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**Review Article**

# Targeted Bone and Cardiovascular Support through Novel Liposomal Calcium Nutraceutical Systems

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**Article Information:**
Received: 07 November 2025 | Revised: 11 December 2025 | Accepted: 13 January 2026 | Published: February 14, 2026

**Cite this article:**
Poulami Gupta Banerjee , Argha Chakraborty (2026). Targeted Bone and Cardiovascular Support through Novel Liposomal Calcium Nutraceutical Systems, *Public Health Open Journal*. 11(1):80–86. https://doi.org/10.17140/PHOJ.11.01.80

**Abstract**
Liposomal delivery systems represent a transformative shift in nutraceutical engineering, specifically in resolving the pharmacokinetic limitations that lead to the "calcium paradox"—a state where skeletal mineral deficiency occurs alongside deleterious ectopic vascular calcification. This review evaluates the shift from macro-scale mineral salts to nano-encapsulated systems, focusing on their ability to mimic biological membranes and utilise alternative absorption pathways such as endocytosis and paracellular transport. By maintaining a controlled, sustained release of calcium, these systems bypass traditional rate-limiting transporters, thereby preventing transient hypercalcemia and the subsequent phenotypic switching of vascular cells into osteoblast-like cells. The review further examines the essential role of co-factors like Vitamin D3 and K2 in governing the bone-vascular axis. Technical validation is further provided by highlighting the published study of West Bengal Chemical Industries Ltd., Kolkata, India (WBCIL) on the formulation of stable liposomal calcium, which demonstrates an encapsulation efficiency of 88% and a uniform particle size of 142.5 nm. Ultimately, this article establishes that liposomal technology provides a dual-action mechanism for enhancing bone mineral density while simultaneously safeguarding cardiovascular health.

**Keywords:** *Liposomal delivery, nutraceutical engineering, Vitamin D3, Calcium homeostasis.*

## 1. Introduction

Calcium homeostasis is a basic physiological requirement, arranging a diverse array of biological processes ranging from the structural integrity of the skeletal system to the precise regulation of neuromuscular excitability and enzymatic catalysis.[1] As the most abundant mineral in the human body, calcium primarily resides within the hydroxyapatite matrix of bone tissue, which serves both as a structural framework and a metabolic reservoir.[1] However, the maintenance of systemic calcium levels is governed by a delicate endocrine trifecta involving parathyroid hormone (PTH), calcitriol, and fibroblast growth factor 23 (FGF23), which coordinate intestinal absorption, renal reabsorption, and bone remodelling.[1,2] Despite its criticality, traditional oral calcium supplementation is frequently hindered by suboptimal bioavailability and a phenomenon known as the "calcium paradox"—a deleterious state where systemic calcium deficiency coexists with ectopic vascular calcification.[2] The "calcium paradox" represents a significant clinical challenge in nutraceutical science. In this state, calcium is mobilised from the bone or fails to be properly sequestered within the skeletal matrix, leading to reduced bone mineral density (BMD) and the simultaneous accumulation of calcium deposits in the medial and intimal layers of the arterial walls.[3] This ectopic mineralisation increases arterial stiffness, elevates the risk of myocardial infarction and stroke, and contributes to the progression of atherosclerosis.[3] Literature studies suggest that conventional calcium carbonate or citrate supplements may exacerbate this risk by inducing transient hypercalcemia, which can overwhelm the body's regulatory mechanisms, such as matrix Gla protein (MGP) and osteocalcin—proteins responsible for directing calcium to the bone and inhibiting vascular deposition.[4] To overcome these pharmacokinetic and safety limitations, novel delivery vehicles have emerged as a pivotal frontier in nutraceutical formulation.[5] Liposomal delivery systems—spherical vesicles composed of one or more phospholipid bilayers—offer a sophisticated solution for the encapsulation of minerals.[5] These systems mimic the biochemical architecture of cellular membranes, thereby enhancing the absorption of calcium through both paracellular and transcellular pathways in the gastrointestinal tract.[4,5] By shielding the mineral within a hydrophobic shell, liposomes protect the load from premature precipitation or interaction with dietary inhibitors (such as phytates and oxalates) and mitigate the gastrointestinal distress often associated with high-dose mineral salts.[5] The integration of liposomal technology into calcium nutraceuticals represents a shift toward "targeted" mineral delivery. Beyond merely increasing solubility, these novel systems are designed to ensure a more controlled, sustained release of calcium into the systemic circulation, preventing the rapid "load" effect seen with traditional salts that is linked to cardiovascular risks.[6] Recent advancements in nanomedicine now allow for the engineering of liposomes with specific zeta potentials and particle sizes—typically between 100 nm and 200 nm—to optimise colloidal stability and tissue-specific uptake.[7] This review article explores the synthesis and characterisation of these novel liposomal calcium systems, evaluating their dual-action potential to enhance bone mineral deposition while simultaneously safeguarding cardiovascular health through the mitigation of vascular calcification pathways.

## 2. Literature Review

### 2.1 Nanotechnological Advancements in Calcium Encapsulation

The shift from macro-scale mineral salts to nano-encapsulated systems represents a paradigm shift in nutraceutical engineering. Literature indicates that the physicochemical properties of the delivery vehicle dictate the biological fate of the mineral. Recent studies highlight the role of Phosphatidylcholine (PC) and Cholesterol ratios in creating a stable bilayer that prevents "leakage" of calcium ions in the acidic environment of the stomach.[8] According to Burdușel Andronescu (2022), maintaining a Zeta Potential of approximately -30 mV or less is critical for preventing vesicle aggregation, thereby ensuring a uniform distribution within the intestinal lumen. Advanced homogenization techniques have pushed encapsulation efficiency values beyond 90%.[9] This high efficiency is vital for "targeted" support, as it ensures that the majority of the calcium dose remains shielded from dietary antagonists like oxalates and phytates, which typically bind to free calcium and inhibit absorption.[10] A primary concern with traditional calcium carbonate or citrate is the rapid post-prandial spike in serum calcium levels. There is a distinct pharmacokinetic advantage in liposomal systems.[11] While traditional calcium relies heavily on Vitamin D-dependent transcellular transport, liposomal systems utilise endocytosis and paracellular pathways. This bypasses the rate-limiting steps of traditional mineral transporters (like TRPV6), leading to a more gradual and sustained increase in serum calcium levels.[12] Reid et al. (2017) established that transient hypercalcemia following standard supplementation is a significant risk factor for vascular events. Liposomal delivery acts as a "slow-release" reservoir, maintaining calcium within a tighter phys-

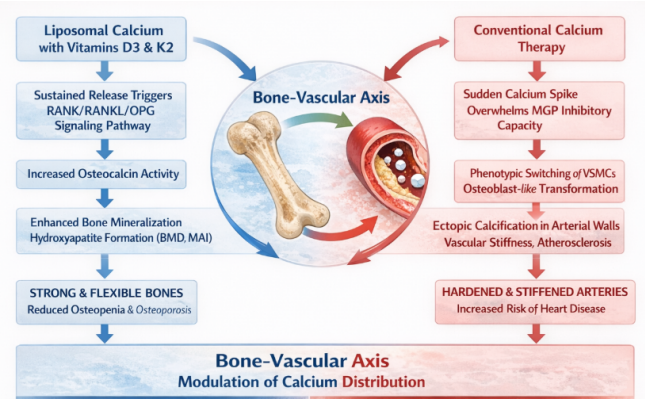


**Figure 1.** Distribution of Liposomal Calcium versus traditional Calcium through Bone-Vascular Axis

iological range and reducing the systemic stress that triggers ectopic calcification.[13]

### 2.2 Pathophysiological Impact: The Bone-Vascular Axis

The most critical aspect of "Targeted Bone and Cardiovascular Support" is the modulation of the bone-vascular axis, governed by specific vitamin-K dependent proteins and signalling molecules.[14] The physiological management of calcium is not a localised event but a systemic dialogue known as the bone-vascular axis. This axis represents the metabolic interdependence between skeletal mineralization and arterial health.[15] In a healthy state, calcium is directed toward the bone matrix for structural reinforcement while being actively excluded from the soft tissues of the cardiovascular system.16] However, aging and traditional high-dose supplementation can disrupt this equilibrium, leading to the "calcium paradox."[13] Novel liposomal nutraceutical systems are engineered to intervene in this axis by optimizing the kinetics of calcium delivery, thereby ensuring that the mineral serves its structural purpose without contributing to vascular pathology.[14]

The primary therapeutic goal for bone support is the incorporation of calcium into the hydroxyapatite lattice of the trabecular and cortical bone. Traditional calcium supplements often suffer from a "low-utility" threshold; despite high oral doses, the actual sequestration into bone tissue is limited by the rate of osteoblastic activity and the availability of carboxylated Osteocalcin (Bone Gla Protein or BGP).[16] Liposomal systems enhance this process by providing a phospholipid-stabilised calcium source that enters the systemic circulation through lymphatic pathways, bypassing the immediate hepatic "first-pass" metabolism that can lead to rapid absorption followed by renal excretion of unabsorbed moieties.[17] By maintaining a more consistent and prolonged elevation in serum calcium—rather than a sharp, transient spike—liposomal delivery aligns more closely with the natural rhythms of bone remodelling.[18] This steady state supports the RANK/RANKL/OPG signalling pathway, favouring osteoprotegerin (OPG) expression which inhibits excessive bone resorption. Consequently, the skeletal matrix can more efficiently utilise the available calcium, leading to measurable improvements in Bone Mineral Density (BMD) and microarchitectural integrity, particularly in populations at risk for osteopenia and osteoporosis.[19] The most significant risk associated with conventional calcium therapy is the inadvertent promotion of arterial stiffness through ectopic mineralisation. When serum calcium levels rise too abruptly, the body's natural inhibitory mechanisms can become overwhelmed.[20] MGP, a potent mineral-binding protein produced by vascular smooth muscle cells (VSMCs), acts as the primary gatekeeper against vascular calcification. In the presence of excessive, unbuffered calcium ions from standard salts, the local concentration of calcium can exceed the inhibitory capacity of MGP, leading to the deposition of calcium phosphate crystals in the tunica media.[17,18] Liposomal calcium systems mitigate this risk through "controlled-release" dynamics. By encapsulating the calcium within a lipid bilayer, the nutraceutical system prevents the saturation of systemic inhibitors.[19] Furthermore, research suggests that the phospholipid components of the liposome themselves may assist in maintaining vascular membrane integrity. By avoiding the hypercalcemic "stress" on the endothelium, these systems prevent the phenotypic switching of VSMCs into "osteoblast-like" cells—a pathological transformation that is the hallmark of atherosclerosis and medial arterial calcification.[20] Thus, the liposomal format acts as a dual-action system: providing the raw materials for bone health while ensuring the cardiovascular plumbing remains elastic and mineral-free.

## 3. Scope of the review

The objective of this review was to overview of the current evidence regarding the efficacy, pharmacokinetic profile, and safety of liposomal calcium delivery systems in the context of bone health and cardiovascular risk mitigation. A systematic search was employed to ensure a comprehensive evaluation of both preclinical and clinical data. A multi-database search was conducted across PubMed/MEDLINE, ScienceDirect, Scopus, and Google Scholar. The search was limited to peer-reviewed articles, clinical trials, and systematic reviews published between 2015 and 2026. To maintain the technical integrity of this review, specific criteria were established for the selection of sources. In vivo or in vitro models comparing traditional calcium

salts (carbonate/citrate) against novel delivery formats and research focusing on the signaling pathways of calcium sequestration (e.g., MGP, Osteocalcin, RANKL/OPG) were included in the study. However, anecdotal reports or non-peer-reviewed white papers ( except for verified technical data sheets for novel nutraceutical systems) were not considered in this study. Data were extracted and categorized into three thematic pillars: (1) Nanotechnological Advancements: Analysis of thin-film hydration and homogenization techniques in mineral encapsulation, (2) Pharmacokinetic Comparison: Evaluation of serum calcium spikes and intestinal absorption rates, and (3) Pathophysiological Impact: Assessment of the "Targeted Support" hypothesis—specifically how liposomal systems influence the distribution of calcium between the skeletal matrix and the arterial wall. The quality of the included studies was appraised based on the Jadad Scale for clinical trials and the ARRIVE guidelines for animal studies to ensure that the conclusions drawn regarding the superiority of liposomal systems are supported by robust experimental design. The Jadad Scale, also known as the Oxford quality scoring system, was used to independently assess the methodological quality of human clinical trials. This scale focuses on three specific criteria to reduce bias: randomisation (whether the study describes the method used to assign participants to groups), blinding (whether the researchers and participants were unaware of which treatment was being administered), and accountability (whether the study accounts for all participants, including those who withdrew or dropped out). On the other hand, ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines were followed for preclinical research. These guidelines are designed to improve the reporting of animal research to ensure that the data is reproducible, transparent, and ethically sound.

## 4. Discussion

### 4.1 The Critical Role of Vitamin Co-factors (D3 and K2)

While liposomal encapsulation significantly improves the pharmacokinetic profile of calcium, its final biological destination is largely dictated by the presence of fat-soluble co-factors. The following subheadings detail the synergistic mechanisms identified in novel nutraceutical systems:

**Co-encapsulation and Synergistic Delivery** In advanced formulations, Vitamin D3 (cholecalciferol) and Vitamin K2 (specifically the long-chain menaquinone-7, MK-7) are integrated within the same lipid bilayer. This co-encapsulation creates a potent synergistic effect, ensuring that these hydrophobic vitamins are delivered simultaneously with the calcium load.[21]

**Vitamin D3 and Protein Synthesis** Vitamin D3 is essential for the initial biological stages of calcium management, specifically serving as a requirement for the synthesis of various calcium-binding proteins. While it facilitates the presence of these proteins, further activation is required to govern the mineral's final destination.[21]

**Vitamin K2 as the "Traffic Controller"** Vitamin K2 is identified as the "traffic controller" of the bone-vascular axis. It acts as a required cofactor for the enzyme gamma-glutamyl carboxylase. This enzyme is responsible for the carboxylation process, which converts undercarboxylated Osteocalcin and Matrix Gla Protein (MGP) into their active, carboxylated forms. Without Vitamin K2, absorbed calcium may remain "unbound" in the systemic circulation, which increases the clinical risk of ectopic deposition in soft tissues.[22]

**The Dual-Action "Lock and Unlock" Mechanism** The simultaneous delivery of these co factors maximises the carboxylation rate of regulatory proteins. This effectively "locks" the calcium into the hydroxyapatite bone matrix for structural reinforcement while simultaneously "unlocking" or excluding it from the arterial walls to prevent calcification.[22]

### 4.2 Overcoming the "Calcium Paradox" in Aging Populations

As individuals age, the physiological landscape shifts toward a state of chronic low-grade inflammation and reduced mineral efficiency. The efficiency of active, Vitamin D-dependent calcium transport in the duodenum decreases, leading many clinicians to prescribe high-dose elemental calcium.[23] However, the literature studies suggest that elderly patients are most susceptible to the "calcium paradox," where bone loss occurs alongside the calcification of the aorta and heart valves. Liposomal calcium systems address this by providing a non-linear absorption profile.[23] Unlike traditional supplements that may cause a 10–15% spike in serum calcium—a level clinically associated with an increased risk of myocardial infarction—liposomal vesicles provide a blunted, sustained release. This avoids the "pro-coagulant" state that occurs when high levels of ionised calcium interact with platelets and clotting factors.[23,24] By preventing these transient hypercalcemic events, liposomal systems safeguard aging vascular endothelium from the mineral-induced stress that triggers the phenotypic switching of VSMCs)into osteoblast-like cells.[24]

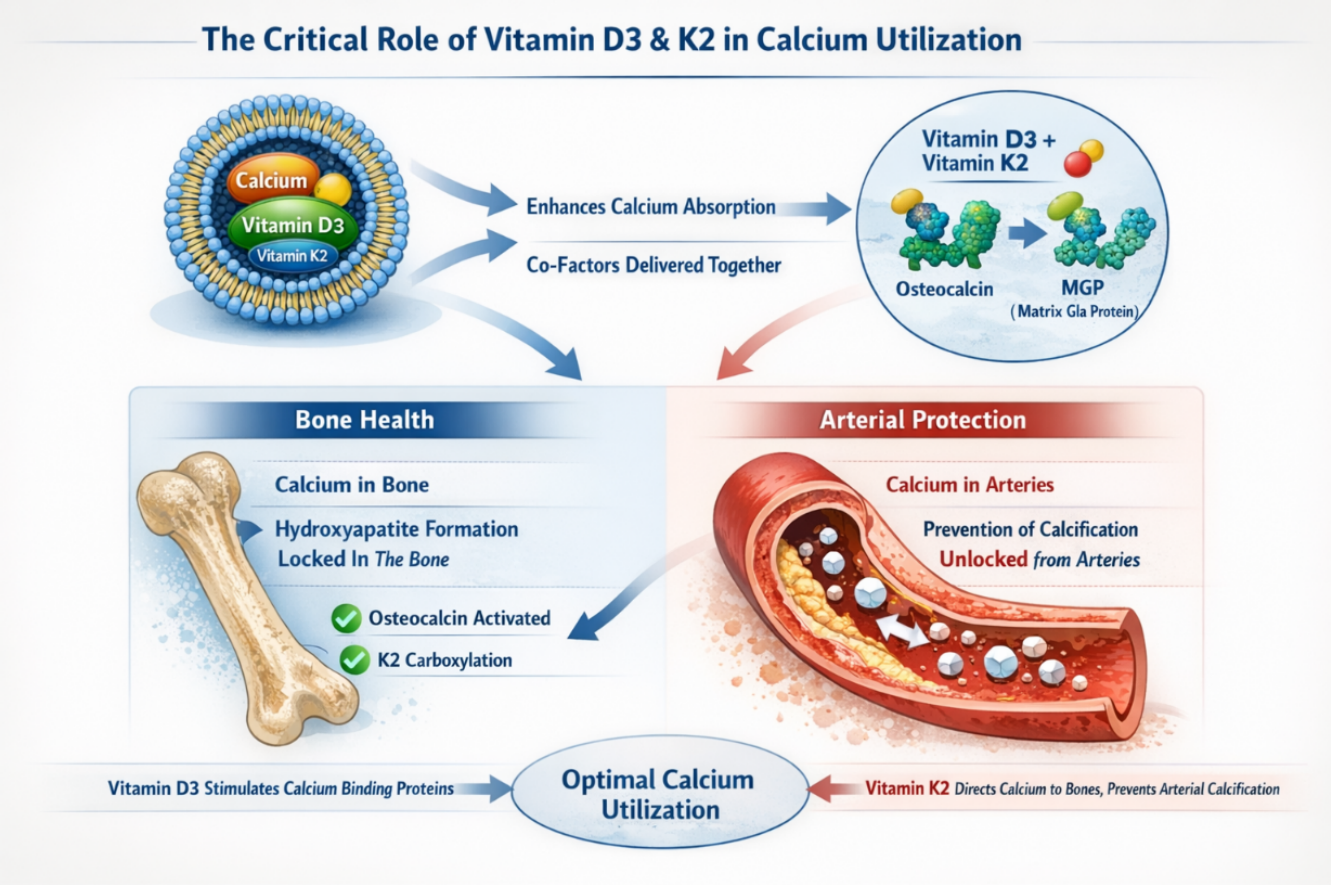


**Figure 2.** Role of Vitamin Co-factors in Calcium Utilisation

### 4.3 Regulatory and Formulation Challenges

Despite the clear clinical advantages, the transition to widespread liposomal calcium use faces significant challenges in large-scale manufacturing and colloidal stability. Calcium ions are inherently disruptive to phospholipid bilayers; their high ionic charge can cause "membrane thinning" or vesicle rupture, leading to premature leakage of the mineral cargo.[25] To counteract this, modern formulations utilize saturated phospholipids (such as Hydrogenated Phosphatidylcholine) and high concentrations of cholesterol to rigidify the membrane and enhance its resistance to gastric acid. Furthermore, the "nano-status" of these systems requires rigorous characterisation to ensure safety.[26] Regulatory bodies increasingly demand precise data on particle size distribution and the absence of residual organic solvents. While the production cost of liposomal systems is higher than that of simple carbonate salts, the health-economic argument is compelling: by improving the bioavailability of the mineral and reducing the incidence of cardiovascular complications and gastrointestinal side effects (such as constipation and bloating), liposomal calcium offers a higher "value-per-mg" than traditional alternatives.[26] Despite the significant physiological advantages of liposomal calcium, large-scale manufacturing is frequently hampered by the inherent instability of calcium ions within phospholipid bilayers. High ionic strength can disrupt the electrostatic balance of the membrane, leading to vesicle rupture and premature cargo leakage. West Bengal Chemical Industries Ltd., Kolkata, India (WBCIL) has addressed these formulation challenges by implementing high-precision lipid chemistry and rigorous characterization protocols.[27] By utilising Phosphatidylcholine (PC)—a primary component of natural cellular membranes—WBCIL has developed a biocompatible bilayer that ensures structural integrity while achieving a high encapsulation efficiency of 88%. Furthermore, their formulation maintains a robust zeta potential of -30.67 mV.[27] This value indicates strong repulsive forces between the vesicles, effectively mitigating the common challenge of particle aggregation and ensuring long-term colloidal stability. To ensure regulatory compliance and shelf-life stability, the WBCIL formulation has been subjected to accelerated stability studies under ICH Q1A(R2) guidelines (40°C ± 2°C; 75% ± 5% RH).[27] These tests confirmed that the elemental calcium content remained stable at 31.2% w/w, with minimal leakage even under high-temperature stress. The structural robustness was further validated through Differential Scanning Calorimetry (DSC) and FTIR analysis, which demonstrated that the encapsulated calcium is thermally protected and chemically compatible with the lipid matrix. By optimizing the lipid-to-calcium

ratio and employing advanced characterization like Dynamic Light Scattering (DLS) to maintain a uniform particle size, WBCIL has successfully transitioned liposomal calcium from a laboratory concept to a stable, clinical-grade nutraceutical system.[27]

## 5. Conclusion

This review establishes that liposomal calcium nutraceutical systems offer a solution to the clinical challenges of traditional mineral supplementation. By leveraging advanced lipid chemistry, these systems effectively intervene in the bone-vascular axis, ensuring that calcium is sequestered within the skeletal hydroxyapatite lattice rather than depositing in arterial walls. The integration of fat-soluble vitamins (D3 and K2) within the liposomal bilayer is identified as a critical factor for maximising the carboxylation of regulatory proteins like MGP and Osteocalcin. While large-scale manufacturing faces challenges related to membrane stability and ionic interference, the study highlights that high-precision formulation techniques—such as those utilizing Phosphatidylcholine and specialised homogenization—can yield stable, clinical-grade products with high encapsulation efficiency and robust zeta potentials. The technical findings from the WBCIL study further support the commercial and clinical viability of these nanocarriers, demonstrating their ability to maintain elemental stability even under accelerated stress conditions. In conclusion, liposomal calcium systems represent a superior delivery platform that prioritizes long-term metabolic homeostasis, offering significant potential for the management of aging populations at risk for both osteoporosis and cardiovascular disease.

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