Outrunning Precipitation: Supersaturable SNEDDS for Oral Naringenin

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Abstract*—Naringenin, the citrus flavanone aglycone of naringin, has an unusually broad preclinical pharmacology — antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, cardioprotective and anticancer — and an unusually poor record of clinical translation. The reason is biopharmaceutical rather than pharmacological: an aqueous solubility of the order of tens of micrograms per millilitre, extensive intestinal and hepatic glucuronidation, and susceptibility to intestinal efflux together hold its reported oral bioavailability near the single-digit percent range. A long list of nanocarriers — cyclodextrin complexes, polymeric nanoparticles, nanosuspensions and nanocrystals, liposomes, mixed micelles, solid dispersions, solid lipid nanoparticles, nanostructured lipid carriers and self-nanoemulsifying drug delivery systems (SNEDDS) — has been applied to the problem, with reported gains in oral exposure ranging from roughly two-fold to more than thirteen-fold. Conventional SNEDDS occupy a favourable position in that list, but they share a structural weakness: drug loading is bounded by equilibrium solubility in the oil–surfactant blend, and the fine dispersion formed on dilution in gastrointestinal fluid is a solution that wants to crystallise. Supersaturable SNEDDS (S-SNEDDS) address this directly by incorporating a small proportion of a water-soluble polymeric precipitation inhibitor, converting a transient concentration spike into a sustained, kinetically stabilised supersaturated state — the "spring and parachute". The approach has repeatedly outperformed its conventional counterpart for paclitaxel, AMG 517, silybin, fenofibrate and curcumin, yet it has not been systematically applied to naringenin. This review consolidates what is known about naringenin's absorption barriers, audits the delivery systems reported for it, sets out the mechanism and polymer selection logic of supersaturable lipid formulations, and argues that a Quality by Design-optimised naringenin S-SNEDDS is both a rational and an unoccupied position in the field.

***Index Terms*—Naringenin; supersaturable SNEDDS; precipitation inhibitor; oral bioavailability; lipid-based formulation; Quality by Design; Box–Behnken design**

I. INTRODUCTION

Poor aqueous solubility is the defining formulation problem of the modern pharmaceutical pipeline. Roughly forty per cent of marketed compounds and the majority of current development candidates are poorly water-soluble, and such molecules are predisposed to low and variable oral bioavailability and, consequently, to variable clinical response [1]. The same arithmetic applies with greater force to plant-derived actives, which were never optimised by medicinal chemistry for developability and which frequently arrive with a second liability attached — extensive pre-systemic conjugative metabolism.

Naringenin (4′,5,7-trihydroxyflavanone) is a textbook case. It is the aglycone of the citrus flavanone glycoside naringin, abundant in grapefruit, oranges and tomato skin, and it has been credited across a very large preclinical literature with antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, cardioprotective, neuroprotective and anticancer activity, mechanistically linked to free-radical scavenging, modulation of nuclear factor-kappa B and mitogen-activated protein kinase signalling, suppression of pro-inflammatory cytokine expression, and favourable effects on lipid and glucose handling [2,3]. Reviews of the clinical trial evidence have reached a consistent and somewhat deflating conclusion: the preclinical promise is real, but clinical translation is held back principally by poor and erratic

oral bioavailability, and advanced delivery strategies are explicitly called for [3,4].

The numbers justify that framing. Naringenin is a crystalline, hydrophobic solid whose reported aqueous solubility is of the order of 46 ± 6 μg mL^{-1} and whose oral bioavailability has been reported at approximately 5.8% [6]. It is variously assigned to class II or class IV of the Biopharmaceutics Classification System depending on the permeability data invoked [4,5]. Dissolution is therefore rate-limiting, and whatever does dissolve must then survive first-pass glucuronidation and sulfation in the enterocyte and the hepatocyte before it reaches the systemic circulation as the pharmacologically active aglycone [7].

A great deal of formulation effort has been directed at the first of those barriers. Cyclodextrin complexation, polymeric nanoparticles, nanosuspensions and nanocrystals, liposomes, mixed micelles, amorphous solid dispersions, solid lipid nanoparticles, nanostructured lipid carriers and self-nanoemulsifying systems have all been reported to improve naringenin's dissolution and, in most cases, its in vivo exposure [5]. Among lipid-based options, self-nanoemulsifying drug delivery systems (SNEDDS) are attractive because they present the drug already molecularly dissolved, generate an enormous oil–water interfacial area in situ without external energy, and can additionally modulate intestinal efflux through their surfactant component.

Conventional SNEDDS nevertheless carry a built-in ceiling. Drug loading is conventionally set at or below the equilibrium solubility of the drug in the oil–surfactant–cosurfactant blend, and the colloidal dispersion generated on aqueous dilution is thermodynamically disposed to shed its payload as crystals. When that happens, the absorption window closes before the dose has been absorbed. Supersaturable SNEDDS (S-SNEDDS) attack precisely this step: a small proportion of a water-soluble polymeric precipitation inhibitor is included so that the supersaturated state generated on dilution is held, kinetically, for long enough to be useful [32,36].

This review has three purposes. First, to assemble, in one place and with the reported figures attached, what is actually known about naringenin's pharmacokinetic limitations in animals and in humans. Second, to audit the delivery systems reported for the flavanone and ask what each achieved. Third, to set out the mechanistic and polymer-selection logic of supersaturable lipid formulations, and to argue that their application to naringenin — under a Quality by Design framework — is a rational and, at present, largely unoccupied position.

II. NARINGENIN: THE MOLECULE AND ITS ABSORPTION PROBLEM

2.1 Physicochemical identity

Naringenin is 5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one, $C_{15}H_{12}O_5$, molecular weight 272.25 g mol^{-1}, an off-white to pale yellow crystalline powder. It is practically insoluble in water and freely soluble in dimethyl sulfoxide and ethanol. Published aqueous solubility values cluster in the tens of micrograms per millilitre — 46 ± 6 μg mL^{-1} is the figure most often quoted in the lipid-nanoparticle literature [6] — although higher values appear elsewhere depending on temperature, pH and the analytical method used [5]. The molecule carries three phenolic hydroxyls and a chiral centre at C-2; commercial material is normally racemic, and stereoselective disposition has been proposed as one contributor to the variability of its reported activity.

Two consequences follow for formulation. The phenolic hydroxyls are hydrogen-bond donors, which matters a great deal when selecting a precipitation-inhibiting polymer, since drug–polymer hydrogen bonding is one of the principal mechanisms by which such polymers retard nucleation [37,38]. And the crystalline, relatively high-melting character of the solid means that simple dissolution in an oil phase is not guaranteed; solubility screening across oils, surfactants and cosurfactants is a necessary first step rather than a formality [26].

2.2 Pharmacokinetics in humans

Human data for naringenin are better than is sometimes assumed, and they tell a consistent story of rapid absorption, near-complete conjugation and short residence.

Erlund and colleagues characterised plasma kinetics and urinary excretion of naringenin and hesperetin in healthy volunteers after orange juice and grapefruit juice. Peak plasma concentrations were 0.6 ± 0.4 μmol L^{-1} for naringenin from orange juice and 6.0 ± 5.4 μmol L^{-1} from grapefruit juice; elimination half-lives fell between 1.3 and 2.2 h, and relative urinary excretion was 30.2 ± 25.5% from grapefruit juice

against 1.1 ± 0.8% from orange juice. Interindividual variation in bioavailability was described as remarkable [9]. The standard deviations in those figures are as informative as the means: they are of the same order as the central estimates.

Kanaze and co-workers went further and dosed the pure aglycones as solid dispersion capsules, reporting an area under the curve for naringenin of 9424.52 ± 2960.52 ng·h mL^{-1} and an elimination half-life of 2.31 ± 0.40 h, with absorption occurring rapidly and almost entirely in conjugated form. Cumulative urinary recovery indicated low bioavailability for both flavanone aglycones, attributed to extensive first-pass metabolism including bacterial C-ring cleavage to phenolic acids [8].

The most formal human dataset comes from a Phase 1 single-ascending-dose, placebo-controlled, double-blind crossover trial in 18 healthy adults given 150, 300, 600 and 900 mg naringenin as a whole-orange extract. No relevant adverse events or changes in blood safety markers were observed at any dose. Maximal serum concentrations were 15.76 ± 7.88 μM after 150 mg and 48.45 ± 7.88 μM after 600 mg; times to peak were 3.17 ± 0.74 h and 2.41 ± 0.74 h respectively; the 24-hour area under the curve after 600 mg was 199.05 ± 24.36 μM·h, apparent oral clearance was 10.21–13.70 L h^{-1}, and the half-life was 2.65–3.0 h. Serum concentrations were proportional to dose, and the authors concluded that 300 mg twice daily would be likely to produce a physiological effect, given that 8 μM is active in primary human adipocytes [10].

That last point frames the formulation task precisely. Naringenin is safe at gram-scale oral doses and its exposure scales with dose — but reaching a pharmacologically useful concentration currently requires hundreds of milligrams, administered repeatedly, with substantial inter-subject scatter. A formulation that raises and stabilises exposure does not merely improve a number on a chart; it reduces dose, reduces variability, and makes a twice-daily regimen defensible.

Species comparison reinforces the mechanistic picture. In a study spanning rats, dogs and humans dosed with naringin, naringenin showed a considerable lag time in human plasma — 5.74 ± 2.38 h — attributable to intestinal metabolism, with concentrations rising to C_{max} at approximately 3.62 ± 3.19 h. Twelve metabolites were detected in rat and human liver and kidney microsomes, and metabolism proved to be a complex process catalysed simultaneously by multiple human enzymes, with clear species differences [7].

2.3 The three barriers

It is useful to separate the obstacles, because different formulation strategies address different ones and a strategy that addresses only the first will plateau.

The first barrier is dissolution and luminal solubilisation. At tens of micrograms per millilitre, a 300 mg dose cannot dissolve in the available gastrointestinal volume. This is the barrier that particle-size reduction, complexation, amorphisation and lipid solubilisation all target, and it is the barrier that has received almost all the attention.

The second is pre-systemic conjugative metabolism. Naringenin is extensively glucuronidated and, to a lesser extent, sulfated in the intestinal wall and the liver, so that most of what is absorbed appears in plasma as conjugates rather than free aglycone [7,8]. Conjugated forms account for the great majority of circulating flavanone. A delivery system that promotes intestinal lymphatic transport can in principle bypass part of the hepatic component of this first-pass loss, which is one of the classical arguments for lipid-based vehicles [27].

The third is efflux. Flavonoids including naringenin interact with intestinal efflux transporters, and apical extrusion back into the lumen reduces net flux across the enterocyte. Here the surfactant component of a lipid formulation is not merely an emulsifier: non-ionic surfactants of the type routinely used in self-emulsifying systems — polyoxyl castor oil derivatives, polysorbates, caprylocaproyl macrogolglycerides — have been reviewed as P-glycoprotein efflux inhibitors capable of improving oral delivery [11]. The same excipient therefore does double duty, and a formulation that reduces surfactant load must be careful not to discard this benefit along with the irritation risk.

No single mechanism explains naringenin's poor performance, which is why multi-mechanistic platforms have tended to do better than single-mechanism ones, and why a supersaturating lipid system — which simultaneously solubilises, supersaturates, supplies efflux-modulating surfactant

and offers a lymphatic route — is an appealing proposition.

III. WHAT HAS BEEN TRIED: AN AUDIT OF NARINGENIN DELIVERY SYSTEMS

Table 1 collects the principal reported systems with their characterisation data and in vivo outcomes. Figure 1A plots the fold increases in oral exposure where a figure was reported. Several observations emerge.

Complexation works, and works early. Hydroxypropyl-β-cyclodextrin increased naringenin solubility by more than 400-fold and its transport across a Caco-2 model of the gut epithelium by 11-fold; in rats, the complex raised the area under the curve 7.4-fold and the peak concentration 14.6-fold. Administered immediately before a meal it reduced very-low-density lipoprotein by 42% and increased the rate of glucose clearance by 64% relative to naringenin alone, with no histological evidence of intestinal, renal or hepatic damage [12]. This remains one of the cleanest demonstrations that naringenin's problem is delivery rather than potency.

Vesicular systems achieve the largest reported gain. An orally administered naringenin liposome of 70.53 ± 1.71 nm, zeta potential −37.4 ± 7.3 mV and entrapment efficiency 72.2 ± 0.8% increased the area under the curve from 16,648 to 223,754 ng mL^{-1}·h in mice — a 13.44-fold rise in relative bioavailability — with distribution predominantly to the liver [16]. Elastic liposomes have also been developed for naringenin, though for topical rather than oral application [17].

Micellar solubilisation delivers the most informative absolute figure. A mixed micelle of naringenin, Pluronic F127 and Tween 80 at 1:10:0.2 (w/w/w), prepared by thin-film hydration, raised solubility 27-fold and increased absolute oral bioavailability in rats from 4.1% to 26.9% [18]. Because this is an absolute rather than a relative figure, it quantifies the headroom available: roughly three-quarters of an oral dose was still being lost even by a well-performing formulation. Particulate and amorphous systems form a consistent middle group. Eudragit-based polymeric nanoparticles improved release and conferred superior hepatoprotection in carbon tetrachloride-intoxicated rats [13]; nanosuspensions improved dissolution and rat pharmacokinetics [14]; nanocrystals improved dissolution, cellular uptake, transcellular diffusion and oral bioavailability, and were effective in collagen-induced arthritic rats [15]; a Soluplus solid dispersion prepared by solvent evaporation gave significantly higher solubility and dissolution than pure drug with a corresponding increase in area under the curve [19]. Nanostructured lipid carriers of 171.9 ± 2.0 nm with 99.9% entrapment and 23.7% loading raised C_{max} and $AUC_{0–t}$, accelerated transepithelial transport in MDCK cells and jejunal and ileal absorption, and reduced hepatic lipid accumulation in a methionine/choline-deficient NAFLD mouse model [20]. Hybrid architectures continue to appear, including naringenin encapsulated in ZIF-8 metal–organic frameworks and then into liposomes of 113.2 ± 1.4 nm [21].

Self-nanoemulsifying systems are well represented and well behaved. The key direct precedent is the naringenin SNEDDS of Khan and colleagues, which produced droplets below 50 nm by transmission electron microscopy, survived freeze–thaw cycling and centrifugation, and gave significantly higher in vitro release and a significantly increased $AUC_{0–24}$ compared with the drug alone [22]. More recently a D-optimal mixture design identified an optimal composition of 10% triacetin, 70% Tween 80 and 20% Transcutol P, yielding 88.74 ± 2.27% transmittance, a particle size of 14.8 nm, drug loading of 51.13 ± 4.53 mg L^{-1} and an emulsification time of 18.58 ± 0.62 s [23]. For the parent glycoside naringin, a cationic arginine-modified SNEDDS based on cinnamon oil, Labrasol and Transcutol gave droplets of 118.47 ± 21.16 nm, increasing to 162.17 ± 19.11 nm on incorporation of the alkylated arginine, with improved antioxidant and anticancer activity [24].

Two things are conspicuous by their absence from this body of work. First, almost none of these reports characterise what happens to the dissolved drug over time after dilution — the dissolution experiments are typically run under sink conditions, which is precisely the condition under which precipitation cannot be observed. Second, no reported naringenin lipid formulation incorporates a precipitation inhibitor by design. The field has optimised the spring and ignored the parachute.

Table 1. Delivery systems reported for naringenin, with characterisation data and in vivo outcomes as published. Fold-increases are relative to free drug or plain suspension in the species indicated and are not directly comparable across studies.

System	Composition / key features	Size, charge, entrapment	Reported outcome	Ref.
HP-β-CD inclusion complex	Hydroxypropyl-β-cyclodextrin (FDA-approved excipient)	Molecular complex	Solubility ↑ >400-fold; Caco-2 transport ↑ 11-fold; rat AUC ↑ 7.4-fold, C_{max} ↑ 14.6-fold; VLDL ↓ 42%	[12]
Polymeric nanoparticles	Eudragit E100 / polyvinyl alcohol	Nanoscale; reduced crystallinity by XRD	Higher release rate and improved solubility; superior hepatoprotection in CCl_4-intoxicated rats	[13]
Nanosuspension	Stabiliser-coated drug nanocrystals	Submicron crystalline particles	Improved in vitro dissolution and rat pharmacokinetic parameters vs plain drug	[14]
Nanocrystals	Stabilised naringenin nanocrystals	Nanocrystalline	Superior dissolution, cellular uptake and transcellular diffusion; improved rat bioavailability; efficacy in collagen-induced arthritis	[15]
Liposomes (oral)	Phospholipid vesicles	70.53 ± 1.71 nm; ·ζ −37.4 ± 7.3 mV; EE 72.2 ± 0.8%	AUC 16,648 → 223,754 ng mL^{-1}·h; 13.44-fold relative bioavailability in mice; liver-predominant distribution	[16]
Elastic liposomes (topical)	Epikuron–cholesterol–Tween 80	Nanovesicular; two-factor three-level design	Enhanced skin permeation and deposition; dermal rather than oral application	[17]
Mixed micelles	Naringenin : Pluronic F127 : Tween 80, 1:10:0.2 (w/w/w), thin-film hydration	Micellar; no significant loss of cell viability	Solubility ↑ 27-fold; absolute oral bioavailability 4.1% → 26.9% in rats	[18]
Solid dispersion	Soluplus carrier; solvent evaporation and kneading	Reduced crystallinity (DSC, XRD)	Significantly higher solubility and dissolution (Higuchi kinetics); increased AUC vs pure drug	[19]
Solid lipid nanoparticles	Emulsification and low-temperature solidification; lipid selected by group contribution method	Submicron lipid matrix	Sustained release and improved pulmonary pharmacokinetics; baseline solubility 46 ± 6 μg mL^{-1}, F ≈ 5.8% reported	[6]
Nanostructured lipid carriers	Thin-film dispersion	171.9 ± 2.0 nm; EE 99.9 ± 0.0%; loading 23.7 ± 0.3%	↑ C_{max} and $AUC_{0–t}$; ↑ MDCK transport and jejunal/ileal absorption; efficacy in MCD-diet NAFLD mice	[20]
MOF-in-liposome hybrid	Naringenin@ZIF-8 encapsulated into liposomes	113.2 ± 1.4 nm; ζ −7.54 ± 0.26 mV	Spherical, uniform, structurally intact vesicles; proof of concept for hybrid carriers	[21]
SNEDDS	Isotropic oil–surfactant–cosurfactant mixture	Droplets < 50 nm by TEM; stable to freeze–thaw and centrifugation	Significantly higher in vitro release ($p < 0.005$) and $AUC_{0–24}$ than naringenin alone	[22]

System	Composition / key features	Size, charge, entrapment	Reported outcome	Ref.
SNEDDS (D-optimal design)	Triacetin 10%, Tween 80 70%, Transcutol P 20%	14.8 nm; transmittance 88.74 ± 2.27%	Emulsification time 18.58 ± 0.62 s; drug loading 51.13 ± 4.53 mg L^{-1}	[23]
Cationic SNEDDS (naringin)	Cinnamon oil–Labrasol–Transcutol with alkylated arginine	118.47 ± 21.16 nm → 162.17 ± 19.11 nm with arginine	Stable to dilution; improved antioxidant capacity and anticancer activity in CML cells	[24]

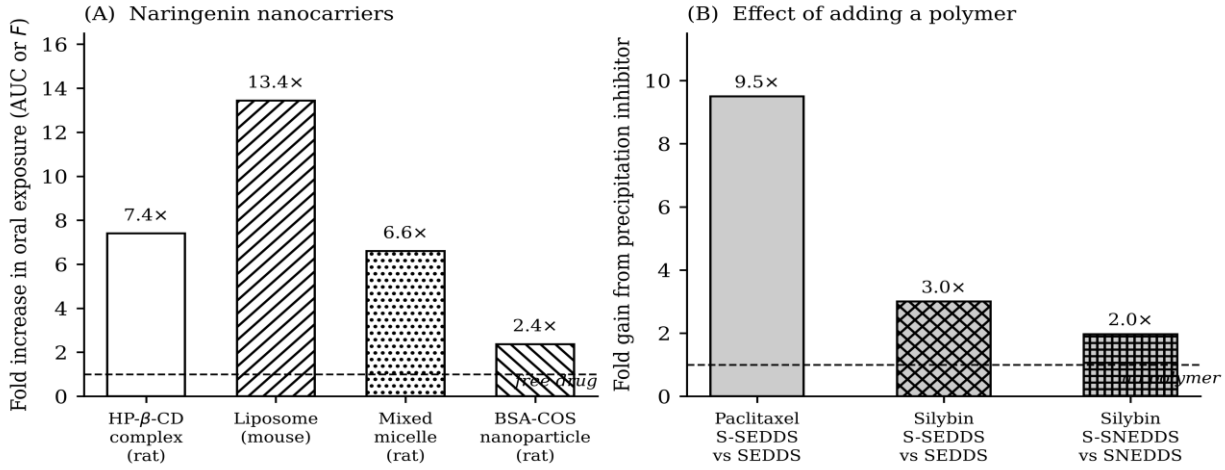


Fig. 1. (A) Reported fold increases in oral exposure for naringenin delivery systems relative to free drug: hydroxypropyl-β-cyclodextrin complex in rats [12], liposomes in mice [16], Pluronic F127/Tween 80 mixed micelles in rats (absolute bioavailability 4.1% → 26.9%) [18], and chitosan oligosaccharide-modified albumin nanoparticles in rats. Values are drawn from different species, doses and assays and are indicative rather than strictly comparable. (B) Incremental gain attributable to the precipitation inhibitor alone, comparing supersaturable against otherwise equivalent conventional lipid formulations: paclitaxel S-SEDDS (F ≈ 9.5% vs ≈ 1%) [33], silybin S-SEDDS ($AUC_{0–12}$) [41], and silybin S-SNEDDS (relative bioavailability 197% of the conventional SNEDDS).

IV. SNEDDS: MECHANISM, CLASSIFICATION AND THE LIMIT

Self-nanoemulsifying drug delivery systems are isotropic mixtures of a lipid phase, a surfactant and usually a cosurfactant, formulated such that the mild agitation supplied by gastrointestinal motility suffices to generate a fine oil-in-water nanoemulsion in situ, without external energy input [25,30]. Pouton's lipid formulation classification system organises these vehicles into four types according to the proportions of oil, water-insoluble surfactant, water-soluble surfactant and hydrophilic cosolvent, and predicts how each will behave on dispersion and digestion — type I requires digestion, types II and III self-emulsify with increasing hydrophilic content, and type IV contains no oil at all [25,26]. The classification matters because loss of solvent capacity on dispersion, which is the proximate cause of precipitation, increases as one moves toward the hydrophilic end of the series.

The mechanisms by which such vehicles improve oral absorption are well established. They present the drug pre-dissolved within nanoscale droplets of very large interfacial area, so that the dissolution step is effectively bypassed; they maintain luminal solubilisation through the colloidal species generated by lipid digestion; they can promote intestinal lymphatic transport for sufficiently lipophilic actives, partially circumventing hepatic first pass; and their non-ionic surfactants can attenuate efflux at the brush border [11,27]. The physical chemistry of spontaneous, low-energy emulsification — governed by surfactant–oil–water phase behaviour rather than by shear input — has been reviewed in detail and underpins the whole platform [28,29].

The limitation is structural rather than incidental. To keep the drug in solution after the substantial aqueous dilution encountered in the gut, a conventional formulation must either load the drug below its equilibrium solubility in the oil–Smix blend or carry a high surfactant concentration, and high surfactant loads bring gastrointestinal irritation potential and capsule-compatibility problems of their own. Even then, dilution and digestion progressively degrade the solvent capacity of the vehicle, and the drug that was comfortably dissolved in the concentrate becomes supersaturated, then nucleates, then crystallises in the lumen. Recent comprehensive reviews of the SNEDDS platform identify supersaturable and precipitation-inhibitor-based strategies as the principal active refinement intended to address exactly this [31].

V. SUPERSATURATION: THE SPRING AND THE PARACHUTE

The conceptual move that defines supersaturable formulations is to stop treating precipitation as a failure to be avoided by conservative loading and to start treating it as a rate process to be manipulated.

Absorption across the intestinal membrane is driven by the concentration of free, dissolved drug in the lumen, not by equilibrium solubility. A supersaturated solution — one in which the dissolved concentration C exceeds the crystalline solubility C_{ek}, giving a supersaturation ratio $SR = C/C_{ek}$ greater than unity — therefore presents a higher thermodynamic activity and a larger driving force for flux than any saturated solution can. Supersaturating drug delivery systems exploit this by containing the drug in a high-energy or rapidly dissolving form such that intraluminal concentrations above saturation solubility are generated [32]. The cost is that such a state is metastable: it will relax by nucleation and crystal growth, and the higher the supersaturation generated, the greater the thermodynamic pressure to do so.

This is the origin of the “spring and parachute” metaphor illustrated in Figure 2. The spring is whatever mechanism generates supersaturation rapidly — in a SNEDDS, the spontaneous emulsification of a concentrate in which the drug is already dissolved. The parachute is whatever slows the return to equilibrium. Without a parachute, the concentration profile is a spike followed by a crash, and the area between the curve and the solubility line — which is what the absorbing membrane actually sees — is small. With one, the same spike is followed by a plateau, and the absorption window widens from minutes to hours.

The approach was established in lipid formulations by Gao and co-workers, who developed a supersaturable self-emulsifying system for paclitaxel using hydroxypropyl methylcellulose as a precipitation inhibitor. In vitro dilution of the supersaturable formulation produced a microemulsion followed only by slow crystallisation on standing, whereas the formulation without the polymer precipitated rapidly to a low solution concentration. In male Sprague-Dawley rats dosed orally at 10 mg kg^{-1}, bioavailability was approximately 9.5% from the supersaturable formulation against approximately 1% without the polymer; co-administration of cyclosporin A as an efflux and CYP3A4 inhibitor raised it further to approximately 22.6% [33]. The design principles were subsequently generalised [34].

A later study of AMG 517 made the mechanism visible. Precipitates recovered from in vitro test media were amorphous when hydroxypropyl methylcellulose was present in the supersaturable formulation, but crystalline when the polymer was absent or when polyvinylpyrrolidone was used instead — direct evidence that the polymer acts on the solid form that separates, not merely on bulk viscosity, and that polymer identity is not interchangeable [35]. The current status of the field, including formulation and biopharmaceutical considerations for dispersion and digestion, has been reviewed comprehensively [36].

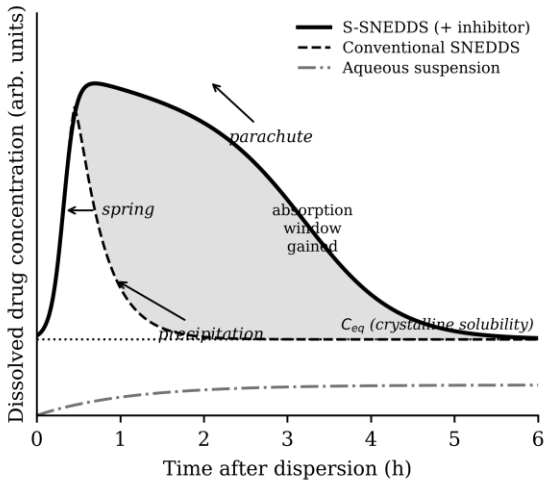


Fig. 2. The spring-and-parachute principle, shown schematically. A conventional SNEDDS generates

supersaturation rapidly on dispersion (the spring) but precipitates quickly back toward crystalline solubility C_{ek}. A supersaturable SNEDDS generates the same initial concentration but the polymeric precipitation inhibitor retards nucleation and crystal growth (the parachute), holding free drug above C_{ek} for a far longer period. The shaded area represents the additional absorption opportunity. A plain aqueous suspension never reaches C_{ek} within the transit window. Curves are illustrative and not drawn from a single dataset.

Table 2. Polymeric precipitation inhibitors in supersaturable lipid-based formulations: reported behaviour and the systems in which it was demonstrated.

Polymer	Reported behaviour	System demonstrated in	Ref.
Hydroxypropyl methylcellulose (HPMC)	Retards nucleation and crystal growth after dilution; precipitate recovered from test media is amorphous rather than crystalline, indicating action on the separating solid phase	Paclitaxel S-SEDDS; AMG 517 S-SEDDS	[33,35]
HPMC (5% w/w in Smix)	Smaller droplets after dilution in 0.1 M HCl than the polymer-free system; sustained the supersaturated state by retarding precipitation kinetics; $AUC_{0–12}$ increased nearly three-fold	Silybin S-SEDDS	[41]
HPMC E4M (with Eudragit RL100, PPGAE)	Most effective of the inhibitors screened in delaying precipitation; in vitro supersaturation correlated well with in vivo exposure in rats	Fenofibrate, type IV formulation	[39]
Polyvinylpyrrolidone (PVP)	Inhibition depends on polymer concentration via drug–polymer molecular interaction, not on medium viscosity; gave crystalline rather than amorphous precipitate in at least one S-SEDDS, and was less effective than HPMC there	AMG 517; model BCS class II drugs	[35,37]
Cellulose derivatives (as a class)	Identified as the most effective group in a screen of 53 polymeric materials against supersaturated solutions of a model drug	Danazol	[37]
Cellulosic polymers (comparative)	Polymer physicochemical properties govern how long a supersaturated concentration survives before nucleation and precipitation occur	Model poorly soluble drugs	[38]
Hydrophilic polymer in SMEDDS	Significantly enhanced in vitro supersaturation maintenance and in vivo oral bioavailability relative to the conventional non-supersaturable system	Curcumin S-SMEDDS	[40]
Soluplus	Used as a supersaturation stabiliser in a solid self-microemulsifying system to improve absorption of a poorly water-soluble drug	Fenofibrate, solid S-SMEDDS	[42]

VI. CHOOSING THE PARACHUTE: POLYMERIC PRECIPITATION INHIBITORS

If the polymer is the active principle of a supersaturable formulation, its selection deserves more than a default choice of hydroxypropyl methylcellulose. Table 2 summarises the reported behaviour of the main candidates.

The most systematic screen remains that of Warren and colleagues, who reviewed the fundamental principles underpinning drug precipitation and its inhibition and presented precipitation-inhibition data for 53 polymeric materials against supersaturated danazol solutions. Their conclusion was that a group of polymers with superior precipitation-inhibition qualities can be identified, the majority of which are cellulose-based, while cautioning that the molecular

determinants of polymer utility remain relatively poorly understood [37]. That caution still stands, and it has a practical corollary: inhibitor selection for a new drug is an experimental question, not a literature-transfer question.

Mechanistically, polymers act by interfering with nucleation and crystal growth. They adsorb at the nascent crystal surface, they hydrogen-bond to dissolved drug molecules and so reduce the activity available for assembly into nuclei, and they can increase the viscosity of the diffusion layer. Work on cellulosic polymers has shown that their physicochemical properties govern the duration for which supersaturation can be maintained before nucleation and precipitation occur [38]. For polyvinylpyrrolidone, precipitation inhibition has been shown to depend on polymer concentration through molecular drug–polymer interactions rather than on the molecular mobility of the drug in solution, since medium viscosity had no influence.

Because naringenin presents three phenolic hydroxyl groups, hydrogen-bond-accepting polymers are mechanistically plausible candidates, and cellulose ethers and esters — hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate — together with polyvinylpyrrolidone and the graft copolymer Soluplus constitute the rational screening set.

The performance evidence across model drugs is encouraging and reasonably consistent. In a type IV lipid formulation of fenofibrate, hydroxypropyl methylcellulose E4M together with the lipid-soluble polymers Eudragit RL100 and poly(propylene glycol) bis(2-aminopropyl ether) were the most effective inhibitors of precipitation, and a good correlation was found between the degree of in vitro supersaturation and in vivo exposure in rats — confirming that relatively brief periods of supersaturation can suffice to promote absorption of a highly permeable drug [39]. For silybin, a high-payload supersaturable self-emulsifying system containing 5% hydroxypropyl methylcellulose produced smaller droplets on dilution with 0.1 M hydrochloric acid than the conventional system and increased $AUC_{0–12}$ by nearly three-fold at a dose of 533 mg kg^{-1}, with the polymer demonstrably sustaining the supersaturated state by retarding precipitation kinetics [41]. Soluplus has been used as a supersaturation stabiliser in a solid self-microemulsifying system for fenofibrate [42].

The most directly relevant precedent for a flavonoid is curcumin. A supersaturatable self-microemulsifying system incorporating a hydrophilic polymer gave significantly enhanced in vitro supersaturation maintenance and in vivo oral bioavailability relative to the conventional, non-supersaturable formulation of the same poorly soluble natural product [40]. Curcumin and naringenin share the relevant properties — polyphenolic, poorly soluble, heavily conjugated — which makes this the closest available analogy and a reasonable basis for expecting the strategy to transfer.

Figure 1B summarises the incremental benefit attributable to the polymer alone across these systems. The gains are not marginal: adding a precipitation inhibitor to an otherwise identical lipid formulation has produced roughly two-fold to nine-fold improvements in exposure.

Table 3. Conventional SNEDDS compared with supersaturable SNEDDS across the attributes that matter in formulation development.

Attribute	Conventional SNEDDS	Supersaturable SNEDDS (S-SNEDDS)
Drug loading relative to equilibrium solubility in oil–Smix	At or below saturation, to avoid precipitation on dilution	May exceed it; the system is designed to generate supersaturation on dispersion
Surfactant content	High, since surfactant is the only means of retaining drug in solution after dilution	Can be reduced; the polymer substitutes for part of the surfactant burden
Additional excipient	None	A small proportion (typically a few per cent w/w) of water-soluble polymeric precipitation inhibitor

Attribute	Conventional SNEDDS	Supersaturable SNEDDS (S-SNEDDS)
Thermodynamic state after dilution	Relaxes toward equilibrium; drug precipitates	Kinetically stabilised non-equilibrium (supersaturated) state
Free-drug concentration at the absorptive site	Falls toward C_{ek} as precipitation proceeds	Held above C_{ek} for a defined period
Duration of the absorption window	Limited by the onset of precipitation	Extended for as long as the parachute holds
Gastrointestinal tolerability risk	Higher where large surfactant loads are required	Potentially lower at equivalent performance
Critical quality attributes	Globule size, PDI, zeta potential, % transmittance, emulsification time	All of the above, plus the extent and duration of supersaturation maintenance
Principal failure mode	Dilution-induced precipitation	Premature nucleation if polymer identity or level is wrong; excess polymer can impair self-emulsification
Characterisation requirement	Sink-condition dissolution is adequate	Requires a dynamic dispersion–dilution assay in biorelevant media under non-sink conditions

VII. CONVENTIONAL VERSUS SUPERSATURABLE SNEDDS

Table 3 sets the two architectures side by side. The practically important differences are three.

The first is where drug loading sits relative to equilibrium solubility. A conventional system is constrained below it; a supersaturable system is deliberately designed to exceed it on dispersion. This is what permits higher payload per capsule and therefore a smaller unit dose — a material consideration for a compound likely to be dosed at 300 mg.

The second is the surfactant trade-off. In a conventional system, surfactant is the only tool available for keeping drug in solution after dilution, which pushes concentrations upward toward the range associated with gastrointestinal irritation. In a supersaturable system, a few per cent of polymer substitutes for part of that burden. The balance must be struck with care, however, because the same surfactants contribute efflux inhibition [11]; reducing them too aggressively trades one mechanism for another rather than adding to it.

The third is what must be measured. A conventional SNEDDS is adequately characterised by globule size, polydispersity index, zeta potential, percentage transmittance, emulsification time and sink-condition dissolution. A supersaturable system is not. Its defining property — how much supersaturation is generated and for how long it survives — is invisible under sink conditions and requires a dynamic dispersion–dilution assay in biorelevant media, with the percentage of drug remaining in solution tracked over several hours. Supersaturation maintenance must be treated as a critical quality attribute in its own right, not as an inference from dissolution data.

A fourth consideration is less often stated. The polymer is not a free addition: at sufficient concentration it can increase viscosity enough to slow self-emulsification, enlarge droplets and degrade the very spring it is meant to protect. The inhibitor level is therefore a genuine optimisation variable with an interior optimum, which is an argument for response-surface methodology rather than one-factor-at-a-time screening.

VIII. QUALITY BY DESIGN AND STATISTICAL OPTIMISATION

The performance of a supersaturable nanoemulsifying system depends jointly on oil concentration, which governs solvent capacity and droplet size; on the surfactant-to-cosurfactant ratio, which governs emulsification efficiency and the extent of the self-nanoemulsification region; and on precipitation-inhibitor concentration, which governs supersaturation maintenance but interacts with the first two through viscosity and phase behaviour. Three interacting factors with at least three responses is

precisely the situation in which sequential univariate screening is both inefficient and liable to miss the optimum.

The Quality by Design framework set out in ICH Q8(R2) replaces that approach with the systematic definition of a quality target product profile, identification of critical quality attributes and critical process parameters, and establishment of a design space within which the product is demonstrably robust [43]. For a naringenin S-SNEDDS the critical quality attributes follow directly from the preceding sections: globule size, to be minimised; percentage transmittance, to be maximised as a surrogate for dispersion clarity and fineness; and the percentage of drug remaining in solution in a dynamic dilution test, to be maximised as the direct measure of supersaturation maintenance.

The Box–Behnken design is well suited to this problem. Introduced as a family of three-level designs for the study of quantitative variables [44], it estimates a full quadratic response surface without the extreme corner combinations of a full factorial — a practical advantage when extreme compositions would not self-emulsify at all. A three-factor, three-level Box–Behnken design requires fifteen runs including three centre-point replicates to estimate pure error. The approach is well precedented for self-nanoemulsifying systems: Yadav and colleagues used a Box–Behnken design with desirability-function optimisation to develop a SNEDDS of ezetimibe, obtaining significantly improved globule size and dissolution relative to non-optimised batches [45]. For naringenin specifically, a D-optimal mixture design has already been applied successfully to a conventional SNEDDS [23], establishing that the formulation space responds predictably to statistical optimisation.

Analysis should proceed through analysis of variance on the fitted polynomials, inspection of contour and three-dimensional response-surface plots to identify significant main effects and interaction terms, numerical optimisation against a composite desirability function, and — the step most often omitted — preparation and evaluation of the predicted optimum with comparison of observed against predicted responses. A design space without a confirmation batch is a model, not a result.

IX. HOW SUCH A SYSTEM SHOULD BE EVALUATED

A credible evaluation package for a naringenin S-SNEDDS has six components, and the second is the one most frequently under-specified.

Preformulation and analytics. Equilibrium solubility of naringenin across candidate oils, surfactants and cosurfactants by the shake-flask method; pseudo-ternary phase diagrams constructed by aqueous titration to map the self-nanoemulsification region; Fourier-transform infrared spectroscopy to exclude drug–excipient incompatibility, including with the candidate polymers. A stability-indicating analytical method validated to ICH Q2(R1) for linearity, accuracy, precision, specificity, detection and quantitation limits, robustness and system suitability underpins everything downstream [47].

Supersaturation assessment. This is the distinguishing experiment. The formulation is diluted into biorelevant media under continuous stirring and the concentration of dissolved drug is tracked over several hours, with the supersaturation ratio computed against measured crystalline solubility in the same medium. Both the maximum supersaturation achieved and its duration should be reported, together with the solid form of any precipitate recovered — amorphous or crystalline — since this discriminates between mechanisms of polymer action [35]. The broader limitations of in vitro models in predicting in vivo performance of oral dosage forms, particularly for supersaturating systems, have been examined in detail and should inform how much weight such data are asked to carry [46].

Physical characterisation. Globule size, polydispersity index and zeta potential by dynamic and electrophoretic light scattering; morphology by transmission electron microscopy; percentage transmittance, emulsification time, robustness to dilution across physiologically relevant ratios and media, and thermodynamic stability testing by heating–cooling cycles, centrifugation and freeze–thaw.

Permeation. Ex vivo everted rat intestinal sac or Caco-2 monolayer transport, with the conventional SNEDDS and a plain suspension as comparators, to establish whether the supersaturation advantage

observed in a beaker translates into increased flux across a membrane.

In vivo pharmacokinetics. A three-arm oral study in rats comparing the optimised S-SNEDDS against the conventional SNEDDS and a plain aqueous suspension, reporting C_{max}, T_{max}, AUC and relative bioavailability. Including the conventional SNEDDS arm is essential: without it, the study measures the benefit of lipid formulation rather than the benefit of supersaturability, and the central claim goes untested.

Stability. Accelerated testing to ICH Q1A(R2) at 40 ± 2 °C and 75 ± 5% relative humidity over at least three months, monitoring globule size, polydispersity index, drug content and — critically for this formulation class — any evidence of drug precipitation or phase separation in the concentrate itself [48].

X. GAPS AND OUTLOOK

Several gaps are worth naming plainly.

No supersaturable naringenin lipid formulation has been reported. Conventional naringenin SNEDDS exist and perform respectably [22,23]; supersaturable systems exist and outperform their conventional counterparts for several model compounds [33,35,40,41]; the intersection is empty. This is the clearest opportunity in the field.

Precipitation is rarely measured. Most naringenin formulation papers report dissolution under sink conditions, which by construction cannot reveal precipitation behaviour. Until dispersion–dilution experiments in biorelevant media become routine, the field will continue to optimise formulations against a response that does not reflect what happens in the gut.

Metabolism is under-addressed. Every strategy reviewed here targets solubility and, incidentally, efflux. None targets glucuronidation, which the human data suggest is at least as important a determinant of free-aglycone exposure [7,8]. Lymphatic transport is the available lever, and long-chain rather than medium-chain lipids would be the formulation choice if that mechanism were being pursued deliberately [27]; whether naringenin is sufficiently lipophilic to be carried in chylomicrons is an open question worth answering experimentally.

Comparators are inconsistent. Fold-increases reported against a plain suspension in different species, at different doses, with different analytical methods are not comparable, and Figure 1A should be read with that caveat firmly in mind. Head-to-head studies against a common comparator would be more informative than further additions to the list of carriers.

Translation is distant. Almost all in vivo work is in rodents. The single formal human pharmacokinetic trial used an unformulated whole-orange extract [10], so the clinical benefit of any of these delivery systems in humans remains entirely unmeasured. A formulation that reduced the 300 mg twice-daily regimen implied by that trial to something smaller and less variable would be a genuine contribution, and solid self-nanoemulsifying intermediates adsorbed onto carriers such as colloidal silicon dioxide or magnesium aluminometasilicate offer a practical route to a capsule dosage form suitable for such a study.

XI. CONCLUSION

Naringenin is a well-characterised pharmacological agent with a well-characterised delivery problem. Its oral bioavailability is limited by low aqueous solubility, extensive pre-systemic glucuronidation and intestinal efflux, and the human data show exposure that is not only low but highly variable between subjects. A substantial body of nanocarrier work has improved matters, with reported gains in oral exposure from approximately two-fold to more than thirteen-fold, and self-nanoemulsifying systems sit well within that range while offering the additional advantages of in situ dispersion, efflux modulation and a potential lymphatic route.

What conventional self-nanoemulsifying systems do not do is control what happens after dilution. The evidence from paclitaxel, AMG 517, silybin, fenofibrate and curcumin is that incorporating a small proportion of a water-soluble polymeric precipitation inhibitor converts a transient concentration spike into a sustained supersaturated state and delivers a further two- to nine-fold improvement in exposure over the same formulation without the polymer. The mechanism is understood, the polymer classes are known, and the closest chemical analogy — curcumin — has already been shown to respond.

A supersaturable, Quality by Design-optimised naringenin SNEDDS is therefore a well-motivated proposition rather than a speculative one. Realising it requires three commitments: treating supersaturation maintenance as a critical quality attribute and measuring it directly under non-sink conditions;

optimising oil content, surfactant ratio and inhibitor level together by response-surface methodology, since the inhibitor has an interior optimum; and including a conventional SNEDDS arm in the in vivo comparison so that the benefit attributable to supersaturability is isolated from the benefit of lipid formulation generally. On that basis the approach is worth pursuing, and the position is currently unoccupied.

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