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Article

Calcium Bioavailability of an Organic Calcium–CPP Granule Formulation: In Vitro Performance and Evidence from Human Studies

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Abstract: The tablet formulation contains calcium citrate malate, calcium L-lactate, casein phosphopeptide (CPP), inulin, resistant dextrin, and microencapsulated vitamin D3. The ingredients are incorporated through a prefabricated-granule process. In comparative tests, the formulation showed greater calcium release and soluble-calcium retention in simulated gastrointestinal media than direct mixing. Objective to examine whether these formulation findings are consistent with human evidence on calcium absorption and bioavailability. The reported formulation composition and comparative test results were used without changing their original values. Human studies were identified through a focused search of PubMed-indexed randomized and crossover trials and relevant primary reports available through 14 August 2026. The search covered calcium citrate malate, CPP, inulin-type fructans, and vitamin D in relation to calcium absorption. The preferred formulation released 84.7% of its calcium within 30 minutes in simulated gastric fluid and retained 61.5% in soluble form after 60 minutes in simulated intestinal fluid. Direct mixing resulted in lower values of 70.4% and 46.7%, respectively. In human studies, CCM was absorbed, although absorption varied with the food matrix. Inulin-type fructans increased calcium absorption in some adolescent and postmenopausal populations. The available CPP trials did not show a clear improvement in fractional calcium absorption, while the effects of vitamin D supplementation differed across study populations. The formulation has a credible physicochemical rationale for delivering soluble calcium, with the strongest ingredient-level clinical support attributable to selected prebiotic strategies and established absorbability of organic calcium salts. The evidence supports further direct stable-isotope evaluation of the finished formulation.

Keywords: Calcium Bioavailability, Calcium Citrate Malate, Calcium L-Lactate, Casein Phosphopeptide, Inulin, Vitamin D3, Stable Isotopes, Translational Evidence

Introduction

Calcium bioavailability is governed by more than the nominal amount of calcium in a product. Solubility before and during intestinal transit, luminal complexation, food matrix, intestinal physiology, vitamin D status, habitual calcium intake and host age can all modify the fraction of ingested calcium that reaches the exchangeable body pool. Consequently, a formulation designed to

keep calcium dispersed and soluble is mechanistically relevant, but formulation behavior must not be used as a surrogate for measured human absorption.

The evaluated tablet platform uses two organic calcium sources—calcium citrate malate (CCM) and calcium L-lactate—together with CPP, inulin, resistant dextrin and microencapsulated vitamin D3. The manufacturing design co-granulates the calcium sources with CPP and the two fiber ingredients, whereas vitamin D3 is incorporated after drying by light-protected geometric premixing. This architecture is intended to separate two technical goals: favorable calcium release/soluble retention and preservation of a low-dose vitamin D3 component [1].

The central question is therefore whether the improved in vitro profile is supported by complementary human evidence at each biological step. This is especially relevant to CPP, for which a plausible calcium-binding mechanism has not consistently translated into enhanced fractional calcium absorption in randomized trials [2,3]. Inulin-type fructans, in contrast, have produced positive absorption signals in selected populations [4–6], whereas vitamin D supplementation has yielded context-dependent effects [7,8].

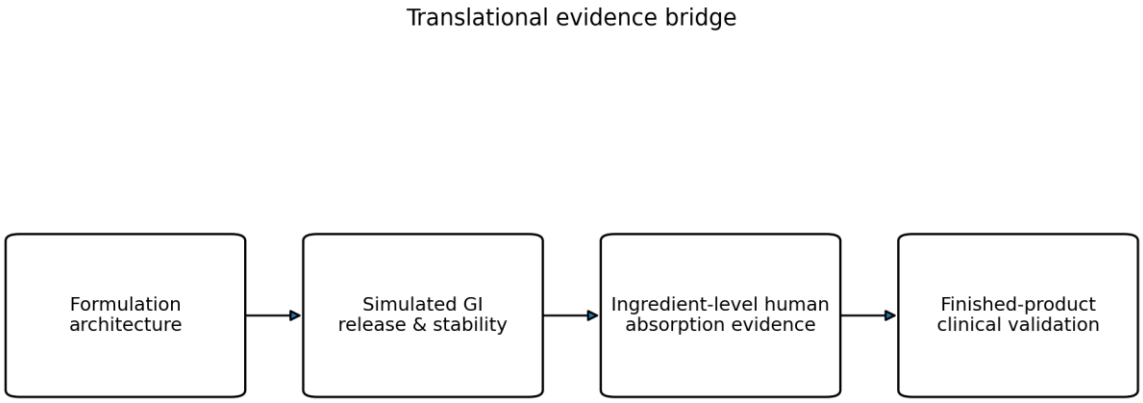

Figure 1. Translational evidence framework used in this article. Formulation-specific simulated gastrointestinal performance supports mechanistic plausibility, whereas human absorption claims require direct clinical measurement.

Materials and Method

2.1 Formulation and comparative testing

The multi-component organic calcium–CPP formulation evaluated in this study was provided as NVTIA® Organic Calcium Complex. The preferred composition, process conditions and comparative experimental results were evaluated at their reported values and cross-checked against the experimental table. The analysis focused on measured endpoints for tablet performance, calcium release, soluble calcium retention and vitamin D3 stability.

2.2 Evidence search and eligibility

A targeted structured evidence search was conducted for human trials directly measuring calcium absorption, calcium balance or closely related acute calcium-metabolism endpoints. Priority was given to randomized crossover designs using stable calcium isotopes and to longer controlled trials that evaluated ingredient-specific absorption. Searches centered on “calcium citrate malate absorption”, “casein phosphopeptide calcium absorption”, “inulin calcium absorption”, and “vitamin D calcium absorption”. Primary reports were checked for intervention dose, population, endpoint, direction of effect and numerical estimates. Because this was a focused translational appraisal rather than a registered systematic review, no pooled effect was calculated.

2.3 Evidence interpretation

Three evidence layers were analyzed in parallel: (i) technical properties of the finished formulation; (ii) human evidence on individual ingredients or closely related ingredient classes; and

(iii) the clinical translation pathway for the complete formulation. Numerical comparisons across human studies are presented descriptively because populations, co-interventions and absorption methods differ.

Table 1. Preferred formulation composition and evidence-relevant role

Component	Mass fraction	Interpretive role
Calcium citrate malate	50.000%	Principal organic calcium source; quantify elemental calcium per tablet for clinical dose matching
Calcium L-lactate	15.000%	Second organic calcium source
Casein phosphopeptide (CPP)	2.500%	Co-granulated calcium-binding peptide ingredient; human absorption evidence is mixed/neutral
Inulin	5.000%	Prebiotic fiber; ingredient-level trials support calcium absorption in selected populations
Resistant dextrin	2.000%	Dietary-fiber co-ingredient; evaluate its contribution within complete-formulation clinical studies
HPMC	1.000%	Granulation/binder component
Microcrystalline cellulose	12.150%	Carrier/filler; part used for vitamin D3 geometric premixing
Mannitol	9.000%	Filler
Croscarmellose sodium	1.800%	Disintegrant
Microencapsulated vitamin D3 powder	0.200%	Potency 90,000–110,000 IU/g; define exposure from assayed tablet content and daily intake
Silicon dioxide	0.550%	Glidant
Magnesium stearate	0.800%	Lubricant

Results

3.1 Formulation behavior in simulated gastrointestinal media.

Example 1 released 84.7% of its calcium within 30 minutes in simulated gastric fluid and retained 61.5% in soluble form after 60 minutes in simulated intestinal fluid. The direct-mix comparator showed lower values of 70.4% and 46.7%, respectively. The formulation without CPP and inulin gave intermediate results, with calcium release of 76.2% and soluble-calcium retention of 50.8%. When vitamin D3 was subjected to wet granulation and drying, the corresponding values were 78.5% and 52.1%. Under the test conditions, Example 1 therefore performed better than the other formulations for both measured calcium endpoints. These results describe formulation behavior in simulated gastrointestinal media only; they do not show how much calcium would be absorbed in humans.

Other measurements were also recorded for Example 1. Vitamin D3 content had an RSD of 2.8%, and retention after three months at 40°C/75% RH was 93.4%. Tablet hardness was 82 N, friability was 0.42%, and disintegration time was 18.6 minutes. These measurements are relevant to dose uniformity and tablet performance, but they do not provide a direct measure of calcium bioavailability.

3.2 Organic calcium source and matrix effects.

In healthy women given 250 mg calcium as CCM in fortified juice, Andon et al. reported fractional absorption of 42±2% with apple juice and 36±1% with orange juice ($P<0.003$) [1]. The calcium source was the same in both conditions, so the difference points to an effect of the

surrounding food matrix. The finding supports CCM as an absorbable calcium source, but it also shows that absorption cannot be assigned a single value based on the calcium salt alone.

3.3 CPP: mechanistic plausibility without a demonstrated fractional-absorption advantage.

In a randomized crossover stable-isotope study of 15 adults, calcium lactate provided 400 mg calcium either alone or with CPP-enriched preparations supplying approximately 100 mg additional CPP-derived calcium [2]. Absolute calcium absorption increased with the additional calcium dose, whereas fractional absorption was 26% with calcium lactate alone and 23% with one CPP preparation (P=0.015). The investigators considered this difference unlikely to be biologically important. A separate double-blind crossover study in nine postmenopausal women also found no acute change in calcium-metabolism indices attributable to CPP [3]. CPP may therefore have a role in the physicochemical behavior of the formulation, but the available human studies do not establish it as an independent enhancer of fractional calcium absorption [9], [10], [11].

3.4 Inulin-type fructans.

In 59 girls with adequate calcium intake, the combination of inulin and oligofructose increased calcium absorption compared with placebo (P=0.01), whereas oligofructose alone did not [4]. In a study of 100 adolescents, 8 g/day of short- and long-chain inulin-type fructans increased calcium absorption by 8.5±1.6 percentage points after 8 weeks (P<0.001) and by 5.9±2.8 percentage points after one year (P=0.04) [5]. In postmenopausal women, 10 g/day of oligofructose-enriched inulin given for six weeks also increased fractional calcium absorption compared with placebo, although the response varied between participants [6]. These findings provide evidence that some inulin-type fructan preparations can affect calcium absorption. For the present formulation, however, the relevance of those studies depends on the daily inulin dose and on whether the fructan used in the tablet is comparable with the preparations tested clinically.3.5 Vitamin D: a modifier rather than a guaranteed absorption amplifier. Two randomized studies illustrate why vitamin D status should be treated as an effect modifier rather than a universal absorption switch. In younger vitamin-D-insufficient women, vitamin D3 at 400–2400 IU/day raised vitamin D status without significantly increasing measured calcium absorption [7]. In postmenopausal women, 4000 IU/day produced a 6.7-percentage-point increase in absorption over eight weeks, with no discrete threshold effect [8]. Population, baseline vitamin D status, calcium intake and dose therefore influence the observed response.

Table 2. Formulation-specific comparative technical results

Test item	Example 1	Comp. 1	Comp. 2	Comp. 3
Tablet hardness (N)	82	78	80	69
Friability (%)	0.42	0.58	0.51	0.86
Disintegration time (min)	18.6	22.4	21.3	27.8
30-min gastric Ca release (%)	84.7	76.2	78.5	70.4
60-min intestinal soluble Ca retention (%)	61.5	50.8	52.1	46.7
Vitamin D3 content RSD (%)	2.8	3.6	4.9	5.7
Vitamin D3 retention, 3 mo, 40°C/75% RH (%)	93.4	91.2	84.6	88.5

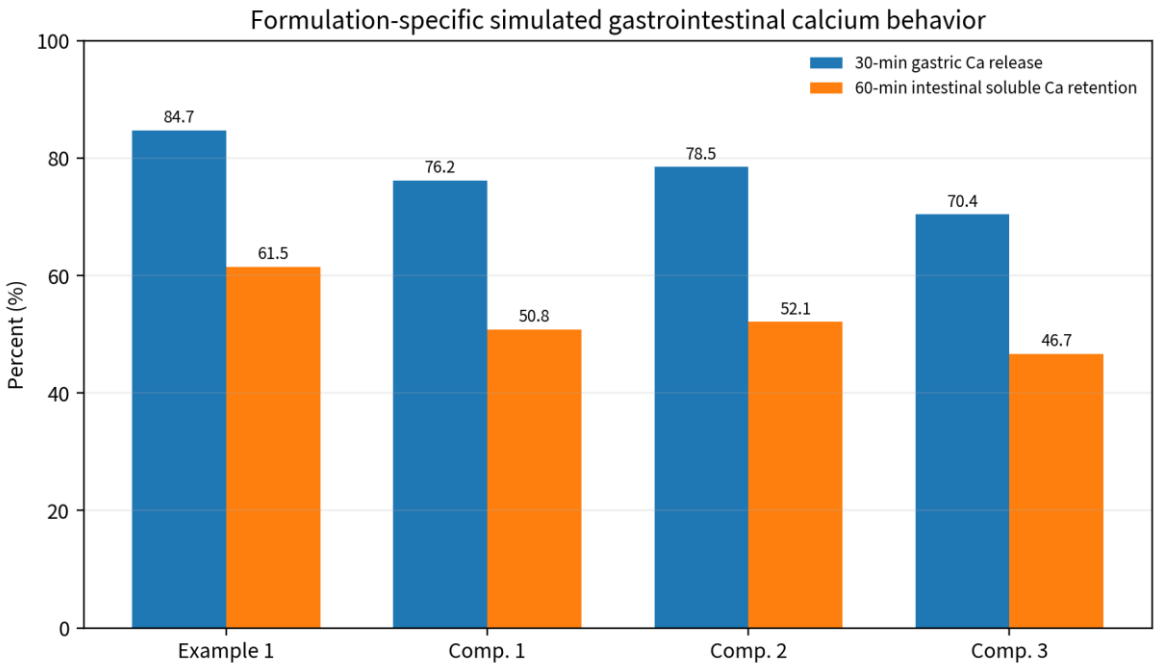

Figure 2. Calcium release and soluble-calcium retention across the evaluated formulation conditions in simulated gastrointestinal media.

Table 3. Human clinical evidence most relevant to calcium absorption

Study	Population	Intervention	Endpoint	Key result	Relevance
Andon et al., 1996 [1]	Healthy women; ~57/group	250 mg Ca as CCM in fortified apple vs orange juice	Fractional Ca absorption	42±2% vs 36±1%; P<0.003	Demonstrates that food matrix alters absorption even with the same calcium salt.
Teucher et al., 2006 [2]	15 adults; randomized crossover	400 mg Ca as lactate alone vs CPP-enriched preparations adding ~100 mg CPP-derived Ca	Stable-isotope Ca absorption	Fractional absorption 26% with lactate alone vs 23% with a CPP preparation; P=0.015	Extra CPP-associated Ca raised absolute absorbed amount but did not improve fractional absorption; authors judged biological significance unlikely.
Narva et al., 2003 [3]	9 postmenopausal women; randomized double-blind crossover	Milk/fermented milk with 1 g CPP	Acute serum/urine Ca and PTH indices	No material acute CPP effect	Supports restraint in assigning a direct CPP absorption advantage in humans.

Study	Population	Intervention	Endpoint	Key result	Relevance
Griffin et al., 2002 [4]	59 girls; randomized crossover	8 g/d placebo, oligofructose, or inulin+oligofructose; ~1500 mg Ca/d	Stable-isotope Ca absorption	Inulin+oligofructose > placebo, P=0.01; oligofructose alone not significant	Prebiotic structure/composition matters.
Abrams et al., 2005 [5]	100 adolescents, 9–13 y	8 g/d short+long-chain inulin-type fructans vs maltodextrin	Ca absorption at 8 wk and 1 y	+8.5±1.6 percentage points at 8 wk (P<0.001); +5.9±2.8 at 1 y (P=0.04)	One of the clearest sustained human signals for prebiotic-enhanced Ca absorption.
Holloway et al., 2007 [6]	Postmenopausal women; double-blind crossover	10 g/d oligofructose-enriched inulin for 6 wk	Fractional Ca/Mg absorption	Significant increase vs placebo (P<0.05); heterogeneous response	Supports a responder-dependent effect in later life.
Gallagher et al., 2014 [7]	198 women, 25–45 y, 25(OH)D <20 ng/mL	Vitamin D3 400–2400 IU/d vs placebo	Calcium absorption	No significant increase despite higher vitamin D status	Vitamin D repletion does not uniformly translate to greater measured Ca absorption.
Aloia et al., 2014 [8]	76 postmenopausal women randomized; 71 completed	Placebo or vitamin D3 800–4000 IU/d for 8 wk	Calcium absorption	4000 IU/d increased absorption by 6.7 percentage points; no threshold identified	Shows population- and dose-context dependence rather than a universal effect.

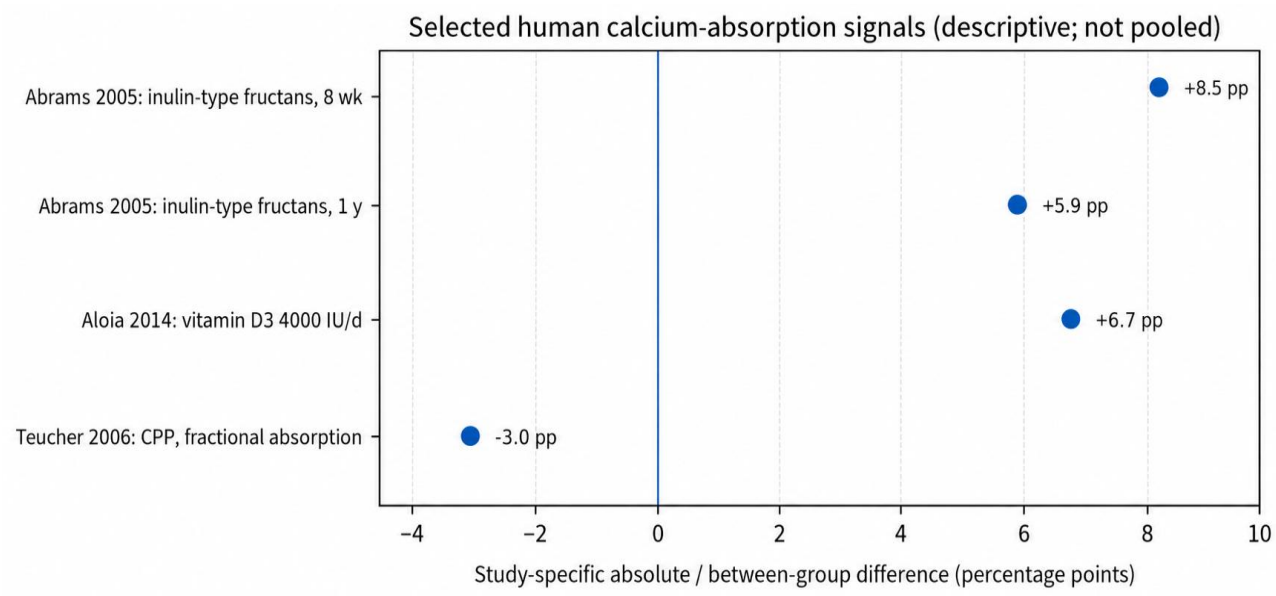

Figure 3. Selected study-specific calcium-absorption contrasts. Values are deliberately not pooled because interventions, populations and study designs differ. "pp" denotes percentage points.

Discussion

The formulation tests and human studies point in the same general direction, but they do not answer the same question. The granule formulation kept more calcium in a releasable and soluble form under the simulated gastrointestinal conditions used in the study. Compared with direct mixing, calcium release at 30 minutes was 14.3 percentage points higher, and soluble-calcium retention at 60 minutes was 14.8 percentage points higher. These differences describe what happened during the formulation tests. They do not show how much calcium would subsequently cross the intestinal epithelium or enter whole-body calcium metabolism.

Among the ingredients examined, the clearest positive human evidence concerns inulin-type fructans. In the adolescent study by Abrams et al., the increase in calcium absorption was still present after one year [5]. The dose, however, was substantially different from the exposure provided by the present tablet. Inulin represents 5% of tablet mass, while the clinical studies generally used several grams per day. The tablet mass and intended daily serving therefore need to be defined before the findings from those studies can be compared directly with the present formulation.

The human data on CPP are less supportive. CPP can bind calcium and may help maintain calcium in solution under some intestinal conditions, but this does not necessarily result in greater fractional absorption. The available clinical studies did not show a clear absorption benefit [2,3]. The formulation-specific finding that omission of CPP and inulin reduced simulated intestinal soluble retention therefore cannot identify which ingredient caused the difference, nor can it establish a clinical CPP effect. A factorial finished-product study would be required for causal partitioning.

Vitamin D3 in this formulation is better understood as a biologically relevant co-nutrient whose contribution depends on host status. The comparative stability results support keeping microencapsulated vitamin D3 out of wet granulation: accelerated retention was 93.4% in Example 1 versus 84.6% when vitamin D3 underwent wet granulation and drying. Preserving consistent vitamin D3 exposure is relevant to the nutritional design, while human absorption responses to supplementation remain context dependent [7,8].

A high-information next experiment would use a randomized, blinded, crossover stable-isotope design comparing the finished tablet with a matched calcium-dose control [12]-[15]. Fractional calcium absorption could be assessed with oral and intravenous stable-isotope tracers. The protocol could also standardize meal composition and account for baseline 25(OH)D status, habitual calcium intake, age, and gastrointestinal status. This approach would allow a direct test of whether the better dissolution and soluble-calcium retention observed in vitro are accompanied by a measurable difference in calcium absorption.

Limitations

This appraisal considers the formulation tests alongside human evidence for the individual ingredients. The two types of evidence were interpreted separately rather than treated as equivalent measures of calcium absorption. Future clinical evaluation should use a defined elemental-calcium dose and tablet intake together with a standardized stable-isotope protocol. This would allow the relationship between formulation performance and measured calcium absorption to be examined directly.

Conclusion

The organic calcium–CPP granule formulation showed higher calcium release and soluble-calcium retention under the simulated gastrointestinal conditions used in this study. The formulation also maintained good vitamin D3 uniformity and stability during accelerated testing. Human studies support CCM as an absorbable calcium source, while the clearest positive evidence among the additional ingredients comes from selected inulin-type fructan interventions. The available CPP studies did not show a consistent increase in fractional calcium absorption, and responses to vitamin D supplementation differed between study populations. A direct stable-isotope study of the finished

formulation is therefore needed to determine whether the favorable in vitro results are associated with greater calcium absorption in humans.

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