The Wrong Kind of Success: EGCG Solid Lipid Nanoparticles and the 800 mg Ceiling

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***Abstract*—Epigallocatechin-3-gallate is lost three times over before it reaches the circulation. It is chemically destroyed in the intestinal lumen, where simulated gastric and small intestinal digestion removes 71 to 91% of it against 7 to 11% for catechin and epicatechin, and where it autoxidises to theasinensin dimers; in sodium phosphate buffer at pH 7.4 roughly 90% is gone within three hours. What survives crosses the epithelium poorly, being a hydrophilic molecule of 458 Da with eight hydrogen-bond donors. What crosses is then conjugated, appearing in mouse plasma 50 to 90% as the glucuronide. The human result is that plasma concentrations exceed 1 μM only above a one-gram oral dose. Solid lipid nanoparticles address the first of these losses directly and the second indirectly, and reported systems reach 108 to 122 nm with entrapment efficiencies from 68.5% to above 93%. This review argues that the interesting problem lies beyond that. First, there is a mismatch that most reports pass over: a hydrophilic molecule is being asked to partition into a lipid matrix, which is why entrapment values scatter so widely and why burst release and expulsion on storage are the characteristic failures. Second, and more consequentially, EGCG has a defined and regulated hepatic ceiling. The European Food Safety Authority concluded in 2018 that supplemental doses at or above 800 mg EGCG per day produce a statistically significant rise in serum transaminases, and the European Union amended its fortification regulation accordingly. That limit is written as a dose in milligrams, not as a plasma exposure, so a carrier that triples bioavailability delivers the systemic exposure of 800 mg from a label-compliant 270 mg. For a compound whose dose-limiting toxicity is hepatic, improving absorption narrows the therapeutic window rather than widening it, and that is a result a formulation study can and should measure rather than inherit.**

***Index Terms*—Epigallocatechin-3-gallate; solid lipid nanoparticles; oral bioavailability; chemical stability; autoxidation; theasinensin; hepatotoxicity; Quality by Design**

I. INTRODUCTION

Epigallocatechin-3-gallate is the most abundant catechin in green tea, accounting for roughly half the polyphenol content of the leaf, and it is among the most intensively studied natural products of the last thirty years [1,2]. Antioxidant, anti-inflammatory, antineoplastic, neuroprotective and metabolic effects have been reported across a very large preclinical literature, and the compound has reached clinical trial in several indications [1,3].

The gap between that literature and clinical use is pharmacokinetic, and it is unusually wide. The concentrations at which EGCG acts on its targets in cell culture are micromolar; the concentrations achievable in human plasma after ordinary intake are nanomolar. Only at oral doses above one gram have maximum plasma concentrations greater than 1 μM been observed [4,5].

What distinguishes EGCG from other poorly bioavailable polyphenols is where the loss occurs. For most such compounds the limiting step is solubility or presystemic conjugation. For EGCG a large part of the dose never reaches the enterocyte as EGCG at all, because the molecule is chemically destroyed in the intestinal lumen before absorption can be attempted [6,7]. That makes it a strong candidate for a carrier whose first function is protection rather than solubilisation, and solid lipid nanoparticles are such a carrier.

This review follows that argument and then presses on it in two places. The first is a mismatch rarely acknowledged in the formulation literature: EGCG is hydrophilic, and a solid lipid matrix is the least natural home for a hydrophilic molecule, which is why reported entrapment efficiencies for the same payload span a range of more than twenty-five percentage points. The second is a consequence of success rather than failure. EGCG has a defined and now regulated hepatic ceiling, expressed as a daily dose in milligrams [8]. A formulation that raises bioavailability raises systemic exposure at every dose below that ceiling, and nothing in the labelling framework registers the change. A formulation study is the right place to measure that, and almost none do.

II. THREE LOSSES BEFORE THE CIRCULATION

2.1 Destruction in the lumen

EGCG is unstable in any environment near or above neutral pH, and the data are unambiguous. In sodium phosphate buffer at pH 7.4, about 90% is lost within three hours and the compound is essentially gone by five [6,9]. In cell culture medium the half-life is under thirty minutes, rising to around 130 minutes in the presence of cells and to more than 24 hours when superoxide dismutase is added, which identifies the mechanism as oxidative [7]. Stability rises sharply below pH 4, which is why the stomach is a comparatively safe compartment and the duodenum is not [10].

The chemistry is autoxidation followed by dimerisation. Molecular oxygen abstracts an electron from the galloyl and B-ring hydroxyls, generating a semiquinone radical and superoxide, and the resulting quinones couple to give theasinensins A and D at m/z 913 and the condensation dimer P-2 at m/z 883 [7,11]. A second route operates thermally: above about 44 °C the C-2 stereocentre inverts, epimerising EGCG to gallocatechin-3-gallate, and the process becomes dominant above 98 °C [10].

The quantitative consequence under digestive conditions is the finding that matters most for formulation. Subjecting catechins to simulated gastric and small intestinal digestion removed 71 to 91% of EGCG, 72 to 100% of epigallocatechin and 60 to 61% of epicatechin gallate, while epicatechin and catechin lost only 8 to 11% and 7 to 8% respectively, with theasinensins A and D and P-2 identified among the products [11]. Table 1 collects these figures. The gallate-bearing, pyrogallol-containing catechins are selectively destroyed, and EGCG is the most vulnerable member of the series.

Two implications follow and both shape the rest of this review. A delivery system for EGCG is first a chemical protection problem and only second an absorption problem. And any measurement of EGCG in a biological or release medium has to be specific enough to distinguish the parent from its epimer and its dimers, because a non-specific assay will report degradation products as drug.

Table 1. Stability and pharmacokinetics of EGCG. The compound is destroyed before absorption, absorbed poorly, and conjugated after absorption; the human consequence is nanomolar exposure except at gram doses.

Study or condition	Principal finding	Reported values	Ref.
Catechins subjected to simulated gastric and small intestinal digestion in vitro	The gallate- and pyrogallol-bearing catechins are selectively destroyed; EGCG is the most vulnerable member of the series	Losses: EGCG 71–91%, EGC 72–100%, ECG 60–61%, against EC 8–11% and catechin 7–8%. Products: theasinensins A and D (m/z 913) and P-2 (m/z 883)	[11]
EGCG in sodium phosphate buffer, pH 7.4	Rapid base-catalysed autoxidation; the same two dimers are formed	About 90% degraded in 3 h; essentially complete loss by 5 h	[9]
EGCG in cell culture medium, with and without cells or added superoxide dismutase	Instability is oxidative in origin and can be suppressed	Half-life under 30 min in medium, about 130 min with cells present, and over 24 h with superoxide dismutase added; some EGCG epimerises to gallocatechin-3-gallate	[7]

Study or condition	Principal finding	Reported values	Ref.
CF-1 mice; 163.8 μmol kg^{-1} intragastrically against 21.8 μmol kg^{-1} intravenously	Absorbed but extensively glucuronidated	Peak plasma 0.28 ± 0.08 against 2.7 ± 0.7 μmol L^{-1}; 50–90% present as the glucuronide; absolute bioavailability 26.5% total and 12.4% unconjugated	[14]
Healthy volunteers; single oral doses of purified EGCG from 50 to 1600 mg	Plasma concentrations exceed 1 μM only above a one-gram dose	1600 mg gave C_{max} 3392 ng mL^{-1} (range 130–3392); peaks at 1.3–2.2 h; t½ 1.9–4.6 h; total $AUC_{0-\infty}$ 442–10,368 ng·h mL^{-1}	[4,5]
Healthy volunteers; EGCG with and without food	Food markedly reduces systemic exposure, so fasted dosing is standard in clinical work	Fasted administration gave roughly 1.5-fold higher peak concentrations than the same dose with breakfast, and several-fold higher than within a food matrix	[15,16]

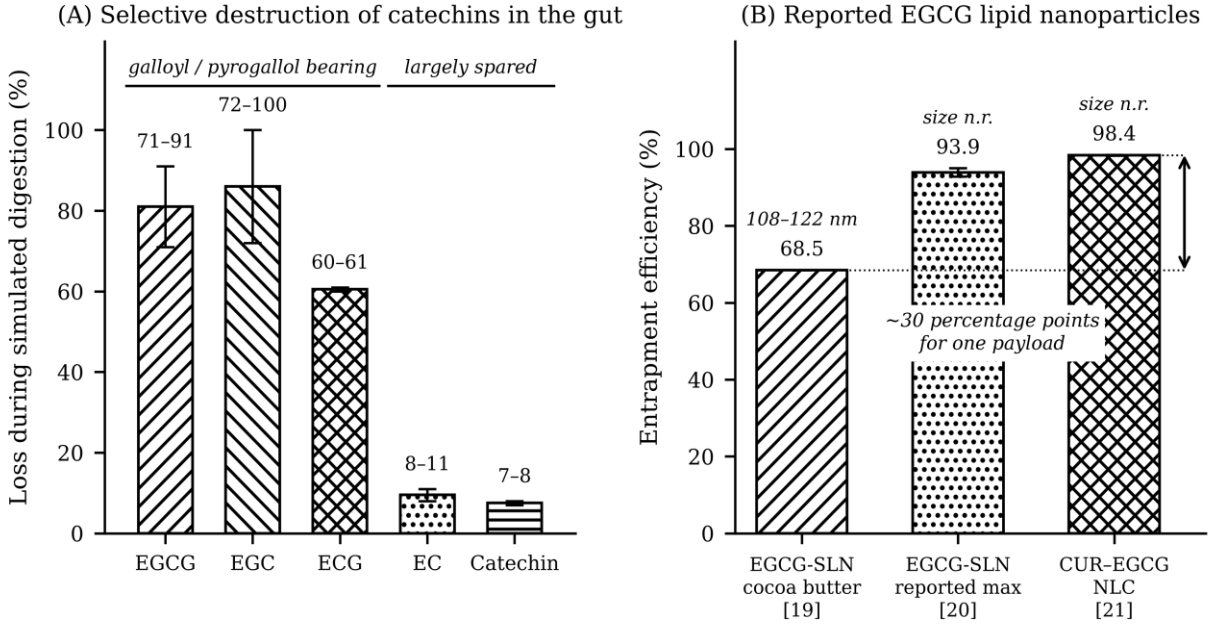


Fig. 1. (A) Loss of individual catechins during simulated gastric and small intestinal digestion in vitro. EGCG, epigallocatechin and epicatechin gallate were substantially degraded while epicatechin and catechin were largely unaffected; bars show the reported ranges [11]. The selectivity identifies the galloyl and pyrogallol groups as the vulnerable features and establishes that for EGCG the first delivery problem is chemical protection rather than solubilisation. (B) Particle size and entrapment efficiency of reported EGCG lipid nanoparticles: a cocoa-butter solid lipid nanoparticle [19], a second reported maximum [20] and a curcumin–EGCG nanostructured lipid carrier [21]. The spread of roughly thirty percentage points in entrapment for one payload reflects how sensitive the partitioning of a hydrophilic molecule is to formulation and process.

2.2 Absorption, conjugation and what reaches plasma

What survives the lumen faces two further filters.

The first is permeability. EGCG has a molecular weight of 458 Da and eight hydrogen-bond donors, violating two of the Lipinski criteria, and it is hydrophilic, so passive transcellular diffusion across the enterocyte membrane is poor [12,13]. It is usually assigned to class III of the Biopharmaceutics Classification System: soluble but poorly permeable.

The second is conjugation. In CF-1 mice given EGCG intragastrically at 163.8 μmol kg^{-1}, peak plasma concentration was 0.28 ± 0.08 μmol L^{-1}

against 2.7 ± 0.7 μmol L^{-1} after 21.8 μmol kg^{-1} intravenously, and EGCG was present mainly, 50 to 90%, as the glucuronide; absolute bioavailability was 26.5% for total EGCG and 12.4% for the unconjugated compound [14]. The same work put peak plasma concentrations after oral dosing at 43.2 nmol L^{-1} in rats and 75.8 nmol L^{-1} in humans [14]. Species differences are large, and a mouse is a flattering model.

In humans the picture is consistent across studies. Single doses from 50 to 1600 mg produced concentrations above 1 μM only above one gram, the 1600 mg dose giving a maximum of 3392 ng mL^{-1} with a range from 130 to 3392 ng mL^{-1}; peaks occurred at 1.3 to 2.2 h, the terminal half-life ranged from 1.9 to 4.6 h, and doses up to 1600 mg were generally well tolerated acutely [4,5]. Food reduces exposure substantially, so fasted administration is the standard in clinical work [15,16].

Set against micromolar in vitro activity, the conclusion is the same as for several other dietary polyphenols: ordinary oral administration cannot deliver pharmacologically relevant systemic concentrations. The difference is that for EGCG the first and largest loss happens outside the body's control, in the lumen, which is exactly the loss a protective carrier can address.

III. SOLID LIPID NANOPARTICLES, AND A MISMATCH

3.1 What the carrier offers

Solid lipid nanoparticles consist of a lipid that is solid at body temperature, dispersed in an aqueous surfactant phase. They are prepared from physiologically tolerated and often food-grade excipients, can be made without organic solvent by hot high-pressure homogenisation or microemulsion techniques, and scale readily [17,18]. Table 2 compares them with the alternatives.

For EGCG the central attraction is the solid matrix itself. A molecule immobilised within a crystalline lipid is physically separated from dissolved oxygen and from the alkaline aqueous environment of the small intestine, which is precisely the combination that destroys it. Encapsulation in cocoa-butter nanoparticles significantly improved EGCG stability at pH 6.8 [19], and improved shelf life is reported consistently across lipid systems [19,20].

Three secondary benefits apply. Lipid nanoparticles of appropriate composition give controlled release, so the payload is not delivered to the duodenum as a bolus. Long-chain lipids can promote uptake into the intestinal lymphatics and thereby bypass hepatic first-pass metabolism, although for EGCG the dominant conjugation is intestinal as well as hepatic, so the benefit is partial. And a particulate carrier can improve apparent permeability for a molecule that crosses membranes poorly on its own.

Table 2. Carriers reported for oral EGCG, with the property each contributes and the limitation that follows from EGCG being hydrophilic and oxidisable.

Carrier	Basis	Contribution for EGCG	Limitation
Unformulated EGCG (capsule or extract)	Drug powder	Simple; the basis of all existing human pharmacokinetic and safety data	71–91% destroyed during simulated digestion; nanomolar plasma exposure below gram doses
Co-administered bioenhancer (e.g. piperine)	Metabolic inhibitor given alongside	Modest, inexpensive improvement with no reformulation required	Reported gains of about 1.1-fold on peak and 1.7-fold on exposure; no protection from luminal degradation
Solid lipid nanoparticle	Lipid solid at body temperature, surfactant-stabilised	Physical protection from oxygen and intestinal pH; controlled release; food-grade, solvent-free manufacture; reported 108–122 nm with improved stability at pH 6.8	A hydrophilic payload partitions poorly into a crystallising lipid, so entrapment scatters widely and surface-associated drug

Carrier	Basis	Contribution for EGCG	Limitation
			gives burst release
Nanostructured lipid carrier	Blend of solid and liquid lipid	Matrix imperfections raise payload and resist expulsion; co-loaded curcumin–EGCG systems reached above 98% entrapment	Requires lipid miscibility screening; oil fraction must be bounded or the matrix softens
Double emulsion / self-double-emulsifying system	Water-in-oil-in-water	Gives a hydrophilic drug an internal aqueous compartment; reported 1.93-fold AUC and 1.44-fold C_{max} increases	Thermodynamically fragile; usually needs high surfactant; limited physical shelf life
Chemically modified EGCG (palmitate, peracetate prodrug)	Acylated derivative	Lipophilic and far more stable in alkaline media; reported plasma AUC for total EGCG 465.0 against 194.6 units for the parent	Requires hydrolysis back to EGCG in vivo; becomes a new chemical entity for regulatory purposes

3.2 The hydrophilicity problem

There is a structural mismatch here that deserves to be stated plainly rather than left implicit, because it explains most of the variability in the published data.

Solid lipid nanoparticles were developed for lipophilic drugs. Loading depends on the drug partitioning into molten lipid and remaining there as the lipid crystallises. EGCG does neither willingly: it is hydrophilic, with eight hydroxyl groups, and during the cooling step it tends to be expelled toward the aqueous interface as the lipid orders itself into a crystal lattice.

The signature of that mismatch is visible in the reported numbers. Entrapment efficiencies for EGCG in lipid nanoparticles span from 68.5% in a cocoa-butter system [19] to 93.89 ± 1.11% in another [20] and to 98.40 ± 0.08% when co-loaded with curcumin in a nanostructured lipid carrier [21], a spread of thirty percentage points for the same payload. For a lipophilic drug in the same carrier class the spread would be far narrower. The difference is not experimental sloppiness; it reflects how sensitive the partitioning of a hydrophilic molecule is to lipid identity, surfactant, cooling rate and the fraction of drug that is in fact surface-adsorbed rather than entrapped.

That last distinction is the one to insist on. Drug adsorbed on the particle surface is counted as entrapped by the usual ultrafiltration or ultracentrifugation assay, but it is not protected from the lumen, and it is released immediately. A high entrapment efficiency accompanied by a large burst phase is the fingerprint of surface association, and for EGCG it is the expected outcome rather than an anomaly. The burst fraction in a release profile is therefore a more honest measure of true encapsulation than the entrapment value itself.

Three formulation responses exist. A nanostructured lipid carrier, blending a liquid lipid into the solid matrix, creates imperfections that accommodate drug and resist expulsion; this is why the co-loaded curcumin–EGCG system reached much higher entrapment [21]. A double-emulsion or water-in-oil-in-water preparation gives a hydrophilic drug an internal aqueous compartment, and a self-double-emulsifying system of this type raised the area under the curve 1.93-fold and the peak concentration 1.44-fold in reported work [13]. And chemical modification — acylation to EGCG palmitate or to the acetylated prodrug — makes the molecule lipophilic before encapsulation, at the cost of requiring hydrolysis back to the parent in vivo [9,22].

3.3 What reported EGCG lipid nanoparticles achieve

Figure 1B plots the reported systems.

The best-characterised oral-relevant example used cocoa butter with a food-grade surfactant blend and a solvent-free high-pressure homogenisation technique, giving particles of 108 to 122 nm with a narrow distribution, polydispersity index between 0.102 and 0.149, and a maximum encapsulation efficiency of 68.5%, with significantly improved EGCG stability at pH 6.8 [19]. Other preparations have reported encapsulation efficiencies between 78.5% and 100% and a maximum of 93.89 ± 1.11% [20]. A curcumin–EGCG nanostructured lipid carrier achieved 98.40 ±

0.08% for EGCG with a loading capacity of 3.935 ± 0.003% [21].

For comparison, non-lipid approaches give the benchmark a lipid system should beat. Co-administration with piperine raised the peak concentration 1.1-fold and the area under the curve 1.7-fold [13]; a self-double-emulsifying system gave 1.93-fold and 1.44-fold respectively [13]; and acetylation to the peracetate raised plasma total EGCG area under the curve from 194.6 to 465.0 units in the reported comparison [22]. Enhancements of this kind, roughly two- to four-fold, are what the field currently achieves, and Section 6 asks what that means for a compound with a hepatic ceiling.

What is missing from the oral EGCG lipid-nanoparticle literature is more striking than what is present: several of the best-characterised systems were developed for food fortification or topical use rather than for oral pharmacokinetics, and in vivo oral exposure data for an EGCG solid lipid nanoparticle are comparatively scarce. That is the opening this project occupies.

IV. FORMULATION VARIABLES AND SYSTEMATIC OPTIMISATION

Table 3 maps the variables to the attributes each governs and names the trade-off that makes each worth treating as a design factor.

Lipid identity is the first decision and for EGCG it is not simply a question of which lipid dissolves the drug best, because none of them dissolves it well. A more ordered lipid such as a triglyceride of uniform chain length crystallises into a tighter lattice and expels drug; a less ordered glyceride mixture such as a behenate or palmitostearate retains more. Chain length also determines whether the absorbed lipid is routed through the lymphatics or the portal vein.

Surfactant type and concentration controls attainable particle size and physical stability, bounded above by tolerability, and for a hydrophilic payload it does something additional: an excess of surfactant solubilises the drug in the aqueous phase and lowers true entrapment while leaving the apparent value unchanged if the assay does not separate surface-associated drug.

Process temperature and cooling rate are unusually important here for a reason specific to this molecule. Hot homogenisation requires the lipid to be melted, typically five to ten degrees above its melting point, and EGCG epimerises above about 44 °C and degrades faster the hotter it gets [10]. Every minute at processing temperature costs payload, and the loss is not recorded by an entrapment assay that cannot distinguish EGCG from gallocatechin-3-gallate. A cold homogenisation route, or a microemulsion method at the lowest workable temperature, deserves to be compared against hot homogenisation with the parent compound measured specifically in each case. To our knowledge that comparison has not been published for EGCG, and it would be a genuine contribution.

Antioxidant and pH control in the aqueous phase is the other variable peculiar to this payload. Since the degradation route is oxidative and base-catalysed, purging with nitrogen, adding ascorbic acid or a chelator, and holding the external phase mildly acidic are all plausible protective measures during manufacture and storage, and all are cheap to test.

The Quality by Design framework of ICH Q8(R2) provides the structure — a quality target product profile, critical quality attributes derived from it, and a design space within which performance is robust [23,24] — and a Box–Behnken design estimates a full quadratic response surface in fifteen runs for three factors including centre-point replicates [25,26]. Designs of exactly this kind have been applied to solid lipid nanoparticles of several other payloads [27,28].

The responses are where an EGCG study should depart from convention. Particle size, polydispersity index, zeta potential and entrapment efficiency are the usual set and none of them reports on the property the carrier exists to provide. Two responses would: the fraction of intact EGCG surviving a defined period in simulated intestinal fluid, and the burst fraction released in the first thirty minutes. Both are measurable with the same HPLC method the project needs anyway.

Table 3. Formulation and process variables for an EGCG solid lipid nanoparticle. The final column names the trade-off that makes each a candidate design factor rather than a fixed value.

Variable	Attributes affected	Trade-off specific to EGCG
Solid lipid identity	Matrix crystallinity; entrapment; expulsion on storage; absorption route	A more ordered lattice expels a hydrophilic payload; a less ordered glyceride retains more but releases faster. Chain length also decides portal against lymphatic routing
Liquid lipid fraction (if moving to an NLC)	Matrix imperfections; payload; resistance to expulsion	Raises entrapment markedly, but too high a fraction softens the matrix toward a nanoemulsion and removes the protection the solid state provides
Surfactant type and concentration	Particle size; PDI; zeta potential; physical stability	Excess surfactant solubilises EGCG in the external aqueous phase, lowering true entrapment while leaving the apparent value unchanged
Drug : lipid ratio	Payload; proportion surface-associated; burst release	Higher loading of a hydrophilic drug increases the surface-adsorbed fraction rather than the encapsulated one; the burst fraction is the honest readout
Process temperature	Lipid melting; droplet formation; payload integrity	Hot homogenisation needs the lipid molten, but EGCG epimerises above about 44 °C and degrades faster the hotter it gets; a cold route should be compared directly
Homogenisation pressure, cycles or sonication energy	Particle size and distribution; lamellarity	More energy gives smaller particles but heats the dispersion, compounding the thermal degradation above
Cooling rate after homogenisation	Polymorphic form adopted by the matrix	Rapid cooling traps a less ordered polymorph that retains drug; slow cooling gives the stable form and expels it on storage
Aqueous-phase pH and antioxidant	Chemical stability of the payload during manufacture and storage	Degradation is oxidative and base-catalysed, so nitrogen purging, a chelator or ascorbic acid and a mildly acidic external phase are cheap protective measures worth testing

V. WHAT TO MEASURE, AND THE ANALYTICAL TRAP

For most compounds the analytical method is a supporting detail. For EGCG it is central, because the degradation products are structurally close to the parent and a careless method will count them as drug. Three species have to be resolved from EGCG itself: gallocatechin-3-gallate, the C-2 epimer formed thermally; the theasinensin dimers A and D at m/z 913; and the condensation dimer P-2 at m/z 883 [7,11]. Ultraviolet detection at the catechin absorbance maximum does not distinguish them, since all retain the chromophore. A reversed-phase gradient capable of separating EGCG from its epimer, validated to ICH Q2(R1) with specificity demonstrated against deliberately degraded samples, is the minimum; mass-spectrometric detection resolves the dimers unambiguously [29].

That requirement runs through every measurement the project makes. An entrapment efficiency determined by ultraviolet absorbance after hot homogenisation may be reporting partly epimerised material. A release profile in phosphate buffer at pH 7.4 is being conducted in a medium that destroys roughly 90% of free EGCG within three hours, so apparent release and actual degradation are confounded unless both the medium concentration and the mass balance are tracked. A stability-

indicating method is therefore not an optional refinement but the foundation of the work.

Two further cautions apply to any cell-based evaluation. EGCG generates hydrogen peroxide in culture media by autoxidation, so apparent activity in a cell assay may be a response to peroxide rather than to the compound; including catalase in a parallel arm distinguishes the two, and the stabilising effect of superoxide dismutase on EGCG half-life makes the same point from the other direction [7]. And the half-life of EGCG in culture medium is under thirty minutes [7], so a 48-hour cell experiment is not an experiment on EGCG for most of its duration — which is, incidentally, one of the better arguments for the carrier.

Supporting work otherwise follows the standard pattern: release data fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models [30,31]; differential scanning calorimetry and X-ray diffraction to establish the crystalline state of the lipid matrix, which governs expulsion on storage; and accelerated stability testing to ICH Q1A(R2) [32], monitoring particle size, zeta potential, and — critically here — intact EGCG content rather than total catechin.

VI. THE CEILING: WHERE MORE EXPOSURE STOPS BEING BETTER

This section is the reason the review carries the title it does.

EGCG has a documented, dose-related hepatic toxicity. Reviewing clinical and case data at the request of the European Commission, the European Food Safety Authority concluded in 2018 that intake of doses equal to or above 800 mg EGCG per day taken as a food supplement produces a statistically significant increase in serum transaminases relative to control, indicative of liver injury; the Panel found no evidence of hepatotoxicity below that dose in trials lasting up to twelve months, but was unable to identify a safe level, and noted that catechins from traditional green tea infusions are not a comparable concern [8]. Fasted intake, which is standard practice precisely because it raises exposure, was identified as increasing the exposure per dose. The European Union subsequently amended Annex III of Regulation (EC) No 1925/2006 to require that a daily portion contain less than 800 mg EGCG and that labelling carry explicit warnings [8,33]. The signal did not come from trials alone: a review of the literature and of case reports had already documented hepatotoxicity associated with green tea preparations [34], and a later systematic review concluded that the risk is concentrated in high-dose extract supplements rather than in the beverage [35].

Now place a successful formulation beside that limit. Reported enhancement factors for EGCG delivery systems cluster between roughly 1.4-fold and 4-fold on peak concentration or area under the curve [13,19,21,22]. Suppose a solid lipid nanoparticle achieves a three-fold increase in systemic exposure. A subject taking 270 mg of EGCG in that formulation then receives the systemic exposure of about 800 mg of unformulated EGCG, while the label reports 270 mg and complies comfortably with the regulation. Figure 2 sets this out.

Three observations follow, and none of them is an argument against the formulation.

The regulatory threshold is expressed in milligrams of administered dose, not in plasma exposure. It was derived from trials of conventional green tea extracts, whose bioavailability is the low baseline described in Section 2. An advanced delivery system falls entirely outside the assumption on which the number rests, and nothing in the labelling framework signals that.

The direction of the effect is unfavourable. For a compound whose efficacy and whose dose-limiting toxicity both scale with systemic exposure, raising bioavailability moves both together. It does not widen the therapeutic window; it slides the whole dose–response relationship toward lower doses. A formulation improves matters only if the toxicity is driven by something other than systemic exposure — by local concentration in the gut, for instance, or by a degradation product — and whether that is so for EGCG is not settled. That makes it an empirical question a formulation study is well placed to ask.

The experiment is straightforward. A rodent study comparing the formulation with unformulated EGCG at matched doses, with serum alanine and aspartate aminotransferase measured alongside the pharmacokinetics and liver histology at the end, costs little beyond what the pharmacokinetic study already requires. A second arm in which the unformulated dose is raised to give matched systemic exposure would separate the two hypotheses directly: if toxicity tracks exposure, the two arms converge; if

the carrier alters it, they do not. Reporting doses in exposure-equivalents rather than milligrams, once such data exist, would be a small and useful discipline.

None of this is a reason to abandon the carrier. It is a reason for an EGCG delivery paper to include a safety readout, which at present they almost never do, and it is an unusually concrete way for a dissertation on this subject to contribute something the field needs.

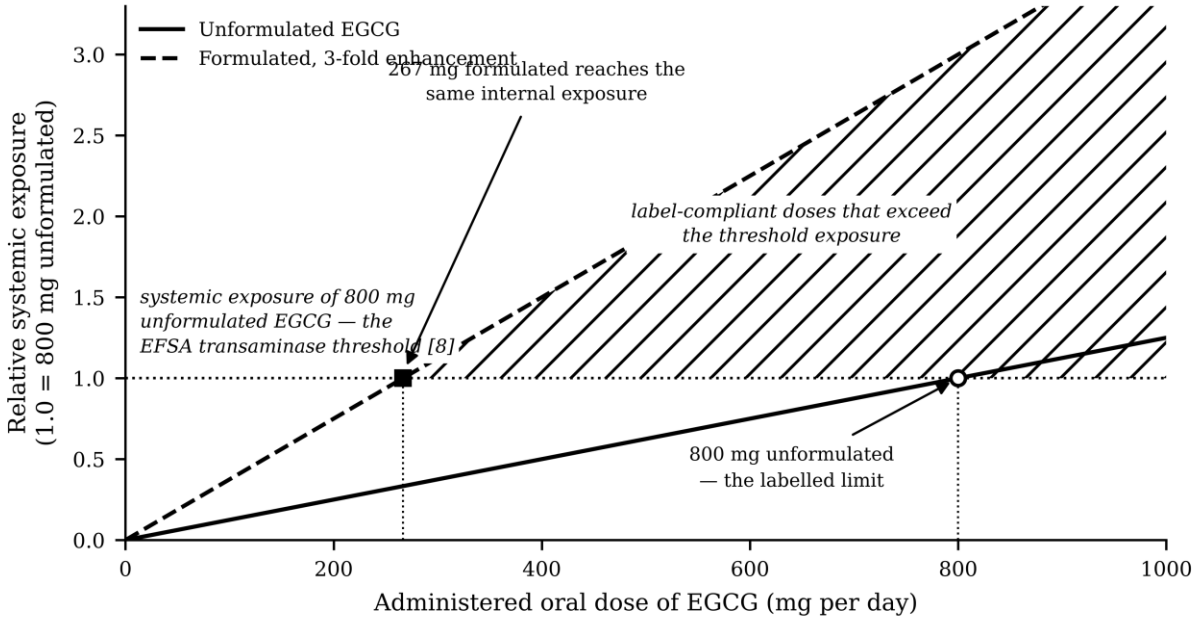


Fig. 2. Why improving bioavailability narrows the margin for EGCG. The lower line shows relative systemic exposure against administered dose for unformulated EGCG; the upper line shows the same relationship for a formulation achieving a three-fold enhancement, within the 1.4- to 4-fold range reported for EGCG delivery systems. The horizontal dashed line marks the systemic exposure corresponding to 800 mg of unformulated EGCG, the daily intake at which the European Food Safety Authority found a statistically significant rise in serum transaminases and which the European Union wrote into Annex III of Regulation (EC) No 1925/2006 as a labelling limit [8,33]. Because that limit is expressed as administered dose rather than exposure, the formulated product reaches the same internal exposure at about 270 mg while remaining label-compliant. The figure is a schematic of the relationship, not measured data; whether hepatic toxicity in fact tracks systemic exposure is the empirical question Section 6 proposes testing.

VII. GAPS AND OUTLOOK

The gaps below follow from the preceding sections and each is addressable at bench scale.

The specificity gap. EGCG is routinely quantified by methods that cannot distinguish it from its thermal epimer or its oxidative dimers. Every number in a formulation paper — entrapment, release, stability, plasma concentration — inherits that ambiguity unless a stability-indicating method is demonstrated.

The surface-association gap. Entrapment efficiency as conventionally measured does not distinguish encapsulated from surface-adsorbed drug, and for a hydrophilic payload in a lipid matrix the distinction is the whole question. The burst fraction and a washed-particle assay together resolve it.

The processing-temperature gap. Hot homogenisation is the default route and EGCG epimerises at the temperatures it requires. A direct comparison of hot against cold homogenisation, with intact EGCG measured specifically, has not been reported and would be straightforward.

The in vivo gap. Oral pharmacokinetic data for EGCG solid lipid nanoparticles are sparse relative to the volume of in vitro characterisation, and several of

the best-characterised systems were built for food or topical use.

The safety-readout gap. Set out in Section 6: a compound with a regulated hepatic ceiling is being given a bioavailability-enhancing carrier, and transaminases are not being measured.

The assay-artefact gap. Cell-based activity data for EGCG are confounded by peroxide generation and by a sub-thirty-minute half-life in medium. Catalase controls and medium stability measurements are cheap and rarely reported.

The translational gap. No EGCG lipid nanoparticle appears to have reached clinical evaluation, despite extensive human pharmacokinetic baselines against which one could be benchmarked [4,5,15]. Given those baselines, an early human comparison would be interpretable in a way that few nanoformulation first-in-human studies are.

VIII. CONCLUSION

EGCG is lost three times before it reaches the circulation, and the first loss is the largest and the least often addressed. Simulated digestion destroys 71 to 91% of it while sparing catechin and epicatechin almost entirely; in buffer at pH 7.4 some 90% is gone in three hours, autoxidising to theasinensin dimers. What survives permeates poorly, being hydrophilic with eight hydrogen-bond donors, and what permeates is conjugated, appearing in mouse plasma 50 to 90% as the glucuronide. In humans, plasma concentrations exceed 1 μM only above a one-gram dose.

Solid lipid nanoparticles are therefore a well-matched carrier, because their first contribution is physical protection rather than solubilisation, and encapsulation demonstrably improves EGCG stability at intestinal pH. They are also a somewhat awkward one: a hydrophilic molecule does not partition readily into a crystallising lipid, which is why reported entrapment efficiencies for the same payload range from 68.5% to above 93%, why burst release and expulsion on storage are the characteristic failures, and why the burst fraction is a more honest figure than the entrapment value.

The argument this review would press hardest is the one about the ceiling. The European Food Safety Authority found in 2018 that 800 mg EGCG per day as a supplement raises serum transaminases, and the European Union wrote that number into its fortification regulation as a limit on administered dose. A carrier that triples bioavailability delivers that systemic exposure from roughly 270 mg, and the label will not say so. For a molecule whose efficacy and whose dose-limiting toxicity both scale with exposure, improving absorption slides the dose–response curve rather than widening the window.

What a formulation study should therefore do is modest and specific. Build the carrier, and measure intact EGCG with a stability-indicating method at every step rather than total catechin. Report the burst fraction alongside the entrapment efficiency. Compare hot and cold processing with the parent measured specifically. And add transaminases and liver histology to the in vivo arm, with a matched-exposure comparator if resources allow. These are small additions to a conventional protocol, and together they would let the resulting paper say something about EGCG delivery that the present literature, extensive as it is, cannot.

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