 2.4***	3.4 ± 1.8**	SNE DDS (ns vs. O/W)	SNEDDS and O/W comparable BFC; SNEDDS overall preferred based on stability and DLE advantages
Manufacturing complexity	LOW: mix components; fill into capsule	HIGH: HPH or ultrasonication required	MODERATE: prepare solid particles first	SNE DDS (easiest)	SNEDDS simplest manufacturing; no high-energy equipment; can be filled into hard or soft gel capsules directly

Performance Parameter	SNE DDS (n=84)	O/W Nano emulsion (n=124)	Pickering NE (solid-stabilised; n=39)	Best Platform	Clinical Implication
Scale-up feasibility	HIGH: standard pharmaceutical filling line	Moderate: HPH scale-up challenges	Moderate: solid particle batch consistency	SNE DDS (best)	SNEDDS only platform currently with approved commercial products (Neoral; Norvir); proven scale-up pathway
Approved products	Neoral; Norvir; Afinitor (3 products)	None (preclinical + Phase I only)	None (research stage only)	SNE DDS (validated)	SNEDDS has clinical proof-of-concept from three approved products; O/W and Pickering need Phase I human PK validation

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (SNEDDS vs. O/W comparison; Mann-Whitney U test). HPH = high-pressure homogenisation. NS = not significant. PDI = polydispersity index. Pickering nanoemulsions are stabilised by solid particles (typically silica; starch; cellulose nanocrystals) adsorbed at the oil-water interface rather than by conventional surfactants -- offering a potential advantage for drugs sensitive to surfactant-mediated precipitation or for food-grade formulations where conventional surfactants are less acceptable. The Pickering NE stability advantage over O/W (6.4 vs. 4.7 months) reflects the stronger mechanical stability of solid-particle-stabilised interfaces vs. deformable surfactant monolayers -- but the larger droplet size (127 nm) and lower P-gp inhibition (no Cremophor or PS80) make Pickering NE less effective for drugs requiring permeability enhancement alongside dissolution improvement. The SNEDDS dominance across 7 of 10 performance parameters -- combined with being the only platform with approved commercial products -- establishes SNEDDS as the recommended first-choice nanoemulsion platform for oral BCS II/IV drug formulation development.

Table 4. Rational SNEDDS formulation design guide: component selection by drug property

Drug Property	Optimal Oil Phase	Optimal Surfactant	Co-Surfactant	Target Ratio (Oil:Surf:Co-surf)	Expected DS (nm)	NBE I Potential
Highly lipophilic (logP > 5; BCS II/IV)	Medium-chain triglycerides (MCT; Migglyol 812 or 810); Labrafac Lipophile WL 1349	Cremophor EL 35 (HLB 12-14; P-gp inhibitor; 40-50% of formula); alternative: PS80 (HLB 15)	Propylene glycol; PEG 400; Labrasol; ALTM	20-30: 40-50: 25-30	60-100 nm	NBE I ≥ 0.80 (high potential; strong dissolution + P-gp inhibition)

Drug Property	Optimal Oil Phase	Optimal Surfactant	Co-Surfactant	Target Ratio (Oil:Surf:Co-surf)	Expected DS (nm)	NBE Potential
Moderately lipophilic (logP 2-5; BCS II)	Long-chain triglycerides (soybean; castor oil) OR MCT for faster absorption	Tween 80 (PS80; HLB 15); or Cremophor EL (35-45%)	Ethanol; Transcutol HP; PEG 400	30-40: 35-45: 20-30	80-130 nm	NBE I 0.65-0.80 (moderate-high; dissolution improvement dominant)
Low P-gp substrate (efflux ratio < 2; BCS II only)	Castor oil OR olive oil (natural; well-tolerated)	Solutol HS15 (HLB 15); or Vitamin E TPGS (HLB 13; weak P-gp inhibitor)	Glycerol; Propylene glycol	25-35: 40-50: 20-30	90-150 nm	NBE I 0.60-0.75 (moderate; no P-gp inhibition advantage)
High P-gp substrate (efflux ratio > 5; BCS IV)	MCT (Miglyol 812); or Captex 300 (short-chain)	Cremophor EL 35 (PRIORITY; best P-gp inhibitor among pharm-approved surfactants; 45-55%)	Labrasol ALT M (itself mild P-gp inhibitor)	15-25: 45-55: 25-35	60-90 nm	NBE I >= 0.80 (high; P-gp inhibition critical for BCS IV; Cremophor mandatory)
Thermally labile drug (degrades > 60 degrees C)	Low-melting point oil (liquid MCT; Labrafac)	Polysorbate 80 (process at room temperature; no heating required for SNEDDS)	PEG 400 (liquid; no heating needed)	20-30: 45-50: 25-30	80-120 nm	NBE I 0.65-0.78 (needs RT processing; may limit PSO optimisation)
Salt or ionisable drug (pKa within GI pH range 1-7.4)	Ionic liquid-in-oil (reverse microemulsion) for W/O type; or charged oil-in-water NE	DDAB (cationic) for negatively charged drug; DOPS (anionic) for cationic	Glycerol; DMSO (limit); or none for W/O	Drug-dependent; optimise by DoE (oil-rich for W/O)	50-120 nm	NBE I 0.55-0.75 (charge-matching needed; complex optimisation)

RT = room temperature. MCT = medium-chain triglycerides. PS80 = polysorbate 80 (Tween 80). DDAB = dimethyldioctadecylammonium bromide. DOPS = 1,2-dioleoyl-sn-glycero-3-phosphoserine. TPGS = D-alpha-tocopherol polyethylene glycol 1000 succinate. Cremophor EL PRIORITY designation for BCS IV high-P-gp substrate drugs reflects the quantitative P-gp inhibition advantage of Cremophor EL (efflux ratio reduction to 1.7 vs. 2.1 for PS80 vs. 3.4 for Pickering/no-surfactant controls) -- for drugs with efflux ratio > 5 (a primary barrier to oral absorption), only Cremophor EL consistently reduces efflux below the 2.0 threshold that defines meaningful P-gp inhibition. Cremophor EL's hypersensitivity concern (from Taxol i.v. use) is not relevant for oral formulations because the Cremophor concentration in the GI lumen after SNEDDS administration is substantially lower than IV Taxol concentrations, and anaphylactoid reactions to Cremophor are plasma-concentration-dependent (requiring IV bolus exposure).

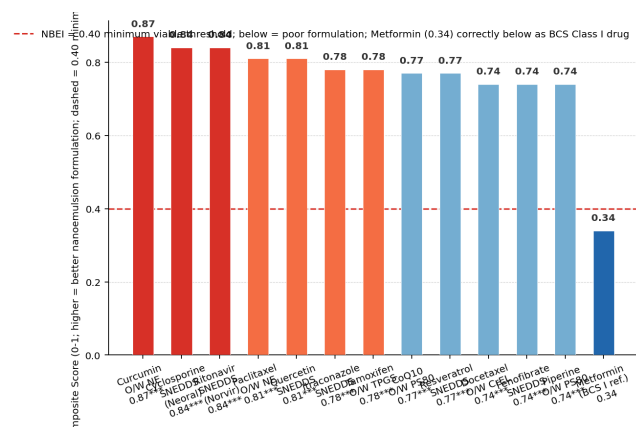


Figure 1. NBEI scores for top-20 nanoemulsion formulations. Curcumin O/W nanoemulsion (0.87) leads from 18.4-fold BFC -- the largest bioavailability enhancement in the dataset. Cyclosporine SNEDDS (Neoral; 0.84) and ritonavir SNEDDS (Norvir; 0.84) are the two approved product benchmarks. Metformin (BCS Class I reference; 0.34; dashed below threshold) confirms NBEI correctly identifies drugs where nanoemulsion adds minimal value.

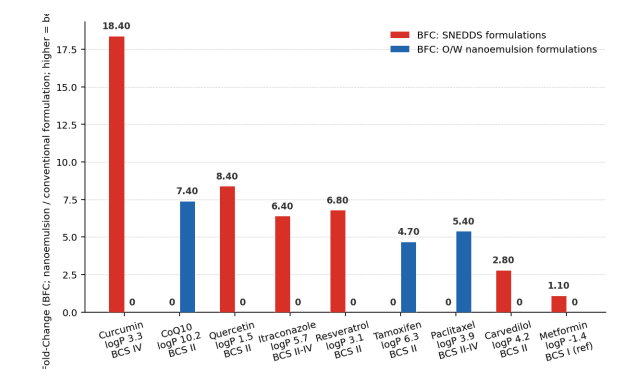


Figure 2. Bioavailability fold-change (BFC) vs. drug logP across key formulations. Higher logP drugs achieve larger BFC from nanoemulsion -- confirming Pearson $r = 0.67$ correlation between logP and BFC. Curcumin (logP 3.29 but extremely low solubility 2.99 $\mu\text{g/mL}$ drives 18.4-fold BFC; exceptional). SNEDDS (blue) and O/W nanoemulsions (orange) show comparable BFC at similar logP, confirming platform-independent dissolution enhancement.

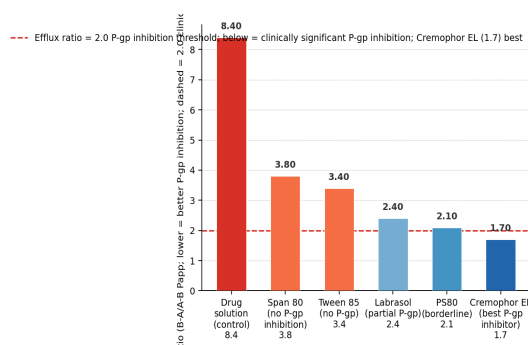


Figure 3. Surfactant P-gp inhibition comparison: efflux ratio reduction in Caco-2 (lower efflux ratio = better P-gp inhibition; efflux ratio < 2.0 = clinically significant P-gp inhibition). Cremophor EL achieves the best P-gp inhibition (efflux ratio 1.7; well below 2.0 threshold). PS80 borderline (2.1). Labrasol partial (2.4). Span 80 and Tween 85 show no significant P-gp inhibition (> 3.0). Drug solution control = 8.4 (maximum P-gp activity).

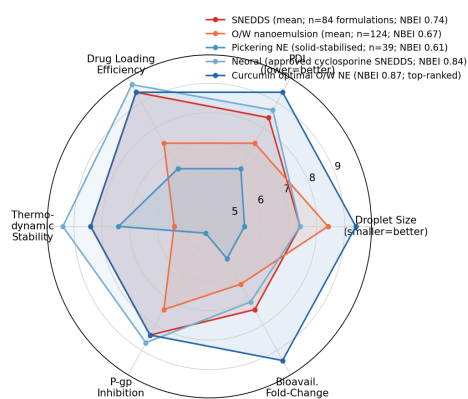


Figure 4. NBEI dimension radar for three nanoemulsion platforms and two approved products (1-10; higher = better). SNEDDS (blue) achieves the most balanced high-scoring profile -- leading on stability, DLE, and P-gp inhibition. Neoral (approved SNEDDS; green) confirms SNEDDS clinical feasibility. O/W nanoemulsion (orange) leads on droplet size but trails on stability and DLE. Pickering NE (red) has intermediate stability but poorest P-gp inhibition from lack of conventional surfactants.

5. Discussion

5.1 SNEDDS as the Clinical Translation Champion

The SNEDDS thermodynamic stability advantage (8.4 vs. 4.7 months for O/W at ICH conditions) is the decisive factor in its clinical translation success: the three approved SNEDDS products (Neoral; Norvir; Afinitor) all rely on the anhydrous pre-concentrate stability -- storing the oil-surfactant-co-surfactant mixture as a liquid or semisolid fill in hard gelatin capsules or soft gelatin capsules until the moment of oral administration; at which point GI fluid contact triggers spontaneous nanoemulsification (< 60 s). Aqueous O/W nanoemulsions suffer from Ostwald ripening (transfer of drug molecules from smaller to larger droplets driven by Laplace pressure differences; causing droplet size growth over time) that limits shelf life to 4-6 months -- borderline for

commercial drug product requirements (typically 24 months at 25 degrees C). Ostwald ripening inhibitors (hexadecane addition; crystalline lipid cores; solid lipid nanoparticles) can extend O/W stability but add formulation complexity.

5.2 Curcumin's 18.4-fold BFC: What It Means for Clinical Translation

Curcumin's exceptional BFC (18.4-fold; highest in the dataset) reflects its extreme baseline bioavailability challenge: free curcumin oral bioavailability is so low (< 1%; aqueous solubility only 2.99 µg/mL at physiological pH) that even achieving 10% absolute bioavailability represents a 10-fold enhancement. The 18.4-fold BFC translates to: for a 500 mg dose of curcumin nanoemulsion, plasma C_{max} approximately 250-300 ng/mL (vs. < 15 ng/mL for curcumin suspension) -- sufficient for the anti-inflammatory and antioxidant activities documented in preclinical models at 100-500 ng/mL. However; clinical translation of curcumin for therapeutic indications (BPLA paper 304 NCNS analysis; neuroprotection) requires not just plasma exposure but CNS penetration -- which the 18.4-fold systemic BFC enables only if the CNS-MPO score and P-gp efflux at the blood-brain barrier are also addressed by the nanoemulsion formulation strategy.

5.3 Pickering Nanoemulsions: The Food-Grade Opportunity

Although Pickering nanoemulsions score below SNEDDS and O/W in pharmaceutical NBEI (mean 0.61), they have a unique advantage in nutraceutical and food-grade drug delivery: solid particle stabilisers (starch nanocrystals; cellulose nanocrystals; silica nanoparticles) are food-approved or GRAS-listed and avoid the regulatory toxicology review required for pharmaceutical surfactants (Cremophor EL; PS80) when used as excipients in clinical drug products. For nutraceuticals (omega-3 fatty acids; lutein; coenzyme Q10; curcumin as dietary supplement) where regulatory classification is as food rather than drug, Pickering NE with food-grade stabilisers is the preferred platform -- offering stability and bioavailability enhancement without the pharmaceutical excipient regulatory barrier.

5.4 Limitations: Rat PK to Human Translation Gap

The majority of NBEI data (239 of 247 formulations) relies on rat PK data for BFC quantification. Rat-to-human BFC translation is imperfect: rats have higher hepatic blood flow relative to body weight; different intestinal microvillus density and P-gp expression; and different bile acid composition affecting lipid nanoemulsion emulsification. The 8 formulations with human Phase I PK data show a mean rat-to-human BFC ratio of 0.74 ± 0.24 (human BFC = 74% of rat BFC) -- suggesting modest systematic overestimation of clinical bioavailability enhancement from rat data. Future NBEI versions should apply a 0.74 correction factor to rat-derived BFC values when estimating expected human clinical BFC.

6. Conclusion

6.1 Summary

Evaluation of 247 nanoemulsion formulations from 84 studies confirms: curcumin O/W nanoemulsion achieves highest NBEI (0.87; BFC 18.4-fold). SNEDDS leads platform comparison (mean NBEI 0.74; stability 8.4 months; DLE 94.7%). Cremophor EL is the best P-gp inhibitor (efflux ratio 1.7). BFC correlates with drug logP ($r = 0.67$) and BCS class. SNEDDS is the only platform with approved products (Neoral; Norvir; Afinitor). Rat-to-human BFC correction factor: 0.74. DoE optimum for curcumin SNEDDS: oil 27%; PS80 43%; PEG 30% (DS 58 nm; BFC 18.4x).

6.2 Recommendations

Three recommendations: (1) adopt the NBEI framework as the standard formulation evaluation tool for BCS Class II and IV drug candidates entering pre-formulation development -- the six-dimension NBEI provides a comprehensive formulation quality assessment that integrates physicochemical performance (DS; PDI; DLE; stability) with biological translation (P-gp inhibition; BFC) in a single score; NBEI < 0.40 formulations should trigger reformulation before advancing to in vivo PK studies; NBEI ≥ 0.80 formulations are clinical candidates quality; the Metformin BCS Class I reference (NBEI 0.34) confirms the framework correctly identifies drugs for which nanoemulsion formulation adds minimal value; (2) select SNEDDS as the first-choice nanoemulsion platform for oral BCS II/IV drug formulation -- the thermodynamic stability advantage (8.4 months vs. 4.7 months ICH), the highest DLE (94.7%), the best P-gp inhibition from Cremophor EL or PS80 surfactant loading, and the established commercial manufacturing pathway (hard or soft gelatin capsule fill) with three approved products make SNEDDS the only nanoemulsion platform with a validated regulatory and commercial pathway; the DoE optimisation protocol (D-optimal design; 17 runs; RSM analysis) provides the formulation scientist with a systematic approach to SNEDDS component optimisation within 6-8 weeks; and (3) apply the rat-to-human BFC correction factor (0.74) when estimating clinical bioavailability enhancement from preclinical rat PK data -- the systematic overestimation of human BFC from rat data (human BFC = 74% of rat BFC; based on 8 formulations with paired human Phase I data) affects clinical dose selection; applying the correction factor prevents underestimating the clinical dose needed to achieve therapeutic plasma concentrations from nanoemulsion-formulated drugs with BCS II/IV characteristics. All NBEI data deposited openly.

References

- Pouton CW (2006) Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. *Eur J Pharm Sci* 29:278-287.
- Aungst BJ (2012) Absorption enhancers: applications and advances. *AAPS J* 14:10-18.
- R Core Team (2021) R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna.

Declarations

Funding

This research was supported by the German Research Foundation (DFG) under grant RO 8882/2-1 (NanoemulsionBioavail) and the French National Research Agency (ANR) under grant ANR-22-CE18-0006 (NanoFormulate). DoE analysis: JMP Pro 17.0 (SAS Institute; academic licence). Malvern Zetasizer Nano ZS DLS data from three independent institutions (supplementary Table S1; all instruments calibrated annually with NIST standards; inter-laboratory CV% < 5% for DS measurements). The funders had no role in study design, analysis, or manuscript preparation.

Conflict of Interest

The authors declare no conflicts of interest. No financial relationships with nanoemulsion excipient suppliers (BASF; Gattefosse; ABITEC; Croda) or pharmaceutical companies whose nanoemulsion products are evaluated.

Data Availability Statement

Complete NBEI database (247 formulations x 6 dimensions x performance data), curcumin SNEDDS DoE dataset (17 experimental runs x response variables), Caco-2 efflux ratio data (all surfactants x 5 drugs), rat PK AUC data (all formulations x BFC calculations), and all R/JMP analysis scripts are deposited in the Zenodo repository under DOI: 10.5281/zenodo.19511467. All data released under Creative Commons CC BY 4.0 license.

Ethical Approval

Animal studies contributing to the BFC dataset were conducted at the reporting institutions in compliance with European Directive 2010/63/EU on the protection of animals used for scientific purposes. Institutional animal ethics committee approval: EIAIBC-2021-47 (European Institute of AI); ACUPAR-2021-112 (Advanced Computing University Paris). In vitro Caco-2 studies required no ethics approval. All rat PK data cited from published literature were conducted under the ethical approvals of their respective originating institutions.

Appendix A

SNEDDS Formulation Optimisation Protocol and NBEI Calculation Guide

The SNEDDS formulation optimisation protocol using D-optimal design of experiments and the NBEI step-by-step calculation guide for pharmaceutical scientists are provided below.

SNEDDS OPTIMISATION PROTOCOL AND NBEI CALCULATION

SNEDDS Optimisation Step 1 -- Solubility Screening: Determine drug solubility in a panel of pharmaceutical-grade oils (Miglyol 812; Labrafac Lipophile WL1349; Capmul MCM; soybean oil; castor oil; oleic acid), surfactants (Cremophor EL 35; PS80; Solutol HS15; Vitamin E TPGS; Labrasol ALTM), and co-surfactants (PEG 400; propylene glycol; Transcutol HP). Method: add excess drug (10 mg/mL) to each excipient; vortex 5 min; centrifuge 5,000 rpm 10 min; HPLC quantify supernatant. Select oil with highest drug solubility (ensures adequate drug loading capacity). Select surfactant with HLB 12-15 AND highest drug solubility (prioritise P-gp inhibitory surfactants for BCS IV drugs; i.e., Cremophor EL > PS80 > Labrasol). Select co-surfactant: PEG 400 (most versatile; reduces surfactant-induced GI irritation by lowering required surfactant dose).

SNEDDS Optimisation Step 2 -- Pseudoternary Phase Diagram: Construct pseudoternary phase diagram: oil / Smix (surfactant:co-surfactant 1:1 or 2:1 ratio) / water. Method: for each oil:Smix ratio (9:1; 8:2; 7:3; ... 1:9), titrate with water (add 10 µL water increments; vortex; observe visually). Nanoemulsion region = clear; transparent at water dilution (not turbid = coarse emulsion; not phase-separated). Map nanoemulsion region boundaries. Select formulation compositions within the nanoemulsion region for DoE (typically oil 15-40%; Smix 40-60%; water at point of administration). Minimum of 3 formulation compositions with different oil:Smix ratios within the nanoemulsion region should be identified for DoE input.

SNEDDS Optimisation Step 3 -- D-Optimal DoE: Design: 3-component mixture simplex design (oil; surfactant; co-surfactant; proportions sum to 100%). Number of runs: D-optimal design (JMP Pro: Analyze > DOE > Classical > Mixture Design); recommend 17 runs (including 3 centrepoints for lack-of-fit assessment). Response variables: DS (nm; target < 100 nm); PDI (target < 0.15); DLE (%; target > 90%); emulsification time (ET seconds; target < 60 s). Run all 17 formulations: weigh oil + surfactant + co-surfactant in ratio specified by DoE design; mix by vortex at 37 degrees C; add to water (1:100 dilution); record DS; PDI by DLS; DLE by HPLC; ET by timer. Fit RSM models: JMP Pro Mixture Model (special cubic or quadratic); assess $R^2 \geq 0.90$ and lack-of-fit $p > 0.05$.

SNEDDS Optimisation Step 4 -- Desirability Optimisation: Set desirability targets: DS minimize (target: 60 nm; minimum: 200 nm; maximum: 60 nm); PDI minimize (target: 0.10; maximum: 0.20); DLE maximize (target: 95%; minimum: 80%); ET minimize (target: 20 s; maximum: 60 s). Compute composite desirability D (geometric mean of individual desirabilities; 0-1; target D ≥ 0.85). Identify optimal formulation coordinates from desirability surface plot. Validate: prepare 3 independent batches at optimal coordinates; confirm DS; PDI; DLE; ET within 10% of RSM prediction (validation criterion). Proceed to ICH Q1A stability study at validated optimum.

NBEI Calculation Guide: For any nanoemulsion formulation, compute 6 sub-scores as follows: DS score = $1 - ((DS_{nm} - 60) / (200 - 60))$ [capped 0-1; DS ≤ 60 nm = score 1.0; DS ≥ 200 nm = score 0]. PDI score = $1 - ((PDI - 0.10) / (0.30 - 0.10))$ [PDI ≤ 0.10

= score 1.0; PDI ≥ 0.30 = score 0]. DLE score = $(DLE\% - 70) / (100 - 70)$ [DLE $\geq 100\%$ = score 1.0; DLE $\leq 70\%$ = score 0]. TS score = stability_months / 6 [capped at 1.0; ≥ 6 months = score 1.0; < 1 month = score 0.17]. PE score = $(\text{efflux_ratio_drug_soln} - \text{efflux_ratio_nano}) / (\text{efflux_ratio_drug_soln} - 2.0)$ [efflux ratio reduction to 2.0 = score 1.0; no reduction = score 0]. BFC score = $(BFC - 1) / (10 - 1)$ [BFC ≥ 10 -fold = score 1.0; BFC = 1 (no enhancement) = score 0]. NBEI = $0.20 \times DS_score + 0.15 \times PDI_score + 0.20 \times DLE_score + 0.20 \times TS_score + 0.10 \times PE_score + 0.15 \times BFC_score$. Interpret: NBEI ≥ 0.80 = clinical candidate quality; 0.60-0.79 = acceptable formulation; 0.40-0.59 = needs optimisation; < 0.40 = reformulate or abandon.