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A Solid-State Liposomal Delivery System for Improving Oral Calcium Bioavailability: A Human Absorption Study

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ABSTRACT

Calcium is an essential mineral for bone health; however, its oral bioavailability is often limited by gastrointestinal conditions and absorption mechanisms. Liposomal technology, particularly in solid-state formulations, has been proposed to enhance nutrient stability and bioavailability. This study aimed to evaluate the effects of solid-state liposomal calcium on blood calcium response and absorption efficiency compared with non-liposomal calcium. A randomized crossover design was employed. Subjects received a single dose of either solid-state liposomal calcium or non-liposomal calcium, and blood calcium levels were measured over an 8-hour period. The area under the curve (AUC) was calculated to assess overall calcium exposure. Solid-state liposomal calcium significantly increased blood calcium levels at early time points (1–2 h; $p < 0.05$) and maintained elevated levels up to 8 h post-administration. The AUC was higher in the liposomal group (2.94 mg·h/dL) compared to the non-liposomal group (1.88 mg·h/dL), representing a 1.56-fold increase in systemic calcium exposure. Solid-state liposomal technology enhances both the rate and extent of calcium absorption, demonstrating its potential to improve calcium bioavailability.

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Introduction

Oral administration remains the most widely adopted route for nutritional supplementation due to its convenience, safety, and high subject compliance. However, many bioactive compounds exhibit limited oral bioavailability, which restricts their clinical efficacy and functional performance [1]. This limitation can be attributed to several factors, including poor gastrointestinal solubility, low membrane permeability, competition with dietary components, and the saturation of transport mechanisms [2]. In particular, minerals such as calcium rely on tightly regulated intestinal transport systems, whereby increasing the administered dose does not proportionally enhance absorption efficiency, but may instead lead to reduced fractional absorption and increased excretion [3]. Therefore, simply increasing calcium intake is not an effective strategy and may impose additional metabolic burden [4]. These limitations highlight the need for advanced delivery systems that can improve absorption efficiency while maintaining safety and scalability [5].

To overcome these challenges, various formulation strategies have been developed, including particle size reduction, nanoemulsions, phospholipid complexes, solid lipid nanoparticles, and encapsulation technologies [6]. Although these approaches have demonstrated progress in enhancing bioavailability, they still face challenges related to physicochemical stability, reproducibility of particle size distribution, scalability of manufacturing processes, and cost-effectiveness. Among emerging technologies, liposomal systems have gained increasing attention due to their structural versatility and functional adaptability [7]. Conventional liposomal formulations are typically presented as dispersed systems, while different dosage forms exhibit distinct characteristics in terms of stability, process integration, and application scenarios [8]. Consequently, solid-state liposomal systems have recently been developed to expand formulation possibilities.

Liposomes are spherical vesicles composed of phospholipid bilayers that structurally resemble biological cell membranes [9]. This amphiphilic architecture enables the encapsulation of both hydrophilic and lipophilic compounds within the aqueous core and lipid bilayer, respectively [10]. Owing to their membrane-mimetic properties, liposomes may facilitate cellular uptake via membrane fusion or endocytosis, thereby enhancing intestinal absorption [11]. In addition, phospholipid encapsulation may reduce calcium precipitation under gastric conditions and minimize interactions with dietary inhibitors such as oxalates and phytates, thereby improving its stability and bioaccessibility in the gastrointestinal tract [12]. With the increasing demand driven by aging populations and bone health concerns, the market for high-absorption mineral supplements continues to expand, further promoting the application of liposomal technologies.

Calcium is an essential mineral that plays a critical role in bone mineralization, neuromuscular function, vascular contraction, and intracellular signaling [13]. Adequate calcium intake is crucial for maintaining bone density and preventing osteoporosis, particularly in aging populations [14]. However, calcium absorption efficiency is influenced by multiple physiological factors, including vitamin D status, age, gastrointestinal conditions, and the presence of dietary inhibitors such as oxalates and phytates. Conventional calcium supplements, such as calcium carbonate and calcium citrate, may exhibit variable absorption performance under conditions of low gastric acidity or altered intestinal function, resulting in inconsistent supplementation outcomes [15].

TCI Co., Ltd. has developed the DOUBLE NUTRI ® SOLID liposomal delivery platform, a solid-state liposomal system designed to enhance the stability and absorption efficiency of mineral nutrients. This technology utilizes high-pressure homogenization at 400 bar to generate phospholipid vesicles with a particle size ranging from 0.5 to 2 μm, which are subsequently transformed into a solid dosage form [16]. Through precise control of processing conditions, uniform vesicle formation is achieved, improving encapsulation stability and maintaining structural integrity. While preserving the fundamental characteristics of liposomal systems, this solid-state formulation provides an alternative dosage form to conventional dispersed systems and demonstrates reproducible manufacturing performance and formulation stability.

Therefore, the present study aimed to evaluate the oral bioavailability of calcium formulated using the DOUBLE NUTRI ® SOLID liposomal technology. A human absorption study was conducted to assess pharmacokinetic parameters, including maximum plasma concentration (Cmax) and area under the concentration–time curve (AUC), and to compare these outcomes with those of non-liposomal calcium. This study seeks to determine the potential of this solid-state liposomal platform to enhance systemic calcium exposure and to provide scientific evidence for improving oral supplementation strategies.

Materials and Methods

Clinical Design

This clinical study was approved by the Ethics Committee of National Yang Ming Chiao Tung University (NYCU112181AE), and the study protocol was registered at ClinicalTrials.gov (NCT06372158). A total of 13 healthy adults aged 20–60 years were recruited for this study. Eligible subjects were required to be free from major systemic diseases, including cardiovascular, hepatic, renal, endocrine, or other significant organ-related disorders, and capable of complying with study procedures. Subjects were excluded if they had impaired renal function or were undergoing dialysis, had a diagnosis of cancer, had a body mass index (BMI) ≤ 17 or ≥ 27 kg/m², were taking chronic medications, had systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, fasting blood glucose ≥ 100 mg/dL, fasting triglycerides ≥ 150 mg/dL or total cholesterol ≥ 200 mg/dL, known calcium hypersensitivity, psychiatric disorders, were pregnant or lactating, had iron overload conditions, a history of kidney stones, or long-term use of calcium supplements. This study was conducted using an single-blind, two-period crossover design, in which each subject completed two intervention phases separated by a 14-day washout period to minimize carryover effects. Subjects were randomly assigned to one of two sequences to determine the order of intervention, receiving either the conventional calcium formulation followed by the liposomal calcium formulation, or vice versa, ensuring that each subject received both treatments without repetition within the same phase.

The two test products included a conventional calcium powder containing 500 mg of calcium carbonate and a liposomal calcium formulation (DOUBLE NUTRI ® SOLID) containing 500 mg of calcium carbonate encapsulated with phospholipids. A total of 13 subjects participated in the study. Subjects were instructed to fast for at least 8 hours prior to each test day. On each study day, a baseline blood sample (~6 mL) was collected prior to administration of the test product (time 0), with 3 mL used for calcium analysis and 3 mL for routine biochemical assessments, including liver function, renal function, glucose, and lipid parameters. Following ingestion of the assigned product, additional blood samples (~3 mL each) were collected at 1, 2, 4, 6 and 8 hours post-dose for calcium concentration analysis. During the study period, subjects consumed 150 mL of water every hour. Blood samples were analyzed for fasting glucose, triglycerides, total cholesterol, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (GOT), and alanine aminotransferase (GPT), while calcium concentrations in blood were determined using standard analytical methods. The primary endpoint was blood calcium concentration at 8 hours post-administration, and pharmacokinetic parameters, including maximum plasma concentration (Cmax) and area under the concentration–time curve (AUC), were also evaluated.

Test Samples

Two oral formulations were evaluated: a liposomal calcium carbonate formulation based on DOUBLE NUTRI ® SOLID (Lipo) and a non-liposomal calcium carbonate formulation (non-Lipo). Both formulations were manufactured by TCI Co., Ltd. and provided in single-dose powder sachets. Each sachet contained 500 mg of calcium carbonate. The Lipo formulation consisted of calcium carbonate, isomalt (hydrogenated palatinose), citric acid, flavor powder, sucralose. The non-Lipo formulation contained the same composition.

Serum Calcium Determination

Venous blood samples were collected into appropriate collection tubes at each time point and allowed to clot before centrifugation to obtain serum. Serum samples were stored at 4°C until transportation to an independent certified clinical laboratory (Lezen Reference Laboratory, Taipei, Taiwan) for the determination of serum calcium concentrations. Quantification was performed using validated analytical methods with appropriate calibration and internal quality control procedures for each analytical batch.

Statistical Analysis

Data are presented as mean ± SD. Because of the crossover design, comparisons between the Lipo and non-Lipo formulations were performed using paired t-tests. A two-tailed p-value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism 10 (GraphPad Software, San Diego, CA, USA).

Results

Enhanced Blood Calcium Response with Liposomal Calcium

Following administration of the test products, the liposomal calcium group exhibited a consistently greater increase in blood calcium levels compared to the non-liposomal calcium group across all measured time points (1–8 h). At 1 h post-administration, the Lipo group showed an early increase in blood calcium concentration (0.17 mg/dL), whereas the non-Lipo group demonstrated a slight decrease from baseline (−0.05 mg/dL),

indicating a delayed absorption response. This divergence became more pronounced at 2 h, where the Lipo group reached a markedly higher level (0.42 mg/dL), compared to a modest increase in the non-Lipo group (0.13 mg/dL). The elevated calcium levels in the Lipo group were sustained over time, peaking at 4 h (0.45 mg/dL) and remaining relatively stable through 6–8 h (0.38–0.43 mg/dL). In contrast, the non-Lipo group showed a gradual and limited increase, reaching only 0.27 mg/dL at 8 h. Notably, the differences between the two groups were statistically significant at early time points (1–2 h; $p < 0.05$), suggesting that liposomal calcium facilitates a more rapid onset of absorption (Figure 1).

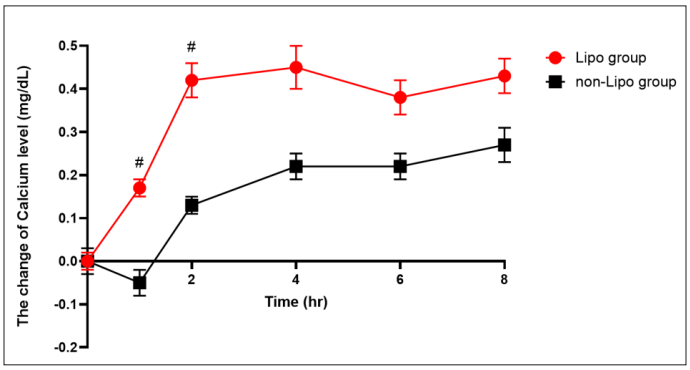

Figure 1: Time-course changes in blood calcium levels following oral administration of liposomal and non-liposomal calcium formulations in healthy subjects (n = 13). Subjects received one sachets (total dose: 500 mg calcium) in a randomized crossover design with a 14-day washout. Blood samples were collected at 0, 1, 2, 4, 6, and 8 h. Data are presented as mean ± SD. # $p < 0.05$ vs. non-Lipo at the same time point.

Increased systemic calcium exposure with liposomal calcium to further evaluate the overall extent of calcium absorption, the area under the curve (AUC) for blood calcium levels was calculated. The Lipo group exhibited a substantially higher AUC (2.94 mg·h/dL) compared to the non-Lipo group (1.88 mg·h/dL), corresponding to a 1.56-fold increase in systemic calcium exposure (Figure 2). This finding indicates that, in addition to enhancing early-phase absorption, liposomal calcium also improves the cumulative bioavailability of calcium over time. Taken together, these results demonstrate that liposomal calcium not only accelerates the rate of calcium absorption but also increases the total absorbed amount, with sustained elevation in blood calcium levels observed for up to 8 h post-administration.

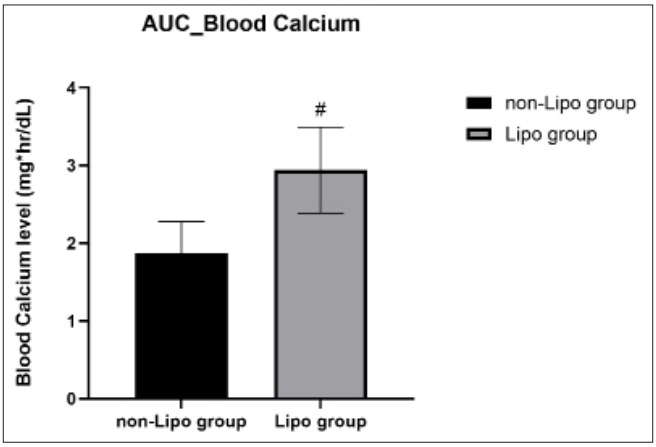

Figure 2: Area under the curve (AUC) of blood calcium levels following oral administration of liposomal and non-liposomal calcium formulations in healthy subjects (n = 13). Subjects received one sachets (total dose: 500 mg calcium) in a randomized crossover design. Blood calcium levels were measured over 8 h, and AUC was calculated to assess overall calcium exposure. # $p < 0.05$ vs. non-Lipo. Data are presented as mean ± SD.

Discussion

The present study demonstrates that liposomal calcium significantly enhances both the magnitude and extent of blood calcium elevation compared to non-liposomal calcium following a single administration. In terms of temporal dynamics, the liposomal group exhibited an early increase in blood calcium concentration at 1 h (0.17 mg/dL), followed by a significantly higher level at 2 h (0.42 mg/dL vs. 0.13 mg/dL in the non-liposomal group), indicating a more rapid onset of absorption. This difference was statistically significant at early time points (1–2 h; $p < 0.05$), supporting the enhanced early-phase absorption of liposomal calcium. Moreover, the elevated calcium levels in the liposomal group were sustained over time, reaching a peak at 4 h and remaining stable through 8 h, suggesting a prolonged absorption profile. Consistently, the area under the curve (AUC) for blood calcium was 1.56-fold higher in the liposomal group than in the non-liposomal group (2.94 vs. 1.88 mg·h/dL), indicating increased systemic exposure. Collectively, these findings suggest that liposomal calcium improves both the rate and extent of calcium absorption, resulting in enhanced bioavailability.

Although clinical evidence on the application of liposomal technology to calcium absorption remains relatively limited, existing studies provide supportive insights. Conventional oral calcium supplementation typically involves single doses ranging from 300 to 1000 mg of elemental calcium, with fractional absorption rates generally between 20% and 40%, depending on dose and physiological conditions [17]. Notably, absorption efficiency decreases at higher doses (e.g., above 500 mg per intake), reflecting saturation of intestinal transport mechanisms [18]. In this context, liposomal delivery systems have been proposed to improve absorption efficiency. Previous human and animal studies have reported that liposomal formulations can increase mineral bioavailability by approximately 1.2- to 1.6-fold, which is consistent with the 1.56-fold increase in AUC observed in the present study [19, 20]. Furthermore, liposomal systems have been shown to accelerate the onset of absorption, leading to earlier increases in circulating nutrient levels, in agreement with the early-phase differences observed at 1–2 h in this study. Although large-scale clinical trials are still lacking, current evidence supports the potential of liposomal formulations to enhance calcium absorption.

The enhanced absorption of liposomal calcium may be attributed to multiple mechanisms. First, the phospholipid bilayer structure of liposomes can encapsulate calcium ions, thereby reducing their interaction with dietary inhibitors such as phytates and oxalates in the gastrointestinal tract [21]. This protection helps maintain calcium in a soluble and bioavailable form. Second, liposomes may interact with intestinal epithelial cell membranes through fusion or endocytic processes, facilitating transcellular transport of calcium and improving absorption efficiency [22]. In addition, liposomal encapsulation may modulate the release kinetics of calcium, enabling a more sustained and controlled release profile that prevents local saturation of absorption pathways [23]. Furthermore, liposomes may enhance membrane fluidity and influence the activity of ion channels or transport proteins involved in calcium uptake [24]. These combined effects likely contribute to both the accelerated absorption and increased systemic exposure observed in this study.

From a formulation and application perspective, solid-state liposomal technology offers several advantages in terms of stability and product development [25]. Solid formulations are less susceptible to environmental factors such as moisture and oxidation, thereby ensuring consistent product quality and maintaining the integrity of the liposomal structure [26]. In addition, solid liposomal systems can be incorporated into various dosage forms, including powders, capsules, and tablets, allowing for precise dosing and improved user compliance [27]. In practical applications, this technology is particularly suitable for bone health maintenance, prevention of sarcopenia, sports nutrition, and nutritional support in middle-aged and elderly populations [28]. Moreover, it can be integrated with other functional ingredients, such as vitamin D or protein, to further enhance efficacy. With increasing consumer demand for high bioavailability and scientifically validated products, solid-state liposomal calcium is expected to play an important role in the development of next-generation functional mineral supplements [29].

Despite the promising findings of this study, several limitations should be acknowledged. First, the sample size was relatively small, which may limit the generalizability of the results. Second, the study was conducted under a single-dose, acute design, and therefore does not provide information on long-term calcium absorption or its impact on clinical outcomes such as bone mineral density. Third, although blood calcium levels were used as a surrogate marker of absorption, additional biomarkers, such as urinary calcium excretion or calcium balance, were not assessed, which may provide a more comprehensive evaluation of calcium metabolism. Furthermore, the study did not directly investigate the underlying mechanisms of liposomal calcium absorption at the cellular or molecular level. Future studies with larger sample sizes, longer intervention periods, and mechanistic investigations are warranted to further elucidate the benefits of liposomal calcium supplementation.

References

1. Yang X, Linzixuan Z, Zhiling Z, Robert L, Ana J (2025) Advanced Oral Delivery Systems for Nutraceuticals. Adv Healthc Mater 14: 2500271.
2. Vllasaliu D (2025) Grand challenges in oral drug delivery. Front Drug Deliv 5: 1571982.
3. Joydeb M, Oleh T, Tamara M (2019) Nanocarrier-based systems for targeted and site specific therapeutic delivery. Adv Drug Deliv Rev 144: 57-77.
4. Jonas R, Katharina L, Volker M (2018) The challenges of oral drug delivery via nanocarriers. Drug Deliv 25: 1694-1705.
5. Wei S, Xi Z, Min L, Lian L, Jiaju Z, et al. (2015) Overcoming the diffusion barrier of mucus and absorption barrier of epithelium by self-assembled nanoparticles for oral delivery of insulin. ACS Nano 9: 2345-2556.
6. Hwa SH, Song YK, Ki YC (2022) Emerging nanoformulation strategies for phytocompounds and applications from drug delivery to phototherapy to imaging. Bioactive Materials 14: 182-205.
7. Hwa SH, Song YK, Ki YC (2025) Liposomes and Extracellular Vesicles as Distinct Paths Toward Precision Glioma Treatment. International Journal of Molecular Sciences 26: 6775.
8. Zhensheng M, Kaiying Z, Jiayu L, Shuoling C, Shenglong T, et al. (2026) Liposome-based drug delivery systems for skin wound healing: a promising drug delivery strategy. Front Bioeng Biotechnol 14: 1756872.
9. Hamdi N, Dima K, Usama S, Fadwa O, Abeer AB, et al. (2022) Liposomes: structure, composition, types, and clinical applications. Heliyon 8: 09394.
10. Ruihan H, Hongdong S, Sen L, Xiao G (2025) Selection strategy for encapsulation of hydrophilic and hydrophobic ingredients with food-grade materials: A systematic review and analysis. Food Chemistry X 25: 102149.
11. Abolfazl A, Rogaie RS, Soodabeh D, Sang WJ, Nosratollah Z (2025) Liposomes for drug delivery: Classification, therapeutic applications, and limitations. Next Nanotechnology 8: 100209.
12. Megan WB, Steven AA, José MB, Erick B, Gabriela C, et al. (2022) Interventions to improve calcium intake through foods in populations with low intake. Ann N Y Acad Sci 1511: 40-58.
13. Bonny BW, Erik BF, Kellene AI (2024) Vitamin D and Calcium—An Overview, Review of Metabolism, and the Importance of Co-Supplementation. Dietetics 3: 588-608.
14. Judith AB (2015) The role of calcium in human aging. Clin Nutr Res 4: 1-8.
15. Tondapu P, Provost D, Adams HB, Sims T, Chang C, et al. (2009) Comparison of the absorption of calcium carbonate and calcium citrate after Roux-en-Y gastric bypass. Obes Surg 19: 1256-1261.
16. Chiung JW, Chi FC, Chung SL, Yung HL, Jaw ST (2022) Double Nutri (Liposomal Encapsulation) Enhances Bioavailability of Vitamin C and Extends Its Half-Life in Plasma. J Biomed Nanotechnol 18: 922-927.
17. Ian RR (2025) Calcium Supplementation- Efficacy and Safety. Curr Osteoporos Rep 23: 8.
18. James CF, Ryan DS (2010) Molecular mechanisms for regulation of intestinal calcium absorption by vitamin D and other factors. Crit Rev Clin Lab Sci 47: 181-195.
19. Aygul C, Taskeen N, Arwen IIT, Alan RM (2026) Impact of bile salts, biopolymer coatings, and food matrix on bilosome-mediated delivery of trans-resveratrol. Food Chem 34: 103547.
20. Anitra CC (2025) Do Liposomal Vitamin C Formulations Have Improved Bioavailability? A Scoping Review Identifying Future Research Directions. Basic Clin Pharmacol Toxicol 137: 70067.
21. Muhammad AR, Hamdy AZ, Hafiza MJ, Saadia A, Mohamed F, et al. (2025) Liposomal Encapsulation in Food Systems: A Review of Formulation, Processing, and Applications. Food Sci Nutr 13: 70587.
22. Xiaofan W, Keke W, Yitan F, Youxi Z, Lixin Y, et al. (2026) Strategies for overcoming multiple barriers of oral administration of protein and peptide therapeutics. Mater Today Bio 37: 102763.
23. Remo E, Simone A, Julia BB, Davide B, Laura B, et al. (2026) Physiologically controlled release from an in situ forming liposomal depot. Journal of Controlled Release 392: 114739.
24. Nelson M, Albino M, Rui LR, Nuno MN (2014) Liposomes in tissue engineering and regenerative medicine. J R Soc Interface 11: 20140459.
25. Lisa S, Tejaswi V, Fatemeh M, Sherry YW, Anil KS, et al. (2015) Advances and Challenges of Liposome Assisted Drug Delivery. Front Pharmacol 6: 286.
26. Mohammad T, Manisha S, Asgar F, Mehran G, Mina D (2026) Plant-based delivery systems for bioactive compounds: Mechanisms of release and functional food applications. Advances in Colloid and Interface Science 350: 103787.
27. Chrystalla P, Ioannis T, Siva SK, Dennis D, Costas D, et al. (2026) Formulation and in vitro evaluation of liposomal and self-microemulsifying drug delivery systems for oral delivery of cannabidiol. Journal of Pharmaceutical Sciences 115: 104053.

28. Simin L, Lin Z, Shuangqing L (2023) Advances in nutritional supplementation for sarcopenia management. Front Nutr 10: 1189522.

29. Minglu H, Xiaonan T, Kang L, Ning X (2025) Nanoencapsulation of nutraceuticals enhancing stability and bioavailability in functional foods. Front Nutr 12: 1746176.