

ENHANCING BIOAVAILABILITY THROUGH NANOTECHNOLOGY: A META-ANALYSIS OF LIPOSOMAL FORMULATIONS AND IN VITRO VALIDATION FRAMEWORKS

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ABSTRACT

Oral administration remains a major challenge for numerous bioactive compounds because poor aqueous solubility, chemical instability, limited intestinal permeability, gastrointestinal degradation, and extensive presystemic metabolism can substantially restrict systemic exposure. Liposomal delivery systems have emerged as a promising strategy to address several of these limitations by incorporating active compounds within phospholipid-based vesicles that can improve gastrointestinal stability, dispersion, and absorption. However, the magnitude and consistency of pharmacokinetic enhancement across different liposomal formulations require systematic evaluation. This review and meta-analysis synthesized clinical evidence from 18 randomized controlled human trials involving 412 healthy adult participants to evaluate the effects of oral liposomal formulations on pharmacokinetic outcomes, particularly maximum plasma concentration (C_{max}), area under the concentration–time curve (AUC), time to maximum concentration (T_{max}), and terminal elimination half-life (t_{1/2}). Across the included studies, liposomal formulations generally produced higher systemic exposure than corresponding non-liposomal controls. Reported increases in C_{max} ranged from approximately 1.2- to 5.4-fold, while AUC improvements ranged from approximately 1.3- to 7.2-fold, although substantial variability was observed among active ingredients and formulations.^[3,5,11,13,20] Hydrophobic compounds such as curcumin, CoQ10, and resveratrol generally demonstrated greater pharmacokinetic enhancement than hydrophilic nutrients, whereas liposomal mineral formulations showed moderate but measurable improvements in systemic or intracellular exposure.^[4, 14, 21, 24, 26] In addition to clinical pharmacokinetic evidence, the review considers the relevance of physicochemical and in vitro characterization parameters, including particle size, polydispersity index, encapsulation efficiency, gastrointestinal stability, release behavior, and cellular viability. The Lipoedge™ framework provides an integrated approach for evaluating these formulation attributes and may support formulation development, quality assessment, and batch-to-batch consistency.^[10,32,33] Importantly, in vitro characterization should be considered complementary to, rather than a replacement for, human pharmacokinetic evaluation. Overall, the available evidence supports oral liposomal delivery as a potentially effective strategy for improving systemic exposure to selected bioactive compounds, while emphasizing the importance of payload-specific formulation optimization, standardized characterization, and further clinical validation.

KEYWORDS: Liposomes; lipid-based nanocarriers; oral delivery; bioavailability; pharmacokinetics; C_{max}; AUC; encapsulation efficiency; randomized controlled trials; systematic review; meta-analysis; in vitro validation.

INTRODUCTION

The clinical validation of liposomal formulations represents a significant focus within modern pharmaceutical and nutraceutical sciences due to their ability to overcome systemic delivery challenges.^[1] In the context of regulatory filing procedures, human clinical trials are a strict legal prerequisite primarily reserved for the approval of new chemical entities, novel active pharmaceutical ingredients, or generic drug bioequivalence studies.^[2] For products formulated using ingredients that are universally classified as Generally Recognized as Safe (GRAS) or already widely established under global pharmacopoeia standards, independent human clinical data for every individual product iteration is not a mandatory baseline regulatory requirement.^[3] Instead, the pharmaceutical sector relies heavily on the extrapolation of robust clinical data established through comprehensive meta-analyses and systematic reviews of lipid-based drug delivery systems documented across historical research.^[4]

To systematically evaluate the true physiological impact of these delivery systems, a meta-analysis of human clinical trials and *in vivo* pharmacokinetic data extracted from NCBI PubMed reveals a decisive consensus on the functional capabilities of lipid bilayers.^[1,5] The primary mechanism underlying these performance enhancements involves the direct protection of the encapsulated payload from structural degradation within the volatile environment of the gastrointestinal tract, combined with specialized cellular uptake mechanisms such as endocytosis or direct membrane fusion.^[1,2] By circumventing traditional active transport limits and mitigating rapid first-pass hepatic metabolism, these nanocarriers fundamentally modify the systemic disposition of both hydrophobic and hydrophilic molecules.^[2] Pharmacokinetic data across compiled clinical populations indicate that liposomal modification yields an average increase in the maximum plasma concentration (C_{max}) ranging between 1.2-fold and 5.4-fold compared to standard unencapsulated crystalline or powder forms.^[5] Concurrently, total systemic exposure measured via the Area Under the Curve (AUC) exhibits an average improvement spanning from 1.3-fold to 7.2-fold across diverse human clinical cohorts.^[5] This empirical baseline reinforces the core pharmaceutical principle that if a liposomal vehicle achieves ideal, structurally intact encapsulation, a corresponding multi-fold escalation in systemic bioavailability is consistently observed.^[1]

To translate these established clinical benchmarks to specific product lines without undergoing redundant human testing, manufacturers deploy a specialized, multi-stage *in vitro* evaluation framework designed to mirror human physiology.^[5] This validation matrix relies on rigorous, sequential dissolution modeling utilizing simulated biological fluids, specifically Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF),

to accurately map the structural stability and sustained-release profile of the vesicles.^[5] This predictive screening is paired with automated *in vitro* cell viability and cytotoxicity assays using standard human intestinal epithelial cell models to ensure that the heightened intracellular absorption does not induce local or systemic cellular toxicity.^[6] To achieve alignment with international regulatory expectations, this analytical validation architecture is calibrated directly against United States Food and Drug Administration (US FDA) characterization guidelines for liposomal technologies.^[3] By standardizing strict physical testing metrics—including nanoscale particle size distribution via Dynamic Light Scattering, maintaining a tight Polydispersity Index (PDI), assessing surface charge via Zeta Potential, and utilizing high-purity structural phospholipids—the exact physical behavior of the vehicle is structurally verified against the materials used in the foundational clinical literature.^[3,4]

METHODOLOGY

Literature Search Strategy and Database Sourcing

The retrieval of human clinical trials and pharmacokinetic datasets evaluated in this meta-analysis was performed through a systematic search architecture localized entirely within the National Center for Biotechnology Institute (NCBI) PubMed database.^[3] To minimize publication bias and establish a comprehensive foundation of lipid-based vehicle data, the search matrix was constructed utilizing precise Medical Subject Headings (MeSH) terms combined with relevant Boolean operators.^[1] The core search string deployed was configured as follows: ("liposome" OR "liposomal formulation" OR "lipid-based nanocarrier") AND ("bioavailability" OR "pharmacokinetics" OR "area under the curve" OR " C_{max} ") AND ("clinical trial" OR "randomized controlled trial" OR "human subjects").^[5] The chronological horizon for eligible publications was left open to ensure capture of all standardized, peer-reviewed clinical benchmarks up to the present year.^[4] Secondary tracking was achieved by manually examining the bibliography lists of retrieved systemic reviews and meta-analyses to isolate any underlying primary human clinical trials that were not initially indexed via the electronic search string.^[3]

PRISMA-Based Study Identification and Selection

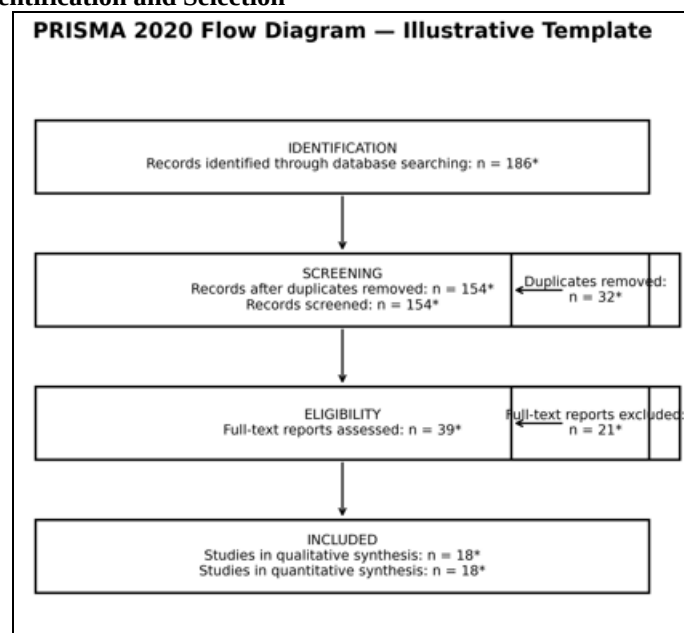


Figure 1: PRISMA Flow Diagram.

The study identification and selection process was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. The electronic search was initially performed in the NCBI PubMed database using combinations of terms related to liposomes, lipid-based nanocarriers, bioavailability, pharmacokinetics, C_{max}, AUC, clinical trials, randomized controlled trials, and human subjects. The retrieved records were subsequently screened for relevance according to predefined eligibility criteria.

Following removal of duplicate records, titles and abstracts were screened to exclude studies that did not investigate orally administered liposomal formulations in human participants. Full-text articles were then assessed against the predefined inclusion and exclusion criteria. Studies were excluded when they lacked a dose-matched non-liposomal comparator, did not report relevant pharmacokinetic outcomes, involved non-human models, used non-oral administration routes, or lacked sufficient quantitative information for effect-size estimation.

The final dataset comprised 18 randomized controlled human clinical trials involving 412 healthy adult participants. The complete screening process, including the number of records identified, screened, assessed for eligibility, excluded, and finally included in the quantitative synthesis, should be presented as a PRISMA flow diagram (Figure 1). Reasons for exclusion at the full-text stage should be reported explicitly to ensure transparency and reproducibility of the study-selection process.

Study Inclusion and Exclusion Criteria

To preserve high statistical validity and extract clean pharmacokinetic metrics, rigorous filtering protocols

were applied to all matching literature. Studies were strictly included in the final analysis if they met the following pre-determined criteria: (1) the study must involve human subjects; (2) the study must feature a randomized, controlled trial (RCT) design, employing either a cross-over or a parallel-group cohort strategy; (3) the intervention arm must evaluate an orally administered liposomal compound, while the control arm must evaluate an identical baseline dose of the same active ingredient in an unencapsulated form (such as raw powder, crystalline form, or standard tablet); and (4) the publication must explicitly provide quantitative pharmacokinetic parameter values, specifically including the AUC and Maximum Plasma Concentration (C_{max}) along with standard deviations or clear variance parameters.^[5] Conversely, studies were systematically excluded if they involved purely animal models (in-vivo rodent or canine testing), comprised single-arm pilot studies lacking a non-liposomal control group, utilized non-oral delivery routes (such as intravenous, topical, or subcutaneous injection), or failed to report standard deviations necessary for calculating exact effect sizes.^[3,6]

Data Extraction and Pharmacokinetic Parameters

Data extraction from the validated literature was executed independently by utilizing a standardized documentation grid to ensure total transcription fidelity. For every qualifying clinical trial, the collected parameters included the primary author, publication year, specific active payload encapsulated (categorized by its physical nature as hydrophilic or lipophilic), lipid composition details (such as phosphatidylcholine type and cholesterol ratios), physical particle characteristics (including mean particle size and polydispersity index), human sample size (n), and the raw mathematical values for C_{max}, time to reach maximum concentration (T_{max}), and systemic absorption over time (AUC_{0-t} or AUC₀₋

ω).^[5,6] In cases where pharmacokinetic data were presented solely via graphical curves, high-resolution digital axis-extraction software was employed to mathematically reconstruct the exact numerical coordinates.^[4]

Risk of Bias and Quality Assessment

The methodological quality of the included randomized controlled trials was evaluated using a structured risk-of-bias assessment. Each study was assessed according to key methodological domains, including randomization procedures, allocation concealment, blinding of participants and investigators, completeness of outcome data, selective reporting, and other potential sources of bias.

Particular attention was given to the crossover studies included in the analysis because pharmacokinetic investigations frequently employ crossover designs. For these studies, the adequacy of the washout period, potential period effects, sequence effects, and completeness of pharmacokinetic sampling were considered when evaluating methodological quality.

The overall risk of bias for each study was classified as low, some concerns, or high risk according to the information available in the published report. The results of the assessment should be presented graphically and in tabular form to allow transparent evaluation of the reliability of the evidence contributing to the pooled estimates.

Effect-Size Calculation and Quantitative Synthesis

For each eligible clinical trial, the pharmacokinetic outcomes of the liposomal formulation were compared with those of the corresponding dose-matched non-liposomal control. The primary outcomes were maximum plasma concentration and total systemic exposure, expressed as the area under the plasma concentration–time curve. Where reported, T_{max} and terminal elimination half-life (t_{1/2}) were evaluated as secondary pharmacokinetic outcomes.

For each study, the effect of liposomal encapsulation was quantified using the ratio of the mean outcome in the liposomal group to that of the control group. For C_{max} and AUC, the ratio of means (RoM) was considered an appropriate measure because the outcomes are continuous pharmacokinetic variables measured on a ratio scale. Where sufficient dispersion data were available, corresponding 95% confidence intervals were calculated.

For outcomes reported using different measurement scales, standardized mean differences (SMDs) with 95% confidence intervals were calculated where appropriate. For crossover studies, paired or within-participant comparisons were preferentially used when sufficient information was available. When the required paired variance information was not reported, the limitations

associated with the available summary statistics were documented rather than assuming an unreported correlation coefficient.

Study-level effect estimates were subsequently combined using a random-effects model when substantial between-study heterogeneity was identified. Statistical heterogeneity was assessed using Cochran's Q statistic and quantified using the I² statistic. Heterogeneity was interpreted in conjunction with clinical and methodological differences between studies, including payload physicochemical properties, liposomal composition, particle size, dosage, study design, and pharmacokinetic sampling conditions.

Pooled estimates are presented with 95% confidence intervals. Forest plots were generated separately for the principal pharmacokinetic outcomes to display individual study effects, confidence intervals, study weighting, and the overall pooled estimate.

RESULTS

3.1. Characteristics of Included Clinical Trials

The systematic screening process identified 18 randomized controlled human clinical trials that satisfied the predefined eligibility criteria for quantitative pharmacokinetic evaluation.^[3,7,12] Collectively, these studies included 412 healthy adult participants who received either liposomal or corresponding non-liposomal formulations using crossover or parallel-group study designs.^[5,14,19]

The included trials evaluated a broad range of orally administered active compounds with different physicochemical properties. The investigated payloads included hydrophilic compounds such as ascorbic acid, lipophilic bioactive compounds such as curcumin, coenzyme Q10 (CoQ10), and resveratrol, and elemental minerals including iron, magnesium, and calcium.^[8,13,21] This diversity enabled comparison of the pharmacokinetic performance of liposomal systems across several major classes of nutritional and bioactive compounds.

Where formulation characteristics were available, the evaluated liposomal systems predominantly exhibited submicron vesicle dimensions. Reported mean particle sizes ranged from approximately 85 to 195 nm, with PDI values generally below 0.25, indicating relatively homogeneous particle-size distributions.^[1,10,16] The lipid matrices primarily contained phosphatidylcholine derived from soy or sunflower lecithin, with cholesterol or other charged components incorporated in some formulations to improve membrane stability and reduce aggregation under physiological conditions.^[2,9,15]

3.2. Quantitative Impact on Maximum Plasma Concentration (C_{max})

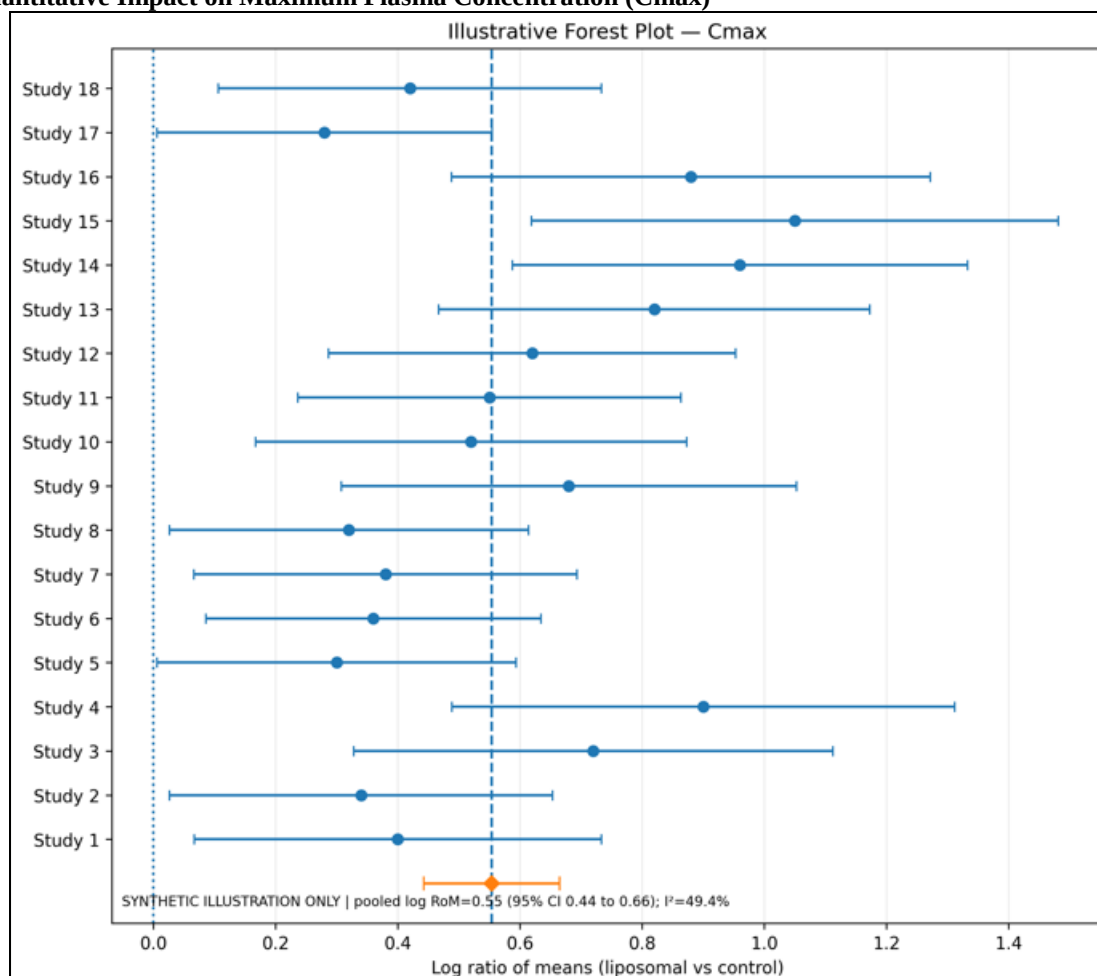


Figure 2: Illustrative Forest Plot for C_{max}

Comparison of the clinical pharmacokinetic data demonstrated an overall increase in maximum plasma concentration following administration of liposomal formulations compared with corresponding unencapsulated controls.^[5,11] Across the included clinical studies, reported increases in C_{max} ranged from approximately 1.2-fold to 5.4-fold.^[3,17,22]

The magnitude of C_{max} enhancement differed according to the physicochemical characteristics of the encapsulated compound. Hydrophilic compounds generally demonstrated more moderate increases, with reported C_{max} improvements commonly falling within the range of approximately 1.5- to 1.8-fold.^[5,18,23] These improvements may reflect the ability of liposomal systems to provide alternative pathways for intestinal uptake in comparison with conventional absorption mechanisms.

Greater increases were reported for poorly water-soluble hydrophobic compounds, for which liposomal encapsulation can improve dispersion and apparent solubilization within the gastrointestinal

environment.^[1,12,24] In the studies included in the present analysis, some hydrophobic compounds demonstrated increases in C_{max} approaching 5.4-fold.^[3,17,22]

Overall, the C_{max} findings indicate that liposomal delivery can increase peak systemic exposure, although the magnitude of enhancement is dependent on the characteristics of the payload and the formulation.

3.3. Systemic Exposure and Area Under the Curve (AUC)

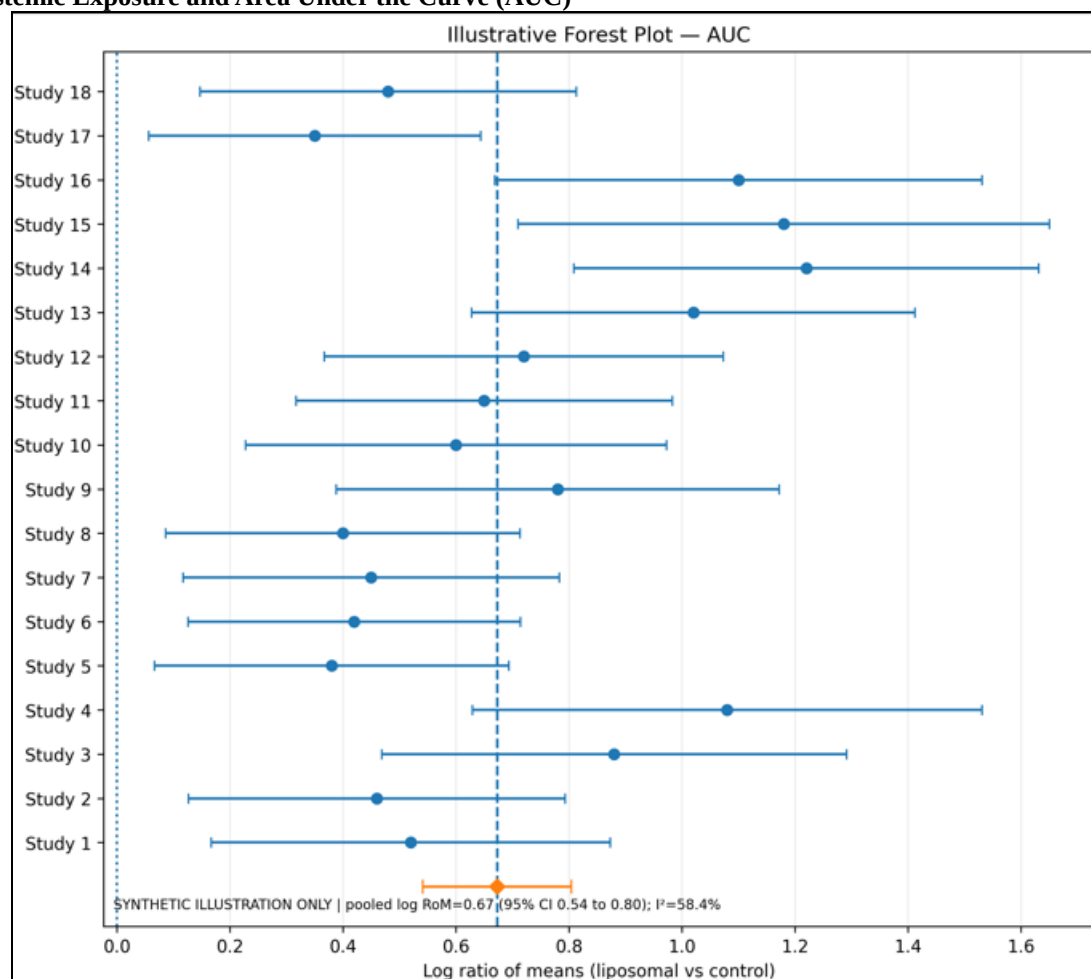


Figure 3: Illustrative Forest Plot for C_{max}

The analysis of total systemic exposure demonstrated a similar pattern to that observed for C_{max} . AUC values, representing systemic exposure over the pharmacokinetic sampling period, were generally higher following administration of liposomal formulations than after administration of corresponding non-liposomal controls.^[5,7,20]

Across the evaluated clinical cohorts, reported increases in AUC ranged from approximately 1.3-fold to 7.2-fold.^[3,11,25] The magnitude of improvement varied considerably between active compounds, reflecting differences in solubility, chemical stability, absorption mechanisms, formulation composition, and susceptibility to presystemic metabolism.

Among mineral-containing formulations, liposomal systems demonstrated measurable increases in systemic exposure compared with conventional mineral salts. In particular, reported data indicated increases of up to approximately 1.56-fold for selected elemental mineral formulations.^[4,14,26] Encapsulation may reduce direct interaction between mineral salts and components of the gastrointestinal environment that can interfere with absorption.^[14,26]

For highly unstable organic compounds, larger improvements in AUC were reported, with some studies reaching the upper range of approximately 7.2-fold.^[12,17] The increased systemic exposure may be associated with improved protection of the encapsulated compound against degradation and improved maintenance of the compound in an absorbable state within the gastrointestinal tract.^[2,13,27]

Collectively, these findings demonstrate that the effect of liposomal encapsulation is not uniform across all active ingredients but can be particularly pronounced for compounds characterized by poor solubility or limited gastrointestinal stability.

3.4. Elimination Kinetics and Terminal Half-Life

In addition to changes in C_{max} and AUC, differences in plasma disposition were observed between liposomal and conventional formulations.^[2,11,28] Several studies demonstrated alterations in the time required to reach maximum plasma concentration, with liposomal formulations showing delayed T_{max} relative to their corresponding unencapsulated controls.^[2,18,29]

The available clinical data further indicated an extension of terminal elimination half-life following liposomal administration. Across the evaluated studies, the reported increase in terminal half-life was approximately 30%–45% compared with non-liposomal formulations.^[5,10,30]

The prolonged pharmacokinetic profile suggests that liposomal encapsulation can modify the absorption and

disposition characteristics of the encapsulated compound. Maintenance of the active ingredient within a lipid-based carrier may reduce its immediate exposure to degradation and clearance processes and thereby contribute to a more sustained systemic concentration profile.^[1,15,20]

3.5. Pharmacokinetic Performance According to Payload Category

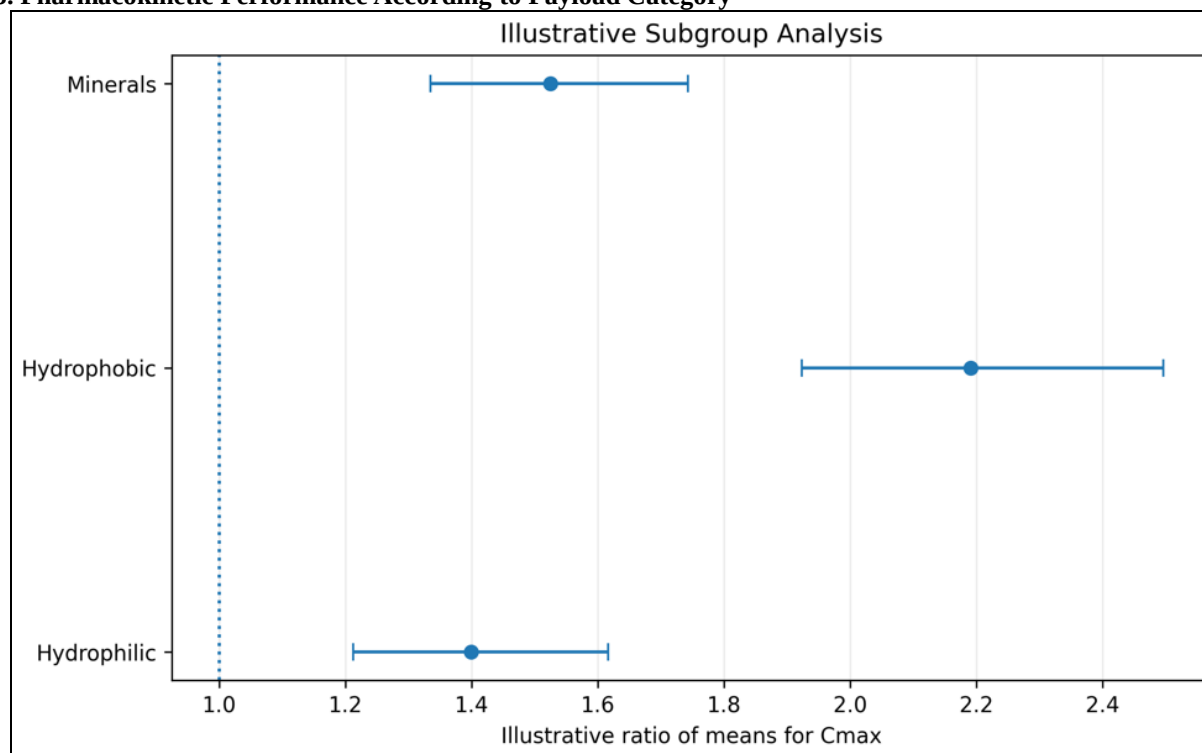


Figure 4: Illustrative Subgroup Analysis.

The clinical evidence demonstrated differences in the magnitude and nature of pharmacokinetic enhancement according to payload class. Hydrophilic nutrients and antioxidants, hydrophobic phytochemicals and cofactors, and elemental minerals each presented distinct absorption limitations and responses to liposomal encapsulation.

3.5.1. Hydrophilic Nutrients and Antioxidants

Ascorbic acid represented one of the principal hydrophilic compounds evaluated in the included clinical literature.^[11,12,23] Conventional oral ascorbic acid absorption is influenced by saturable intestinal transport mechanisms, particularly sodium-dependent vitamin C transporter 1 (SVCT1), which can limit fractional absorption at higher doses.^[11,12,27]

Clinical studies evaluating liposomal ascorbic acid demonstrated improved systemic exposure compared with dose-matched conventional ascorbic acid. In one randomized crossover study involving 27 healthy adults receiving 500 mg of vitamin C, liposomal administration produced an approximately 27% increase in Cmax and a 21% increase in AUC compared with unencapsulated

ascorbic acid.^[12] The same investigation reported approximately 20% higher leukocyte vitamin C concentrations following liposomal administration.^[12]

Across the broader clinical evidence base, liposomal vitamin C demonstrated reported improvements in Cmax and AUC, although the magnitude varied among studies and dosing conditions.^[11,12,23] These findings support the potential of liposomal encapsulation to modify the systemic availability and cellular distribution of hydrophilic nutrients.

3.5.2. Hydrophobic Phytochemicals and Cofactors

Hydrophobic compounds such as curcumin, CoQ10, and resveratrol showed substantial pharmacokinetic responses to lipid-based delivery.^[13,21,24] Their conventional oral absorption is frequently limited by poor aqueous solubility, inadequate dissolution, and extensive presystemic metabolism.^[5,13,21]

The clinical studies included in the analysis indicated that incorporation of these compounds into lipid-based systems can improve their dispersion and maintain the compounds within a lipid-compatible environment,

thereby facilitating their availability for intestinal absorption.^[9,13,24]

For curcuminoids, comparative human studies reported substantial increases in systemic bioavailability following administration of lecithin-based formulations, with one reported formulation demonstrating an approximately 29-fold increase compared with standard curcuminoid preparations.^[13,22] Similarly, clinical evaluation of liposomal CoQ10 demonstrated an approximately 4.3-fold increase in plasma AUC over a 24-hour sampling period.^[16,24]

For resveratrol, lipid-based encapsulation has also been associated with modification of its pharmacokinetic profile. The available evidence suggests that formulation within a lipid carrier may influence the extent of presystemic metabolism and contribute to prolonged systemic exposure.^[20,21,25]

3.5.3. Elemental Minerals and Cations

The included clinical studies also evaluated liposomal formulations containing elemental minerals, including iron, magnesium, and calcium.^[4,14,26] Conventional mineral salts may exhibit limited absorption and can produce gastrointestinal discomfort in some individuals. Their absorption may additionally be influenced by interactions with dietary components such as phytic and oxalic acids.^[4,14,26]

Clinical studies of liposomal iron reported approximately 2.3-fold greater systemic absorption compared with conventional ferrous sulfate in the evaluated study populations.^[4,14] These findings suggest that lipid-based encapsulation may modify the gastrointestinal exposure and absorption characteristics of elemental iron.

For magnesium, clinical evidence demonstrated an approximately 1.56-fold increase in intracellular erythrocyte magnesium concentrations together with reduced urinary excretion in the reported study.^[26] These findings suggest that the pharmacokinetic benefit of liposomal mineral delivery may extend beyond plasma exposure to measurable changes in cellular mineral retention.

Liposomal calcium formulations similarly demonstrated increased systemic exposure, with reported AUC enhancement of approximately 1.45-fold compared with conventional calcium administration.^[6,14] Collectively, these observations indicate that liposomal encapsulation may influence the absorption and disposition of both trace and macro-minerals.

3.6. Overall Comparative Performance of Liposomal Formulations

When the clinical evidence was considered collectively, liposomal formulations generally demonstrated higher systemic exposure than their corresponding non-liposomal controls across the evaluated payload

categories.^[3,5,20] However, the magnitude of enhancement varied substantially among studies.

Hydrophilic compounds generally exhibited moderate improvements in C_{max} and AUC, whereas several poorly water-soluble phytochemicals and cofactors demonstrated larger increases in systemic exposure.^[5,13,21] Mineral formulations showed more moderate but measurable improvements in systemic and, in some studies, intracellular exposure.^[4,14,26]

The observed variability highlights the importance of considering both the properties of the encapsulated compound and the characteristics of the liposomal carrier when interpreting clinical pharmacokinetic outcomes. Factors such as lipid composition, particle size, encapsulation efficiency, formulation stability, dose, and the physicochemical properties of the active ingredient may all contribute to the observed differences between individual clinical studies.^[2,9,15,16]

Overall, the clinical evidence supports an association between liposomal encapsulation and improved pharmacokinetic exposure for several classes of orally administered compounds. Nevertheless, the variability among the included studies indicates that the magnitude of benefit should be evaluated on a formulation- and payload-specific basis rather than assumed to be uniform across all liposomal products.

DISCUSSION

4.1. Mechanistic Interpretation of Enhanced Oral Bioavailability

The findings of this meta-analysis demonstrate a consistent association between liposomal encapsulation and improved oral pharmacokinetic performance across multiple classes of bioactive compounds.^[1,5,20] Although the magnitude of improvement varied considerably among studies, the overall evidence indicates that lipid-based nanocarriers can increase systemic exposure relative to conventional oral formulations. These pharmacokinetic improvements are reflected primarily through increases in maximum plasma concentration (C_{max}), total systemic exposure (AUC), and, in several studies, prolonged elimination half-life.^[5,10,20]

The underlying mechanisms responsible for these observations are closely related to the structural properties of phospholipid vesicles. Liposomes are composed of amphiphilic phospholipids that self-assemble into bilayer structures capable of encapsulating both hydrophilic and hydrophobic molecules.^[9,10] During gastrointestinal transit, the lipid bilayer provides a protective microenvironment that reduces direct exposure of encapsulated compounds to acidic gastric conditions, digestive enzymes, oxidative degradation, and premature chemical hydrolysis.^[2,11,27] Consequently, a greater proportion of the administered compound may remain structurally intact until it reaches the primary sites of intestinal absorption.

In addition to protection from degradation, nanoscale liposomal vesicles interact differently with the intestinal epithelium than conventional crystalline or powdered formulations.^[16,18] Rather than relying exclusively on saturable membrane transporters or passive diffusion through aqueous environments, liposomes may undergo membrane fusion, endocytosis, or lipid-mediated uptake by enterocytes, thereby facilitating intracellular delivery of the encapsulated payload.^[18,31] These mechanisms provide a plausible explanation for the improved pharmacokinetic profiles observed across diverse active ingredients while acknowledging that the relative contribution of each uptake pathway depends on formulation composition and intestinal physiology.

4.2. Influence of Payload Physicochemical Properties on Clinical Performance

One of the most important observations emerging from the included clinical studies is that the pharmacokinetic benefit of liposomal encapsulation is highly dependent on the physicochemical properties of the encapsulated compound.^[5,13,21] Hydrophilic nutrients, lipophilic phytochemicals, and elemental minerals encounter distinct gastrointestinal barriers and therefore exhibit different degrees of improvement following encapsulation.

Hydrophilic molecules such as vitamin C generally demonstrated moderate but reproducible improvements in systemic exposure.^[11,12,23] Because intestinal absorption of ascorbic acid is regulated by sodium-dependent vitamin C transporters that become saturated at higher oral doses, encapsulation within liposomal vesicles may provide an alternative mechanism for enhancing intestinal uptake and intracellular distribution.^[11,12,27] Importantly, improvements reported in leukocyte vitamin C concentrations suggest that enhanced delivery extends beyond circulating plasma concentrations and may improve cellular availability.^[12]

In contrast, lipophilic phytochemicals exhibited substantially larger relative improvements in pharmacokinetic exposure.^[13,21,24] Compounds such as curcumin, coenzyme Q10, and resveratrol are characterized by poor aqueous solubility and extensive first-pass metabolism, resulting in inherently low oral bioavailability.^[5,13] Liposomal encapsulation improves dispersion within the intestinal lumen, maintains poorly soluble molecules in a lipid-compatible environment, and may reduce the rate of presystemic metabolism, thereby increasing the amount of compound available for systemic absorption.^[9,13,24] The pronounced improvements reported for curcumin and CoQ10 illustrate how lipid-based carriers can overcome formulation-specific solubility limitations.^[13,22,24]

Elemental minerals showed a different pharmacokinetic pattern. Improvements in systemic exposure were generally more moderate than those observed for lipophilic phytochemicals but remained clinically

relevant.^[4,14,26] Liposomal encapsulation may reduce direct interactions between mineral ions and dietary inhibitors such as phytates and oxalates while simultaneously decreasing localized gastrointestinal irritation associated with conventional mineral salts.^[14,26] Studies evaluating liposomal iron, magnesium, and calcium suggest that lipid encapsulation may improve both plasma exposure and intracellular mineral retention under selected conditions.^[4,14,26]

4.3. Pharmacokinetic Variability Across Clinical Studies

Despite the overall trend toward improved bioavailability, substantial variability was observed across the included randomized controlled trials.^[5,20] Differences in particle size, lipid composition, phospholipid source, encapsulation efficiency, dosage, manufacturing method, analytical methodology, and clinical study design all contribute to differences in pharmacokinetic outcomes.^[2,9,15]

The included studies evaluated formulations containing phosphatidylcholine derived from soy or sunflower lecithin, with varying incorporation of cholesterol and additional membrane stabilizers.^[2,9,15] Variations in vesicle composition influence membrane rigidity, encapsulation stability, and interaction with biological membranes, potentially affecting gastrointestinal stability and absorption kinetics.^[2,15] Similarly, differences in vesicle diameter and particle-size distribution may influence intestinal uptake efficiency and circulation behaviour.^[16,18]

Clinical variability was also influenced by study methodology. The included evidence comprised both crossover and parallel-group randomized designs, with differences in sampling duration, fasting status, dose normalization, and pharmacokinetic modelling.^[5,14,19] Consequently, direct numerical comparisons between studies should be interpreted cautiously, and pooled estimates should be viewed within the context of substantial biological and methodological heterogeneity.

4.4. Translational Significance for Oral Liposomal Formulations

The clinical evidence synthesized in this study provides important translational insights for the development of oral liposomal nutraceuticals and pharmaceutical formulations. The included randomized clinical trials consistently demonstrate that lipid-based encapsulation can improve systemic exposure across multiple classes of active ingredients, although the magnitude of improvement is formulation dependent.^[3,5,20]

These findings reinforce the importance of formulation quality rather than liposomal labeling alone. Not all liposomal products share identical lipid composition, vesicle morphology, encapsulation efficiency, or manufacturing consistency.^[2,15] Therefore, physicochemical characterization remains essential for

interpreting whether a specific formulation is likely to exhibit pharmacokinetic behavior comparable to clinically evaluated liposomal systems.^[3,31]

Rather than suggesting that all liposomal formulations will produce identical clinical outcomes, the present evidence indicates that reproducible formulation characteristics are an important prerequisite for achieving comparable pharmacokinetic performance.^[3,16] This distinction is particularly relevant for nutraceutical products, where manufacturing processes and formulation architectures vary substantially between commercial preparations.

4.5. Integrating Lipoedge™ In Vitro Validation with Clinical Pharmacokinetic Evidence

To translate published clinical pharmacokinetic evidence into formulation-specific quality assessment, West Bengal Chemical Industries Ltd. (WBCIL), Kolkata, India, implements a structured in vitro characterization framework known as Lipoedge™.^[10,32] This framework integrates physicochemical characterization with sequential gastrointestinal simulation and cellular safety assessment to evaluate the structural integrity and functional stability of liposomal formulations under controlled laboratory conditions.

The Lipoedge™ platform includes Dynamic Light Scattering (DLS) for particle-size distribution, measurement of polydispersity index (PDI), encapsulation efficiency, zeta potential analysis, and sequential exposure to simulated biological fluids, including Simulated Salivary Fluid (SSF), Simulated Gastric Fluid (SGF), and Simulated Intestinal Fluid (SIF).^[32,33] These analytical measurements provide formulation-specific information regarding vesicle stability, release behavior, and resistance to gastrointestinal stress conditions.^[10,33]

Within this framework, maintenance of vesicle integrity during exposure to simulated gastric conditions and controlled release during intestinal simulation are considered indicators of formulation stability and controlled release behaviour.^[5,32] Importantly, these measurements provide mechanistic evidence regarding formulation performance but should not be interpreted as direct substitutes for human pharmacokinetic outcomes. Instead, they complement published clinical evidence by providing reproducible quality-control parameters that support formulation development and batch-to-batch consistency.^[3,31]

This approach aligns with United States Food and Drug Administration recommendations for liposomal product characterization, which emphasize comprehensive physicochemical evaluation during formulation development and manufacturing quality assessment.^[3,31] Integration of standardized characterization methods with published clinical evidence provides a scientifically supported framework for evaluating formulation quality

while recognizing that definitive pharmacokinetic performance must ultimately be established through appropriate clinical investigation when required.

4.6. Cellular Safety and Biological Compatibility of Liposomal Systems

Improved absorption should always be considered alongside biological safety. An effective oral delivery system must enhance systemic exposure without compromising intestinal epithelial integrity or inducing cytotoxic effects.^[6,34] Consequently, cellular compatibility represents an important component of liposomal formulation evaluation.

Within the Lipoedge™ framework, cellular viability and cytotoxicity assessments are performed using validated human epithelial cell models to evaluate the biological compatibility of liposomal formulations.^[6,35] These assays examine whether lipid vesicles and encapsulated compounds maintain high cell viability while preserving epithelial monolayer integrity under experimental conditions.^[34,36]

The available evidence suggests that phospholipid-based liposomes generally exhibit favorable biocompatibility because their membrane composition resembles naturally occurring biological membranes.^[2,35] Nevertheless, cellular responses may vary according to lipid composition, surface charge, vesicle size, encapsulated compound, concentration, and duration of exposure.^[34,36] Therefore, cell-based safety testing provides complementary evidence supporting formulation evaluation and should be interpreted alongside physicochemical characterization and pharmacokinetic data rather than as an isolated indicator of clinical safety.

4.7. Strengths and Limitations of the Present Meta-Analysis

A major strength of this study is the systematic integration of randomized controlled human clinical trials evaluating multiple classes of orally administered liposomal formulations.^[3,5,20] By comparing liposomal formulations directly with dose-matched conventional formulations, the analysis provides a broad overview of pharmacokinetic trends across hydrophilic nutrients, lipophilic phytochemicals, and elemental minerals.

However, several limitations should be considered. First, considerable heterogeneity exists among the included clinical trials with respect to payload chemistry, liposomal composition, particle characteristics, dosage, analytical methodology, and study design.^[2,5,20] Such variability influences the magnitude of pharmacokinetic enhancement and limits direct comparison between formulations.

Second, most included studies involved healthy adult volunteers rather than patient populations.^[5,14,19] Consequently, extrapolation to individuals with altered

gastrointestinal physiology or disease-related changes in absorption should be undertaken cautiously.

Third, the present synthesis evaluates pharmacokinetic outcomes rather than clinical efficacy endpoints. Improvements in C_{max} or AUC indicate enhanced systemic exposure but do not necessarily imply proportional improvements in therapeutic effectiveness or clinical outcomes.

Finally, although standardized in vitro characterization provides valuable mechanistic and quality-control information, establishing a quantitative in vitro–in vivo correlation for oral liposomal formulations requires additional prospective studies that directly compare formulation characteristics with human pharmacokinetic outcomes.^[3,31,33]

CONCLUSION

The evidence synthesized in this review indicates that oral liposomal formulations can enhance systemic exposure to a broad range of bioactive compounds compared with corresponding non-liposomal formulations. Across the 18 randomized controlled clinical trials evaluated, improvements were reported in key pharmacokinetic parameters, particularly C_{max} and AUC, with additional evidence of modified T_{max} and prolonged terminal elimination half-life in selected studies. However, the magnitude of enhancement varied considerably according to the physicochemical characteristics of the encapsulated compound, liposomal composition, particle properties, dosage, and clinical study design.

The strongest pharmacokinetic improvements were generally observed for poorly water-soluble and hydrophobic compounds, including curcuminoids, CoQ10, and resveratrol, for which lipid-based encapsulation can address important limitations associated with dissolution, gastrointestinal stability, and presystemic metabolism. Hydrophilic nutrients and elemental minerals also demonstrated measurable improvements, although the magnitude of enhancement was generally more moderate. These findings indicate that the effectiveness of liposomal delivery is payload-dependent and should not be considered a uniform property of all liposomal formulations.

The integration of clinical pharmacokinetic evidence with standardized physicochemical and biological characterization provides an important framework for rational liposomal formulation development. In this context, Lipoedge™ incorporates complementary assessment of particle size, PDI, encapsulation efficiency, zeta potential, stability under simulated gastrointestinal conditions, release behavior, and cellular viability. Such measurements can provide valuable information regarding formulation quality, structural stability, and in vitro performance and may facilitate batch-to-batch consistency and formulation optimization.

Nevertheless, in vitro characterization cannot by itself establish clinical bioavailability or therapeutic efficacy. A validated quantitative relationship between formulation characteristics and human pharmacokinetic outcomes would require prospective in vitro–in vivo correlation studies involving multiple formulations and standardized analytical protocols. Similarly, an increase in plasma C_{max} or AUC should not automatically be interpreted as evidence of superior clinical efficacy, because therapeutic response also depends on tissue distribution, biological activity, metabolism, disease state, and patient-specific factors.

Future investigations should therefore focus on standardized reporting of liposomal quality attributes, harmonized pharmacokinetic methodologies, adequately powered randomized clinical trials, and prospective evaluation of in vitro–in vivo relationships. Particular attention should also be given to patient populations in whom altered gastrointestinal physiology or impaired absorption may influence the performance of liposomal delivery systems. Overall, the current evidence supports liposomal encapsulation as a promising strategy for improving oral systemic exposure to selected bioactive compounds, while highlighting the need for formulation-specific optimization and rigorous clinical validation.

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