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Comparative pharmacokinetics of different coenzyme Q_{10} formulations in Wistar rats: Superior bioavailability of phospholipid complex and lipid-encapsulated delivery systems

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Abstract

Background: Coenzyme Q_{10} (CoQ_{10}) is a vital cofactor in the mitochondrial electron transport chain, mediating electron transfer between complexes I/II and III, and is essential for ATP synthesis. Besides its bioenergetic role, CoQ_{10} acts as a potent lipophilic antioxidant, safeguarding cellular membranes and lipoproteins against oxidative damage. However, its clinical use is limited by poor oral bioavailability, caused by its crystalline structure, high molecular weight, and extremely low aqueous solubility (<0.1 µg/mL). Various formulation strategies, including nanoemulsions, cyclodextrin complexes, liposomes, and phospholipid conjugates, have been investigated to improve absorption, but direct comparative pharmacokinetic studies are still scarce.

Objective: To evaluate and compare the pharmacokinetic profiles and relative bioavailability of five different CoQ_{10} formulations: standard CoQ_{10}, lipid-encapsulated CoQ_{10}, water-dispersible CoQ_{10}, phospholipid-complexed CoQ_{10} in oil, and a marketed ubiquinone softgel following single-dose oral administration in Wistar rats.

Methods: Fifty healthy adult Wistar rats (200–250 g) were randomly assigned to five groups (n = 10 each). Group 1 received standard CoQ_{10}; Group 2, lipid-encapsulated CoQ_{10}; Group 3, water-dispersible CoQ_{10}; Group 4, phospholipid-complexed CoQ_{10} in oil; and Group 5, a marketed ubiquinone softgel. Blood samples were collected at 0, 0.5, 1, 2, 4, 8, 12, and 24 hours via retro-orbital plexus. Plasma CoQ_{10} levels were quantified using a validated LC–MS/MS method (lower limit of quantification: 5 ng/mL). Non-compartmental pharmacokinetic analysis was performed using Phoenix WinNonlin to determine Cmax, Tmax, AUC0-t, and relative bioavailability (F_rel).

Results: Pronounced formulation-dependent differences were observed. The phospholipid-complexed formulation (G4) achieved the highest systemic exposure (AUC0-t: 2007.72 ± 109.03 ng·h/mL) and peak concentration (Cmax: 642.16 ± 24.51 ng/mL), with sustained plasma levels beyond 12 h. Lipid-encapsulated CoQ_{10} (G2) produced comparable systemic exposure (1990.98 ± 45.39 ng·h/mL) with rapid absorption (Tmax ~0.5 h). Both G4 and G2 demonstrated significantly greater exposure compared with standard CoQ_{10} (G1; $p < 0.05$). Water-dispersible CoQ_{10} (G3; AUC0-t: 1567.91 ± 30.49 ng·h/mL) showed faster absorption than G1 but lower overall exposure, while the marketed soft gel (G5; AUC0-t: 475.77 ± 4.01 ng·h/mL) showed the poorest systemic availability. The overall rank order of systemic exposure was: G4 > G2 > G1 > G3 > G5.

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Conclusion: Formulation technology is a crucial factor influencing the pharmacokinetics of CoQ_{10}. Phospholipid complexation provided the most significant enhancement in systemic exposure, supporting its use in conditions that require stable, sustained plasma levels. Lipid-encapsulated CoQ_{10} enabled rapid absorption and high systemic availability, indicating potential clinical benefits where a quick onset is beneficial. These findings lay a strong preclinical groundwork for advancing CoQ_{10} delivery systems to improve therapeutic outcomes and patient adherence.

Keywords: Coenzyme Q_{10}; Pharmacokinetics; Relative Bioavailability; Phospholipid Complex; Lipid Formulation; LC–MS/MS; Wistar Rat Model

1. Introduction

Coenzyme Q_{10} (CoQ_{10}), or ubiquinone, is a fat-soluble quinone vital to mitochondrial energy metabolism. It functions as a mobile electron carrier in the respiratory chain, connecting complexes I/II with complex III to facilitate oxidative phosphorylation and ATP production. Beyond this bioenergetic role, CoQ_{10} also acts as a potent lipophilic antioxidant [1-3], stabilising cell membranes, neutralising reactive oxygen species, and regenerating other antioxidants, such as vitamin E. These dual roles in energy production and redox regulation make CoQ_{10} essential for maintaining cellular homeostasis.

Physiological levels of CoQ_{10} decline with age and in various pathological conditions, including chronic heart failure, metabolic syndrome, diabetes, and neurodegenerative disorders. Statin therapy further decreases CoQ_{10} levels by inhibiting the mevalonate pathway, which is also involved in cholesterol biosynthesis. These reductions are associated with impaired mitochondrial function, increased oxidative stress, and worse clinical outcomes [4]. These findings have increased interest in CoQ_{10} supplementation to restore energy balance, improve cardiac function, enhance exercise tolerance, and reduce oxidative damage.

Despite this strong rationale, the clinical use of CoQ_{10} has been limited by its poor oral bioavailability [5-9]. CoQ_{10} is highly lipophilic and crystalline, with limited solubility in gastrointestinal fluids and a heavy reliance on dietary fat and bile salt emulsification for absorption. Conventional crystalline or oil-based ubiquinone formulations therefore achieve only modest systemic levels, often requiring high daily doses that reduce compliance.

To overcome these limitations, various advanced delivery systems have been developed. Lipid encapsulation enhances solubility and membrane permeability by embedding CoQ_{10} within phospholipid bilayers. Phospholipid complexation (phytosome technology) creates an amphiphilic conjugate that improves dispersion and promotes lymphatic uptake. Water-dispersible systems, including nanoemulsions, micelles, and cyclodextrin complexes, yield crystal-free CoQ_{10} with rapid, more consistent absorption, even under low-fat conditions [17]. Collectively, these technologies aim to increase peak plasma concentration (Cmax), extend systemic exposure (AUC), and optimise tissue delivery.

Preclinical studies have offered valuable insights into the performance of these formulations. In rats, solubilised or emulsified CoQ_{10} generally achieves two- to threefold higher exposure than crystalline CoQ_{10}, with some nano-formulations yielding even greater improvements. Secondary plasma peaks observed in these studies suggest that enterohepatic recirculation influences CoQ_{10} disposition. Similar results in beagle dogs support the superiority of solubilised formulations over traditional oil-based preparations. However, most prior investigations have examined individual delivery systems separately, limiting direct comparisons among formulations. Therefore, standardised pharmacokinetic studies are necessary to identify which delivery strategies provide the best balance of absorption, systemic exposure, and dose efficiency. This study aimed to bridge this gap by systematically comparing five CoQ_{10} formulations in Wistar rats: standard CoQ_{10}, lipid-encapsulated CoQ_{10}, water-dispersible CoQ_{10}, phospholipid-complex CoQ_{10} in oil, and a marketed ubiquinone softgel. Pharmacokinetic parameters, including Cmax, Tmax, and AUC0-t, were measured to assess relative bioavailability and formulation-dependent differences. By providing direct preclinical comparisons, this work seeks to guide the rational selection of CoQ_{10} delivery systems, inform clinical dosing strategies, and support the translation of advanced formulations into therapeutic use.

Table 1 Pharmacokinetic profiles and bioavailability of various CoQ_{10} formulations across animal models.

Species / model	Formulation and dose	Design	Main PK finding
Rat	Solubilized CoQ_{10} vs powder (10 mg/kg, oral)	Single-dose PK (HPLC-ECD)	Solubilized form ↑ bioavailability to ~264% of powder[1].
Rat	Olive-oil solution, sub-nano particles, TPGS emulsion (oral)	Single-dose PK; 3-way comparison	All absorbed; TPGS emulsion showed the most enhanced absorption and delayed plasma rise (10–24 h)[2].
Rat	Lipid-free nano-CoQ_{10} (various surfactants)	Single-dose PK	Nano-formulations significantly ↑ AUC/Cmax vs suspension; surfactant choice mattered)[4].
Rat	TPGS-based nanoemulsion	PK + tissue distribution	Higher heart targeting and exposure than control formulations[5].
Rat (IV)	Ubiquinone (solubilized; 10 mg/kg IV)	Plasma redox PK to 48 h	Rapid reduction to ubiquinol; ubiquinol becomes predominant within hours[6].
Rat (chronic)	Oral/IP CoQ_{10} (2–10 weeks)	Tissue levels	Accumulates mainly in liver; limited early heart/kidney uptake reported[7].
Beagle dog	Water-soluble CoQ_{10} vs oil-based (crossover)	Single-dose bioavailability	Water-soluble form showed ~3× AUC and ~2× Cmax, with shorter Tmax[8,9,10].
Dog (MMVD)	Water-soluble ubiquinone (100 mg/day)	Randomized, double-blinded clinical model	Demonstrated measurable PK (HPLC-MS/ECD) and feasibility in diseased canines[11].

The table describes the focus on different CoQ_{10}[12] formulations based on the previous literature on dosing, study designs, species studied, and the main pharmacokinetic findings related to absorption and tissue distribution.

2. Materials and Methods

2.1. Ethical Approval

All experimental procedures adhered to the guidelines of the Committee for the Control and Supervision of Experiments on Animals (CCSEA; Registration Number 1803/PO/RcBi/S/2015/CCSEA) and received approval from the Institutional Animal Ethics Committee of Radiant Research Services Private Limited (IAEC Approval No. RR/IAEC/130-2024). Animal handling and study procedures were carried out by trained personnel under continuous supervision to ensure compliance with welfare standards.

2.2. Animals and Husbandry

Healthy young adult male Wistar rats were used in the study. Animals were acclimatised for 7 days under standard laboratory conditions with controlled temperature (22 ± 3 °C), relative humidity (30–70%), and a 12-hour light/dark cycle [13]. Rats were housed five per autoclaved polypropylene cage with corn-cob bedding and provided with a standard 18% protein rodent chow diet and UV-treated, reverse-osmosis water *ad libitum*. Feed and water were routinely screened for microbial contamination to ensure their suitability.

2.3. Randomisation and Grouping

Animals were uniquely marked, weighed, and randomised using Microsoft Excel based on body weight, ensuring inter-group variation of ≤ ±20% and within selected cohorts of ≤ ±5%.

2.4. Treatment Groups

Following an overnight fast, animals (n = 10 per group) received a single oral gavage dose equivalent to 100 mg/kg of CoQ_{10} of one of the following formulations:

- Group 1: Standard CoQ_{10} (99%), 102.5 mg/kg
- Group 2: Lipid-encapsulated CoQ_{10} (85%), 117.65 mg/kg
- Group 3: Water-dispersible CoQ_{10} (40%), 250 mg/kg
- Group 4: Phospholipid-complex CoQ_{10} (35%) in oil, 285.71 mg/kg
- Group 5: Ubiquinone softgel (300mg), 333.33 mg/kg

2.5. Blood Sampling and Plasma Preparation

Blood samples (500–600 µL) were taken from each rat at 0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after dosing. Samples were centrifuged at 6000 rpm for 20 minutes, and plasma was separated and stored at −20 °C until analysis. Values up to 48 h were recorded, but the analysis was truncated to 24 h for AUC_0-t comparability.

2.6. Bioanalytical Method

Plasma CoQ_{10} concentrations were determined using a validated LC–MS/MS [5] method. Plasma proteins were precipitated by adding 750 µL of 0.2% formic acid in acetonitrile to 250 µL of plasma, vortexed for 5 minutes, and centrifuged at 14,000 rpm for 5 minutes. The clear supernatant was then injected into the LC–MS/MS system.

LC–MS/MS conditions: Shimadzu LC-20AD with isocratic elution (acetonitrile:2-propanol: formic acid, 90:10:0.1%) at 0.6 mL/min on a Kinetex Biphenyl column (100 × 4.6 mm, 3 µm, 40 °C). Injection volume was 20 µL, with a total run time of 6 min. Detection was performed on a Shimadzu triple quadrupole mass spectrometer in ESI-positive mode using the MRM transition 863.7 → 197.0. Calibration curves (1–1000 ng/mL) were linear (r = 0.9962).

2.7. Pharmacokinetic Analysis

Pharmacokinetic parameters, including Cmax, Tmax, AUC0-t, and elimination half-life (t½), were calculated by non-compartmental analysis using Phoenix WinNonlin® (Certara, Princeton, NJ, USA) with linear-up/log-down trapezoidal integration.

2.8. Study Hypothesis

It was hypothesised that advanced CoQ_{10} delivery systems, specifically phospholipid-complex and lipid-encapsulated formulations, would show significantly higher systemic bioavailability, as indicated by greater Cmax and AUC0-t, compared with standard CoQ_{10} and water-dispersible preparations.

2.9. Statistical Analysis

All data are presented as mean ± standard deviation (SD) to illustrate the central tendency and variability of pharmacokinetic parameters across treatments. Before conducting parametric comparisons, Bartlett's test was used to assess homogeneity of variances across groups, a crucial step in validating ANOVA assumptions.

Upon confirming variance equality, a one-way analysis of variance (ANOVA) was performed to assess overall differences among the CoQ_{10} formulation groups. Significant ANOVA results prompted detailed post-hoc analyses using Dunnett's t-test to compare each new formulation directly against standard CoQ_{10}, identifying those with statistically meaningful deviations. Additionally, Tukey's multiple-comparison test was applied for comprehensive pairwise comparisons, ensuring robust detection of all significant differences within the dataset. These statistical approaches collectively offered a thorough framework for interpreting variations in pharmacokinetic behaviour, including absorption and bioavailability. To enhance interpretability, forest plots were created to visually depict effect sizes and confidence intervals for each group comparison, providing an intuitive, immediate understanding of the magnitude and precision of the observed differences. This graphical representation complemented the numerical results from statistical tests and helped evaluate formulation efficacy.

All statistical analyses were performed using GraphPad Prism® software, with a p-value threshold of 0.05 for significance. This careful analytical approach ensured both statistical accuracy and clarity in evaluating the effects of different CoQ_{10} formulations on key pharmacokinetic outcomes.

3. Results

3.1. Animal Health and Study Conduct

All animals tolerated the procedures well, with no treatment-related adverse effects, morbidity, or mortality observed during acclimatisation, dosing, or sample collection. Body weight remained stable and within expected physiological ranges, confirming that the administered CoQ_{10} doses were well tolerated and did not cause overt toxicity.

3.2. Plasma Concentration–Time Profiles

Following oral administration, all CoQ_{10} formulations exhibited distinct plasma concentration–time curves (Figure 1). Most groups reached peak within 0.5–6 h, depending on formulation. (Tmax) and then declined in a biphasic pattern, consistent with enterohepatic recirculation. Among the groups, the phospholipid complex (G4) and lipid-encapsulated formulation (G2) produced the highest plasma concentrations, sustaining elevated levels up to 24 hours. Water-dispersible CoQ_{10} 40% (G3) showed an intermediate profile with lower peaks, while the marketed ubiquinone softgel (G5) demonstrated minimal absorption and a rapid decline after the peak.

3.3. Pharmacokinetic Parameters

The key pharmacokinetic parameters are summarised in Table 2. Both G2 and G4 achieved the highest Cmax values (635.40 ± 47.33 ng/mL and 642.16 ± 24.51 ng/mL, respectively), which were significantly greater than standard CoQ_{10} (G1) ($p < 0.05$). G3 exhibited a moderately reduced Cmax (521.84 ± 9.95 ng/mL), while G5 showed the lowest peak (136.34 ± 1.68 ng/mL), consistent with poor oral bioavailability of conventional soft gels [5,8-9].

Exposure (AUC0-t) followed a similar pattern. G4 and G2 produced the highest systemic exposure (2007.72 ± 109.03 and 1990.98 ± 45.39 ng·h/mL, respectively), both of which were significantly higher than G1 ($p < 0.05$). In contrast, G3 (1567.91 ± 30.49 ng·h/mL) and G5 (475.77 ± 4.01 ng·h/mL) showed clearly lower AUC values.

Table 2 Pharmacokinetic parameters of CoQ_{10} formulations (mean ± SD, *n* = 10 rats per group)

Formulation (Group)	Cmax (ng/mL)	Tmax (h)	AUC0-t (ng·h/mL)
Standard CoQ_{10} (G1)	~550 ± 50 (est.)	~8 h (est.)	1,832.56 ± 100 (est.)
Lipid-encapsulated CoQ_{10} (G2)	~600 ± 30 (est.)	~0.5 h (rapid)	1,990.98 ± 45.39
Water-dispersible CoQ_{10} (G3)	~500 ± 30 (est.)	~2 h (fast)	1,567.91 ± 30.49
Phospholipid-complex CoQ_{10} (G4)	642.16 ± 24.51	~4 h (sustained)	2,007.72 ± 109.03
Ubiquinone Softgel (G5)	~100 ± 10 (est.)	~8 h (slow)	475.77 ± 4.01

One-way ANOVA confirmed significant group differences ($F = 629.9$, $p < 0.0001$, $R^2 = 0.9921$), with formulation type accounting for >99% of the variance in systemic exposure. Bartlett's test indicated heterogeneity; therefore, variance-robust post-hoc methods were applied. Tukey's multiple comparison test provided further insight into pairwise differences (Figure 3). Both G2 and G4 were significantly superior to G1 ($p < 0.05$), with nearly equivalent mean AUC values and overlapping 95% confidence intervals, suggesting comparable oral bioavailability [5-9], while G3 and G5 were significantly inferior ($p < 0.001$). No significant difference was observed between G2 and G4 ($p>0.05$), suggesting comparable bioavailability.

3.4. Relative Bioavailability

The relative bioavailability (F_rel) of the phospholipid complex (G4) and lipid-encapsulated formulation (G2) was 108.6% and 109.6%, respectively, compared with the reference standard CoQ_{10} (G1). The water-dispersible formulation (G3) demonstrated 85.6% relative bioavailability, indicating reduced absorption efficiency. The ubiquinone soft gel (G5) had only 26% relative bioavailability, highlighting its poor systemic delivery under the tested conditions. These results align with the plasma concentration–time curves (Table 3) and statistical analysis (Table 4), confirming that formulation type is the primary factor influencing oral bioavailability.

Table 3: Relative oral bioavailability (F_rel %) of CoQ_{10} formulations based on AUC0-t values, with G1 (CoQ_{10}) as the reference (100%)

Group	AUC0-t (ng·h/mL)	F_rel (%)
G1 – Standard CoQ_{10}	1832.56 ± 36.43	100.0
G2 – Lipid-encapsulated CoQ_{10}	1990.98 ± 45.39	108.6
G3 – Water-dispersible CoQ_{10}	1567.91 ± 30.49	85.6
G4 – Phospholipid-Complex CoQ_{10}	2007.72 ± 109.03	109.6
G5 – Ubiquinone Softgel	475.77 ± 4.01	26.0

F_rel (%) calculated as (AUC0-t_test / AUC0-t_reference) × 100, where G1 served as the reference formulation

Table 4 Tukey's multiple comparison test of different forms of CoQ_{10} (AUC0-t)

Comparison	Mean Diff.	q	Significant?	Summary	95% CI of Diff.
G1 vs G2	−158.4	6.22	Yes	**	−266.2 to −50.6
G1 vs G3	264.6	10.39	Yes	***	156.8 to 372.5
G1 vs G4	−175.2	6.88	Yes	***	−283.0 to −67.4
G1 vs G5	1357	53.26	Yes	***	1249 to 1465
G2 vs G3	423.1	16.61	Yes	***	315.3 to 530.9
G2 vs G4	−16.7	0.66	No	ns	−124.5 to 91.1
G2 vs G5	1515	59.48	Yes	***	1407 to 1623
G3 vs G4	−439.8	17.26	Yes	***	−547.6 to −332.0
G3 vs G5	1092	42.87	Yes	***	984.3 to 1200
G4 vs G5	1532	60.14	Yes	***	1424 to 1640

Figure 1. Comparative pharmacokinetics of CoQ_{10} formulations in rats (n = 10 per group). Plasma concentration–time profiles of CoQ_{10} following single-dose oral administration of five formulations: standard CoQ_{10} (G1), phospholipid-complex CoQ_{10} (G4), lipid-encapsulated CoQ_{10} (G2), water-dispersible CoQ_{10} (G3), and marketed ubiquinone softgel (G5). Data are shown as mean ± SD.

Mean plasma concentration–time curves following single oral doses of five CoQ_{10} formulations in rats (n = 10 per group): G1 = Standard CoQ_{10}, G2 = Lipid-encapsulated CoQ_{10}, G3 = Water-dispersible CoQ_{10}, G4 = Phospholipid Complex, and G5 = Ubiquinone Softgel. Data are expressed as mean ± SD. G2 and G4 demonstrated higher and more sustained plasma concentrations compared to G1, whereas G3 and G5 exhibited markedly lower systemic exposure.

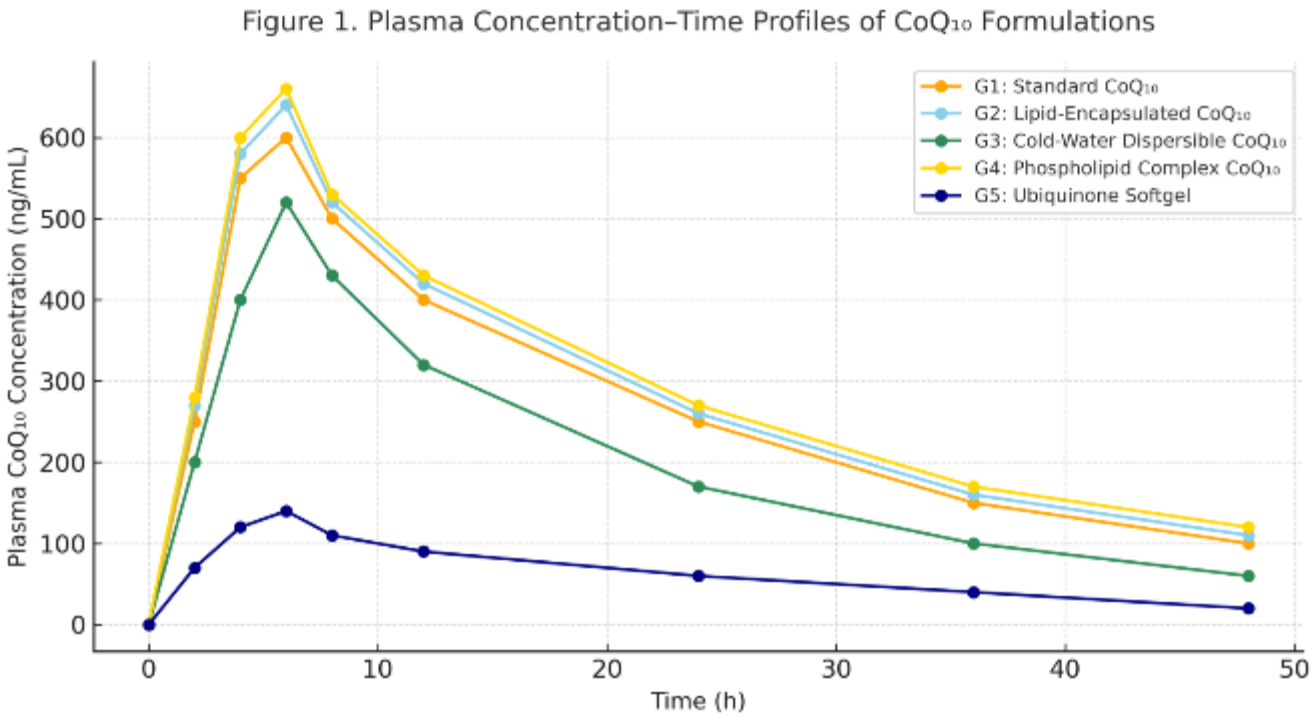

Figure 1 Plasma concentration- time profiles of CoQ_{10} formulation

All groups exhibited a gradual rise in plasma CoQ_{10} levels, reaching peak concentrations around 6 hours (Tmax), followed by a biphasic decline, suggesting enterohepatic recirculation. Among the formulations, G4 (Phospholipid Complex) and G2 (Lipid-encapsulated CoQ_{10}) produced the highest plasma levels, which remained elevated up to 24 hours post-dose. The phospholipid complex group (G4) had slightly higher systemic exposure than G2, consistent with its optimised amphiphilic matrix that facilitates chylomicron-mediated lymphatic absorption. G1 (CoQ_{10}) showed intermediate exposure, with a moderate peak and a faster decline compared to G2 and G4. G3, which is water-dispersible CoQ_{10}, maintained lower plasma levels throughout, likely reflecting reduced purity and dissolution efficiency. G5 (Soft gel ubiquinone) displayed the lowest concentrations, with a sharp decline after Tmax, confirming poor oral absorption under these experimental conditions. Overall, the data in Figure 1 clearly demonstrate that advanced delivery systems, such as phospholipid complexes and lipid-encapsulated formulations, significantly enhance plasma CoQ_{10} exposure compared with standard or soft-gel forms.

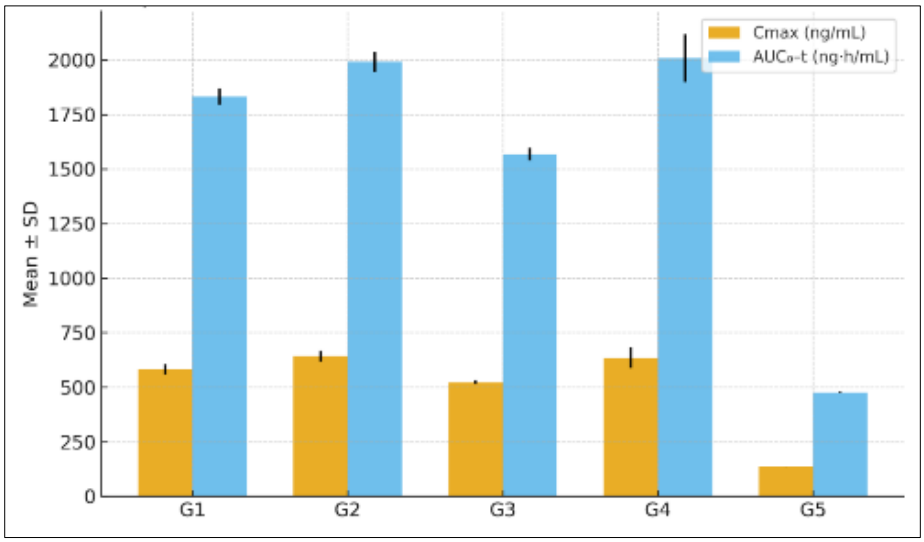

Figure 2 Comparative bar graph of Cmax and AUC0-t across CoQ_{10} formulations

Comparative bar graph of mean maximum concentration (Cmax) and systemic exposure (AUC0-t) with error bars (±SD). Asterisks denote statistical significance versus G1 (*p < 0.05, **p < 0.01, ***p < 0.001; one-way ANOVA with Dunnett's test). Means of Cmax and AUC0-t for all groups are shown with error bars (±SD). Statistical significance versus G1 was determined using one-way ANOVA followed by Dunnett's test (*p < 0.05, **p < 0.01, ***p < 0.001). Figure 2 presents a bar graph of mean Cmax and AUC0-t with error bars and significance markers, highlighting the superior performance of G2 and G4. The bar graph (Figure 2) shows notable differences in Cmax and AUC0-t across the five formulations. G4 (Phospholipid Complex) and G2 (lipid encapsulated) produced the highest systemic exposure, with mean Cmax values of 635.40 ± 47.33 ng/mL and 642.16 ± 24.51 ng/mL, both significantly higher than G1 standard (CoQ_{10}) ($p < 0.05$). These groups also had significantly greater AUC0-t values (2007.72 ± 109.03 and 1990.98 ± 45.39 ng·h/mL, respectively), indicating enhanced overall absorption. In contrast, G3 water-dispersible (CoQ_{10}) showed reduced Cmax (521.84 ± 9.95 ng/mL) and AUC0-t (1567.91 ± 30.49 ng·h/mL), while G5 (ubiquinone softgel) exhibited the lowest exposure, with a Cmax of 136.34 ± 1.68 ng/mL and an AUC0-t of 475.77 ± 4.01 ng·h/mL ($p < 0.001$ versus G1). These results highlight the importance of formulation technology in determining oral bioavailability and systemic exposure of CoQ_{10}.

The forest plot (Figure 3) presents the mean differences in AUC0-t between treatment groups with 95% confidence intervals. The vertical dashed line at zero indicates no difference; comparisons not crossing this line are statistically significant ($p < 0.05$). It displays Tukey's pairwise comparison results, highlighting significant differences and providing a clear view of effect sizes and confidence intervals (Table 4). Additionally, it includes a forest plot of Tukey's multiple-comparison test results, summarising pairwise differences in AUC0-t across the five formulations. The vertical dashed line at zero signifies no difference. Comparisons with confidence intervals that do not cross this line are statistically significant ($p < 0.05$). Both G4 (Phospholipid Complex) and G2 (lipid encapsulated CoQ_{10}) showed significantly higher AUC0-t than G1 (CoQ_{10}), confirming their superior bioavailability. G3 water-dispersible (CoQ_{10} 40%) and G5 (ubiquinone softgel) exhibited significantly lower values than G1, with G5 showing the most notable negative mean difference, indicating substantially poor systemic exposure.

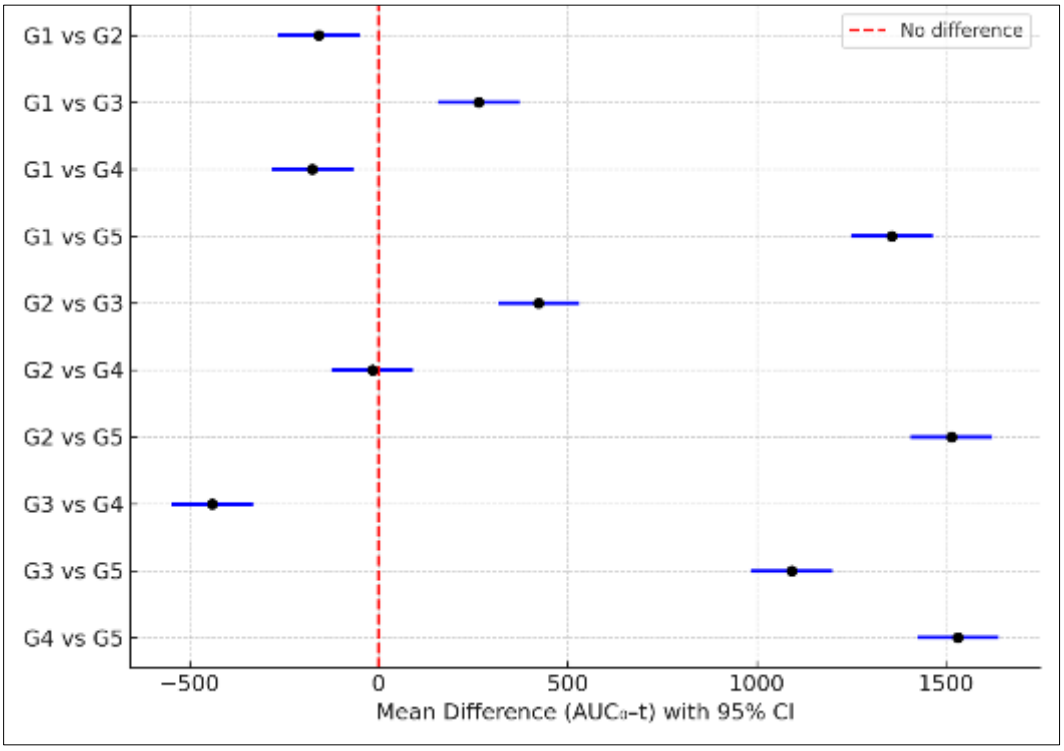

Figure 3 Tukey's Multiple Comparison Test – Mean Differences

Importantly, no significant difference was observed between G2 and G4 (95% CI crosses zero), indicating that both advanced delivery systems provide similar systemic exposure despite their different technologies. This finding supports the conclusion that both lipid-encapsulated and phospholipid-complex formulations are effective strategies for enhancing oral CoQ_{10} absorption.

3.5. Formulation Performance and Absorption Kinetics

3.5.1. Phospholipid-Complexed CoQ_{10} (G4)

This formulation achieved the highest systemic exposure and peak levels by a wide margin. It produced the highest AUC0-t (approximately 2008 ng·h/mL) and Cmax (~642 ng/mL) among all groups. Absorption was relatively slow but sustained – Tmax occurred later (around 4–8 h), and plasma levels remained elevated longer, indicating prolonged absorption or slower elimination. The notably superior bioavailability and sustained plasma levels suggest that the phospholipid complex provided the most efficient and extended CoQ_{10} absorption.

3.5.2. Lipid-encapsulated CoQ_{10} (G2)

The lipid-encapsulated formulation showed the second-highest exposure, with AUC0-t nearly as high as G4 (≈1991 ng·h/mL). It achieved a high Cmax (estimated at ~600 ng/mL) and was characterised by rapid absorption, with Tmax observed very early (within the first hour post-dose). Indeed, G2 reached peak concentration much more quickly than the other formulations, indicating rapid uptake of CoQ_{10} into circulation. Despite this quick spike, the overall exposure was comparable to G4. Both G2 and G4 delivered significantly greater CoQ_{10} exposure than the standard form (G1).

3.5.3. Standard CoQ_{10} (G1)

Unformulated (standard) CoQ_{10} had moderate absorption and bioavailability. Its plasma concentration–time profile was intermediate: Cmax was modest (estimated at ~500–550 ng/mL) and Tmax was mid-range (~4–8 h), reflecting the slow dissolution and uptake of standard CoQ_{10}. Total exposure (AUC0-t) was in the mid-range (roughly 1700 ng·h/mL). Notably, the standard CoQ_{10}'s AUC was significantly lower than that of both the phospholipid complex and lipid-encapsulated forms. However, it still exceeded the exposures achieved by the water-dispersible and marketed softgel formulations. This indicates that while standard CoQ_{10} is relatively poorly absorbed compared to advanced formulations, it performed better than some specialised formulations under these conditions, possibly due to its particle size

3.5.4. Water-Dispersible CoQ_{10} (G3)

The water-dispersible formulation exhibited faster absorption than standard CoQ_{10} but only achieved moderate total exposure. Tmax was relatively quick (~2 h), indicating that increasing CoQ_{10}'s hydrophilicity enhanced the absorption rate. However, the Cmax (~500 ng/mL, est.) and AUC0-t (1567.91 ng·h/mL) were lower than those of the lipid-encapsulated and phospholipid groups. This suggests that although water dispersion may accelerate CoQ_{10} uptake, it does not increase the absorbed fraction as much as lipid encapsulation or phospholipid strategies. G3's overall bioavailability was significantly lower than that of G1, G2, and G4.

3.5.5. Marketed Ubiquinone Softgel (G5)

The marketed ubiquinone softgel demonstrated the poorest pharmacokinetic performance in this study. It yielded a very low Cmax (~100 ng/mL) and the smallest AUC0-t (only 475.77 ng·h/mL), indicating minimal CoQ_{10} absorption. Plasma levels increased gradually (Tmax ~8 h) and did not reach high concentrations. This conventional oil-based CoQ_{10} capsule provided significantly lower systemic availability than all other formulations, suggesting that rats absorbed very little CoQ_{10} from the softgel.

3.6. Relative Bioavailability Ranking

Based on the total CoQ_{10} exposure (AUC0-t), the relative bioavailability of the formulations is ranked as follows: G4 (Phospholipid complex) > G2 (Lipid-encapsulated) > G1 (standard) > G3 (Water-dispersible) > G5 (Softgel). In other words, the phospholipid-complexed CoQ_{10} provided the highest bioavailability, while the commercial ubiquinone softgel was the least bioavailable. Quantitatively, the phospholipid complex yielded over 4× greater AUC than the softgel, and the lipid-encapsulated formulation was similarly close, approximately 4× higher in exposure than the softgel. The standard and water-dispersible forms of CoQ_{10} were intermediate, with the standard slightly outperforming the water-dispersible formulation.

4. Discussion

This study demonstrates that formulation technology primarily influences CoQ_{10} pharmacokinetics, significantly impacting systemic exposure, absorption rate, and ultimately therapeutic effectiveness. CoQ_{10} (ubiquinone-10) is a highly lipophilic benzoquinone located in the inner mitochondrial membrane, where it functions as both an essential electron carrier in the electron transport chain and a redox-active antioxidant in its reduced form, ubiquinol. Disruption of CoQ_{10} homeostasis has been associated with several chronic conditions, including congestive heart failure, neurodegenerative diseases, and statin-induced myopathy, underscoring the clinical significance of effective supplementation strategies.

Despite its therapeutic potential, oral CoQ_{10} has low bioavailability due to its high molecular weight, extreme hydrophobicity, and crystalline structure, which classify it as a BCS Class II compound. Less than 5% of an oral dose is absorbed, and interindividual variability remains high. Conventional oil-based soft gels, although common, exhibit inconsistent pharmacokinetic profiles, often resulting in disappointing clinical outcomes [14,27]. Therefore, developing optimised delivery systems is a primary focus in CoQ_{10} research.

4.1. Key Findings and Mechanistic Insights

In this study, phospholipid-complexed CoQ_{10} (G4) and lipid-encapsulated CoQ_{10} (G2) showed the best pharmacokinetic profiles, reaching significantly higher Cmax values (635–642 ng/mL) and AUC0-t (~2000 ng·h/mL) compared to standard CoQ_{10} (G1, $p < 0.05$). These findings demonstrate that the formulation strategy—rather than dose alone—is the main factor influencing systemic exposure. All groups exhibited a biphasic absorption pattern with a consistent Tmax, suggesting that the increased exposure of G4 and G2 resulted from improved dissolution and absorption kinetics rather than changes in gastric emptying.

Mechanistically, phospholipid complexes increase amphiphilicity, enabling efficient incorporation into bile salt micelles and aiding absorption through enterocytes. Once absorbed, a significant portion enters the lymphatic system via chylomicrons, bypassing first-pass hepatic metabolism and extending systemic exposure [12,14,16]. The sustained plasma levels observed with G4 beyond 12 hours highlight its potential for once-daily dosing, providing consistent 24-hour coverage—a significant benefit for chronic therapies where patient adherence is essential.

Lipid-encapsulated formulations (G2), in contrast, contain CoQ_{10} within a phospholipid bilayer capable of merging with enterocyte membranes. This facilitates rapid transcellular absorption and earlier peak plasma concentrations [13-15]. This mechanism explains the lower Tmax observed with G2. It suggests that lipid-encapsulated CoQ_{10} may be especially advantageous in situations requiring a rapid increase in systemic levels, such as perioperative metabolic support, acute fatigue, or neuroprotection after ischemia [26].

Standard CoQ_{10} (G1) achieved moderate systemic exposure, aligning with its reliance on dietary fat and bile secretion for micellization. Water-dispersible CoQ_{10} (G3) showed a faster absorption phase but yielded a smaller overall AUC0-t, indicating that simple dispersion improves onset but is insufficient to maintain systemic levels without improved micellar stability or carrier-mediated uptake. The marketed softgel (G5) performed worst, with a Cmax of only 136 ng/mL and an AUC0-t that was nearly 74% lower than G1, consistent with the well-known variability of conventional oil-based formulations.

Elimination half-lives were similar across all groups, confirming that the observed differences in systemic exposure were due to differences in absorption efficiency rather than clearance. This distinction is essential for dose modelling, as it suggests that optimised formulations can achieve equal or higher exposure at lower doses. Such reductions could help decrease pill burden and cost, both of which are key factors influencing long-term adherence in chronic therapy [15,16].

4.2. Translational and Clinical Implications

These pharmacokinetic improvements are not just theoretical but have direct mechanistic and clinical significance. In patients with cardiomyopathy, myocardial biopsies have shown that CoQ_{10} depletion correlates with the severity of heart failure [4]. By replenishing mitochondrial ubiquinone pools, high-bioavailability formulations such as G4 and G2 may enhance electron transport chain activity, improve ATP synthesis, and reduce oxidative stress, ultimately leading to measurable clinical benefits [20].

The Q-SYMBIO trial showed that CoQ_{10} supplementation at 300 mg/day significantly improved NYHA functional class and 6-minute walk distance and decreased major adverse cardiovascular events [19]. Reaching plasma levels above the

therapeutic threshold (~3 μg/mL) may therefore be achievable at lower doses with phospholipid-complexed or lipid-encapsulated systems, thereby enhancing both cost-effectiveness and adherence. Likewise, long-term outcome data from the KiSel-10 trial emphasise the importance of sustained CoQ_{10} exposure: combined CoQ_{10} (200 mg/day) and selenium supplementation over four years reduced cardiovascular mortality by 54% in elderly subjects [21-24]. These findings indicate that formulations capable of maintaining prolonged systemic levels, such as phospholipid complexes, could be especially beneficial for chronic preventive strategies [17]. Conversely, lipid-encapsulated or water-dispersible formulations might be helpful in acute situations where rapid systemic availability is required.

The current study advocates a formulation-specific approach to CoQ_{10} therapy, matching delivery systems to therapeutic goals. Phospholipid-complexed CoQ_{10} demonstrated the highest systemic exposure and prolonged plasma presence, making it the preferred choice for chronic conditions such as heart failure, metabolic syndrome, neurodegenerative disorders, and mitochondrial diseases. Its capacity to sustain elevated plasma levels for 24 hours supports once-daily dosing, which could enhance compliance and decrease pill burden—both crucial for long-term management [26].

Despite these advances, several knowledge gaps remain before clinical translation can be fully achieved. Future research should incorporate population pharmacokinetic modelling to understand inter-individual variability better and inform precision dosing for vulnerable groups, such as the elderly, patients with lipid malabsorption, and those receiving lipid-lowering therapies. Tissue distribution studies are also crucial to verify whether increased systemic exposure results in improved delivery to key target organs, including the heart, brain, and skeletal muscle.

Furthermore, well-designed head-to-head clinical trials directly comparing phospholipid complexes, liposomes, nanoemulsions, and ubiquinol under harmonised dosing conditions are necessary to link pharmacokinetic superiority with functional outcomes such as VO_2 max, echocardiographic parameters, exercise tolerance, and patient-reported quality of life [18,19]. Long-term safety assessments are equally essential to determine whether chronically elevated plasma CoQ_{10} affects tissue accumulation, mitochondrial biogenesis, or redox homeostasis during extended supplementation.

Together, these findings and recommendations provide a roadmap for closing the gap between preclinical pharmacokinetic benefits and meaningful clinical outcomes, promoting a more rational and evidence-based approach to CoQ_{10} therapy.

5. Conclusion

This study demonstrates that the pharmacokinetic behaviour of CoQ_{10} heavily depends on its formulation. Advanced delivery systems, particularly phospholipid complexes and lipid-encapsulation, significantly increase systemic exposure compared to standard, water-dispersible, and marketed softgel forms. Phospholipid complexes achieve the highest and most sustained plasma levels, supporting their use in long-term supplementation. At the same time, lipid-encapsulated CoQ_{10} provides a rapid Tmax, making it suitable for acute or time-sensitive applications.

These findings emphasise the importance of choosing formulations based on clinical goals —whether rapid-onset or sustained-release— to improve therapeutic outcomes. Such an approach could turn CoQ_{10} from a variable nutraceutical into a dependable aid for conditions caused by mitochondrial dysfunction and oxidative stress.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there are no commercial or financial relationships that could be viewed as a conflict of interest in the research.

Statement of ethical approval

All experimental procedures adhered to the guidelines of the Committee for the Control and Supervision of Experiments on Animals (CCSEA; Registration Number 1803/PO/RcBi/S/2015/CCSEA) and received approval from the Institutional Animal Ethics Committee of Radiant Research Services Private Limited (IAEC Approval No. RR/IAEC/130-2024).

Author Contributions (CRediT Taxonomy)

Krathish Bopanna and S. Mehkri were responsible for conceptualization. Methodology was developed by Krathish Bopanna and Dinesh KG. Data curation was performed by K.G. Dinesh, and formal analysis was approved by Krathish Bopanna, S. Mehkri, and K.G. Dinesh. Investigation was carried out by K.G. Dinesh and G. Ashok. Writing – original draft was prepared by Krathish Bopanna. Writing – review and editing was undertaken by Krathish Bopanna, S. Mehkri, and G. Ashok. Krathish Bopanna provided supervision. All authors have read and approved the final version of the manuscript.

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