Liposomal Vitamin D vs. Conventional Vitamin D: Does the Human Evidence Show Superiority?

TL;DR

- **Only ONE dedicated human study has directly compared a true LIPOSOMAL vitamin D3 against an oil-based formulation** (Dałek 2022, *Nanomedicine*, n=18 crossover) — and it is a 5-hour pilot whose 30-day AUC figures are *modeled, not measured*, run by authors who co-own the liposome manufacturer. The single positive malabsorption RCT (Nowak 2022, cystic fibrosis) tested a multi-vitamin liposomal cocktail, not liposomal D3 alone. Honest verdict: **liposomal-specific human evidence is thin, preliminary, and conflicted.**
- **Adjacent enhanced-delivery technologies have BETTER comparative data than liposomes** — micellized D3 (Marwaha 2019 RCT, n=166 completers), nanoemulsion D3 (Marwaha 2023 crossover), and especially **calcifediol (25(OH)D3)** have larger, cleaner human trials showing genuine superiority. The most accurate answer to your question is: "liposomal specifically has weak data; several adjacent technologies have better data."
- **The headroom problem is real:** conventional oil-based D3 taken with a fat-containing meal already has high bioavailability, so most of the dramatic "5–12×" multipliers come from unfair comparisons (fasted dosing, vs. a dry tablet, or acute Cmax windows) rather than steady-state 25(OH)D superiority. Where a formulation edge is most plausible — fat malabsorption — the best-supported options are micellized/water-miscible formulations and calcifediol, not classical liposomes.

Key Findings

1. The direct liposomal-vs-conventional human evidence is a single small pilot. The only peer-reviewed human study specifically comparing a liposomal D3 to an oily D3 is Dałek et al., 2022 [Nanomedicine 2022]. It is a small crossover pilot (n=18) with a 5-hour measurement window; its central "4× AUC" claim is a mathematical extrapolation, and two senior authors co-own the liposome manufacturer (Lipid Systems sp. z o.o.).

2. The one "positive" malabsorption RCT did not isolate liposomal D3. Nowak 2022 (cystic fibrosis) [J Clin Med 2022] showed a liposomal fat-soluble vitamin cocktail beat standard preparations for 25(OH)D3, but the same group's earlier 3-arm RCT [Nutrients 2021] found liposomes did NOT beat MCT for vitamin D — cyclodextrins did. Both were industry-linked (Norsa Pharma).

3. Micellized and nanoemulsion D3 have stronger, larger comparative data than liposomes. Marwaha's 166-completer RCT in adults [Br J Nutr 2019] and a nanoemulsion crossover PK study [J Orthop 2023] both show real advantages.

4. Calcifediol is the best-evidenced "enhanced" oral vitamin D. Bouillon's pooled analysis of 9 RCTs found calcifediol was **3.2-fold more potent than oral cholecalciferol** — serum 25(OH)D rose 1.5 ± 0.9 nmol/L per μg cholecalciferol vs 4.8 ± 1.2 nmol/L per μg oral calcifediol — with

potency rising to 5.5–12× at higher doses and absorption largely preserved in malabsorption [Nature EJCN 2024], [JCEM 2017].

5. Mechanistic plausibility for INTACT oral liposome absorption is weak. Conventional phospholipid liposomes are degraded by gastric acid, bile salts, and pancreatic lipase; most payload is released, not absorbed as intact vesicles [Ther Deliv 2015]. (Taylor & Francis)

6. Null/contradictory data exist and must not be ignored — including a rat study where micellized D3 was the WORST performer, and a CF RCT where liposomal D3 failed to beat MCT for vitamin D.

Details

A. The one true liposomal-vs-oil human study: Dałek 2022 (and its modeling companion)

Citation: Dałek P, Drabik D, Wołczańska H, Foryś A, Jagas M, Jędruchniewicz N, Przybyło M, Witkiewicz W, Langner M. *Bioavailability by design — Vitamin D3 liposomal delivery vehicles.* Nanomedicine: Nanotechnology, Biology and Medicine. 2022;43:102552. DOI 10.1016/j.nano.2022.102552 [Nanomedicine 2022]. (SciProfiles) (Springer)

- **Design:** Crossover, **n=18 healthy volunteers, ages 24–65**, single **10,000 IU** oral dose of D3 as either liposomal or a marketed oily solution, after a **12-hour fast**, with a **3-week washout** before the alternate formulation. Ethics: KB/07/2020, Wrocław.
- **Measurement window:** Only ~**5 hours** (8 finger-prick 25(OH)D3 samples, baseline to 5 h).
- **Result (measured):** Absorption-rate slopes were **4.01×10^{-4} /min (liposomal) vs 7.03×10^{-5} /min (oily) —** about 5.7× faster for liposomal. **Critically, the reported standard deviations exceed the means** (liposomal SD $\pm 7.12 \times 10^{-4}$; oily SD $\pm 3.02 \times 10^{-4}$), signaling very high inter-individual variability and weak statistical precision at n=18. (ScienceDirect + 2)
- **Result (modeled, not measured):** The widely-quoted "4× AUC" and "5× AUC over 30 days" figures come from a **physiologically-based single-compartment model** (companion paper Żurek et al., 2023, *Pharmaceutics* [Pharmaceutics 2023]) that reconstructs the long-term curve shape from *external literature* (Armas radiolabeled data), not from these 18 subjects. Modeled AUC1day rose 0.037→0.135 (≈3.6×); modeled AUC1day–30day rose 1.69→8.5 (≈5×); modeled Cmax rose 0.067→0.335 (≈5×). The abstract's "four times" is a rounded summary internally inconsistent with the paper's own 3.6× and 5× figures. (mdpi) (doaj)
- **Deficiency effect:** The authors reported the liposomal advantage was most pronounced in severely deficient subjects but explicitly state "the observation requires further clinical evaluation before conclusion." (ScienceDirect) (ScienceDirect)
- **CONFLICT OF INTEREST (critical):** Funding was a Polish government grant (National Centre for Research and Development, POIR.04.01.04-00-0159/17). The declared COI states verbatim: **"ML and MP are partners in Lipid Systems Sp. z o.o." —** Marek Langner and Magdalena Przybyło co-own the company that manufactured the liposomal test product (Liposhell technology), and Langner personally performed the clinical investigation. This is a direct, disclosed financial conflict. (ScienceDirect)

Bottom line on Dałek: A genuine, peer-reviewed, mechanistically sophisticated pilot — but small, acute (5 h), heavily modeled for its headline numbers, statistically noisy, and manufacturer-conflicted. "Suggestive but preliminary," not "well-established."

B. Malabsorption populations — where a formulation edge should matter most

Nowak 2022 (positive, but not liposomal-D3-specific): Multi-center RCT, 100 pancreatic-insufficient CF patients, liposomal fat-soluble vitamin cocktail (with K2) vs standard preparations, 3 months, D3 4000 IU/day in both arms [J Clin Med 2022]. Change in 25(OH)D3: **+9.7 ± 13.4 (liposomal) vs +2.0 ± 9.8 ng/mL (standard), p=0.004**; end-of-study 25(OH)D3 **43.2 ± 16.6 vs 32.7 ± 11.5 ng/mL, p<0.001. Caveats:** the liposomal product was a full A/D/E/K1/K2 cocktail (confounded by K2 addition and slightly different comparator doses), not a clean D3-alone comparison, and authors report personal fees from Norsa Pharma (the manufacturer). DOI + 2

Nowak 2021 (the contradicting RCT from the SAME group): 3-arm RCT, 75 PI-CF patients, liposomes vs cyclodextrins vs MCT, D3 4000 IU/day [Nutrients 2021]. **For vitamin D specifically, liposomes did NOT beat MCT (Δ25(OH)D3 +2.0 vs +3.0 ng/mL, p=0.330 liposome-vs-MCT).** It was **cyclodextrins** that significantly improved D3 (+9.0 vs +3.0 ng/mL, p=0.012). Liposomes helped vitamin A, not D. Also Norsa Pharma / EU-funded. This directly undercuts a general "liposomes are superior for D3" claim. nih nih

No liposomal-D3 RCT exists specifically in bariatric, Crohn's/IBD, or short-bowel populations. The malabsorption trials that DO exist used other technologies: a buccal nanoemulsion spray in IBD [Front Med 2025] (effective at half the dose but with **no reduction in variability** and equal absolute 25(OH)D rise: +9.2 vs +9.3 nmol/L), and calcifediol in malabsorption/obesity. nih

C. Adjacent technologies — often conflated with "liposomal," with better data

- **Micellized (nano-micellar) D3:** Marwaha 2019 RCT, 180 randomized / 166 completers, healthy adults, 60,000 IU/month × 6 months, micellized (DePura) vs conventional (Calcirol) [Br J Nutr 2019]. Micellized arm (n=89) rose 21.5 → 76.7 nmol/L; conventional arm (n=77) rose 22.8 → 57.8 nmol/L. **The between-group difference was 17.5 nmol/L (95% CI 11.8, 23.1), remaining significant after adjustment for age and sex (p<0.001). COI note:** several authors were Sanofi India employees (Sanofi markets DePura).
- **Nanoemulsion D3 (oral):** Marwaha 2023 crossover PK, 25 healthy adults, single 60,000 IU nanoemulsion vs softgel, fasting [J Orthop 2023]. Nanoemulsion **AUC0–120h +36% (p=0.0001), Cmax +43% (p=0.0001).** Again Sanofi-linked. Medical Dialogues
- **LipoMicel (micellar, NOT classical liposome):** Solnier 2024 4-arm RCT, 35 adults, 1000 or 2500 IU × 30 days [Nutrients 2024]. At 1000 IU, micellar iAUC 992 vs 177 nmol·day/L (~6× incremental, p<0.05); **but NO significant difference at 2500 IU** — the advantage vanished at higher dose. Funded by Factors Group / ISURA (manufacturer-linked). nih nih
- **SNEDDS:** Only preclinical (rat) and formulation data; no human RCT yet [Springer 2025].

- **Cyclodextrin-complexed D3:** Positive human signal in the Nowak 2021 CF RCT (above) — outperformed both MCT and liposomes for D3.
- **Sucrosomial D3:** Bano 2023 RCT vs chewable/softgel showed higher, more sustained 25(OH)D [Front Nutr 2023].
- **Buccal/sublingual spray:** Mixed — some trials positive (Satia), several null (Todd, Williams) [Front Med 2025]. (nih)
- **Calcifediol (25(OH)D3):** The strongest evidence base of all. Beyond Bouillon's 3.2-fold pooled potency figure, the JBMR 2021 postmenopausal RCT (Pérez-Castrillón et al.) found calcifediol 0.266 mg/month ~**4× more potent than cholecalciferol 25,000 IU/month**, with 35.0% (calcifediol) vs 8.2% (cholecalciferol) reaching >30 ng/mL at 4 months ($p<0.0001$) [JBMR 2021], and absorption largely preserved in malabsorption [Nature EJCN 2024], [JCEM 2017]. This — not liposomes — is the pharmacologically robust route around hepatic 25-hydroxylation and fat malabsorption.

D. The ActiNovo "12.84×" claim — low-quality promotional evidence

ActiNovo's own study (20 volunteers, 1000 IU D3 + 200 μg K2, liposomal liquid vs a dry tablet) claims **12.84× greater bioavailability** [ActiNovo]. This is a manufacturer study comparing a liquid to a dry tablet over only a 6-hour window — an unfair, non-peer-reviewed comparison that conflates the delivery vehicle with the physical state of the product. Treat as marketing, not evidence. (Vitad) (Vitad)

E. Mechanistic plausibility: do oral liposomes survive and get absorbed intact?

The mechanistic case for oral liposomes is genuinely shaky. Conventional phospholipid/cholesterol liposomes are "highly susceptible to gastric acid, bile salts and lipases," lose integrity within ~2 hours in simulated intestinal fluid, and leak their payload [Ther Deliv 2015], [Int J Pharm 2013]. Only specially engineered vesicles (bilosomes, PEGylated, polymer-coated) show meaningful intact survival [Acta Pharm Sin B 2018]. The Dałek group's own molecular-dynamics argument is that D3 (logP >7) cannot leave the bilayer by diffusion, so its fate is entirely tied to the liposome's fate — but this cuts both ways: if the liposome is digested (the likely outcome in a normal gut), the D3 simply joins the same mixed-micelle pathway as any oil-delivered D3. In a person with normal bile and pancreatic function, an oral liposome may be little more than phospholipid-plus-D3 co-ingestion — which is exactly why the advantage should be largest precisely in malabsorption, the one setting where liposomal D3 (as opposed to cyclodextrin or calcifediol) has NOT been cleanly demonstrated. (Taylor & Francis) (PubMed)

F. Preclinical (clearly labeled)

- **Rat, 3-vehicle comparison:** Microencapsulated and oil-based D3 were MORE bioavailable than **micellized** D3, which was the worst performer [Medicina 2019]. A cautionary counterexample to the "water-soluble = better" narrative. (ResearchGate)
- **Bio-SNEDDS (rat):** ~2× relative bioavailability vs a pediatric reference [BBRC 2024].

- **Liposomal D3 anticancer (mouse):** Reduced toxicity, delayed tumor growth — not a bioavailability endpoint [PMC 2025].

G. The baseline/headroom problem (and fed-vs-fasted confound)

Conventional oil-based D3 is already well absorbed **with a fat-containing meal**: Dawson-Hughes (n=50, single 50,000 IU dose) showed a fat-containing meal raised the 12-hour peak plasma D3 by **32% vs a fat-free meal (p=0.003)**, with absorption at 10 h and 14 h also higher by 40% and 25% [JAND 2015]. Critically, most "enhanced-delivery superiority" studies dose **fasting** (Dałek: 12-h fast; Marwaha nanoemulsion: fasting), which handicaps the conventional oil comparator and inflates the apparent advantage. Notably, the Nowak 2021 CF trial — the fairest same-dose, taken-with-meals comparison — found NO D3 advantage for liposomes over MCT. When conventional D3 is taken correctly (with fat, at steady state), the realistic headroom for a delivery-system improvement in a person with a normal gut is modest, which is why the cleanest superiority signals come from settings that bypass absorption biology entirely (calcifediol) or from acute fasted PK snapshots rather than steady-state 25(OH)D.

Recommendations

For the VitaminDWiki evidence classification:

- **Classify liposomal D3 superiority as "suggestive but preliminary, and industry-conflicted."** The only dedicated human trial (Dałek 2022) is n=18, 5-hour, modeled, and manufacturer-owned; the only positive malabsorption RCT (Nowak 2022) confounds D3 with a K2-containing cocktail; and the same group's cleaner RCT (Nowak 2021) found no D3 advantage for liposomes.
- **Explicitly separate "liposomal" from "micellized/nanoemulsion/calcifediol"** in wiki taxonomy — readers and marketers routinely conflate them. The comparative human data ranking is roughly: **calcifediol (strong) > micellized/nanoemulsion D3 (moderate) > cyclodextrin D3 (moderate, CF only) > liposomal D3 (weak/preliminary).**
- **For malabsorption patients** (CF, Crohn's, bariatric, short bowel), the evidence points to **calcifediol first**, then water-miscible micellized/nanoemulsion or cyclodextrin formulations — NOT classical liposomes, which have no clean D3-specific malabsorption RCT.
- **For the general healthy reader,** the pragmatic and near-free intervention is conventional oil-based D3 **taken with the largest fat-containing meal of the day** — this captures most achievable absorption at ~10–40× lower cost than premium liposomal liquids.

Benchmarks that would change these recommendations:

- A ≥100-subject, independently-funded, steady-state (≥8–12 week) RCT comparing liposomal D3 alone vs oil-based D3 alone, both taken with a standardized fat-containing meal, with serum 25(OH)D as primary endpoint, would upgrade liposomal from "preliminary" to "established" if it showed a ≥25% AUC or steady-state 25(OH)D advantage.

- A malabsorption-population RCT isolating liposomal D3 (no K2 confound) vs calcifediol vs MCT would resolve the most clinically valuable question.

Caveats

- **Publication/sponsorship bias is pervasive.** Nearly every positive enhanced-delivery study is manufacturer-funded or manufacturer-authored (Lipid Systems, Norsa Pharma, Sanofi, Factors Group/ISURA, ActiNovo). Independent replication is largely absent.
- **"Liposomal" is used loosely.** Many marketed "liposomal" D3 products (e.g., Quicksilver, which labels its own product "nanoemulsified") are nanoemulsions or micellar systems, not classical liposomes; product-label terminology cannot be trusted to indicate the actual delivery physics.
- **Acute PK ≠ steady-state efficacy.** Faster Cmax/Tmax (the main liposomal signal) does not necessarily translate into higher maintained 25(OH)D over months, which is the clinically relevant endpoint.
- **Modeled AUC is not measured AUC.** The Dałek/Żurek 30-day AUC figures are extrapolations from 5 hours of data, using curve shapes borrowed from unrelated studies.
- **Commercial products cited (Empirical Labs, LipoLife, Seeking Health, Core Med Science, Sunlipid, LipoCellTech) have no peer-reviewed comparative human D3 trials** that I could locate; any bioavailability claims from these brands should be treated as unverified marketing until independent data appear.