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Four-Source Oral Iron Delivery Combined with Natural Vitamin C-Rich Cofactors: Formulation Design, Absorption Performance, and Preclinical Repletion of an NVTIA Iron Supplement

Jabar Yassine *, Gael Navarro, Gregg L. Semenza

World Food Supplement Association, New York, USA
*Corresponding Author: info@wfsas.org

ABSTRACT

Background: Oral iron preparations often fail to balance rapid dissolution, complementary uptake routes, storage stability, and gastrointestinal tolerability. In this study, we evaluated an NVTIA four-source oral iron platform that combines heme iron, glycine chelated iron, ferrous gluconate, and ferrous lactate with camu camu and acerola-derived natural vitamin C-rich cofactors. Methods: We organized the formulation dataset and preclinical evaluation program of this platform and interpreted the results together with published evidence on global anemia burden, oral iron transport, amino acid-chelated iron, heme iron, and ascorbic acid-assisted absorption. The disclosed in-house evaluation included accelerated stability, in vitro dissolution, rat in situ intestinal perfusion, and a rat iron-deficiency anemia model. Results: Publicly available evidence confirms that anemia remains a major global problem and that ferrous salts, heme iron, amino acid-chelated iron, and vitamin C each contribute distinct absorption advantages. In our formulation study, vitamin C retention after 6 months of accelerated storage was 93.25% in Embodiment 1 versus 65.17% in the synthetic vitamin C substitution comparator. Cumulative ferrous dissolution reached 98.26% at 60 min, intestinal iron absorption reached 38.72%, and 28-day repletion in iron-deficient rats brought hemoglobin and serum ferritin closer to normal values than the comparator systems. Conclusion: A multi-pathway iron-delivery strategy that integrates complementary iron species with natural vitamin C-rich cofactors produced favorable stability, dissolution, absorption, and repletion profiles. These findings support clinical translation of the NVTIA platform while underscoring the need for prospective human validation.

KEYWORDS

Heme iron; Glycine chelated iron; Ferrous gluconate; Ferrous lactate; Camu camu; Acerola; Vitamin C; Iron absorption; Anemia

1. INTRODUCTION

Iron deficiency and iron-deficiency anemia remain leading public health problems worldwide. The latest World Health Organization estimates indicate that 40% of children 6-59 months of age, 37% of pregnant women, and 30% of women aged 15-49 years are anaemic worldwide [1]. This burden continues to justify innovation in oral iron formulations, particularly for populations that need long-term supplementation and high adherence.

Conventional oral iron therapy is dominated by iron salts, yet routine clinical use is often constrained by incomplete absorption, oxidative instability, and gastrointestinal side effects. The NIH Office of Dietary Supplements notes that ferrous iron is generally more bioavailable than ferric forms and that

high-dose supplemental iron can provoke nausea, constipation, and related gastrointestinal complaints [2]. Recent reviews have therefore emphasized the value of new oral systems that improve absorption efficiency and potentially reduce the effective dose required to restore iron status [3, 4].

We designed the present NVTIA platform around four complementary iron sources. Heme iron contributes a partly distinct intestinal uptake route. Glycine chelated iron adds amino acid-assisted transport. Ferrous gluconate and ferrous lactate provide highly soluble ferrous fractions that support rapid luminal availability. We then paired these iron species with camu camu and acerola extracts as natural vitamin C-rich cofactors intended to preserve reducing capacity and support nonheme iron absorption [7-10].

Our objective was to evaluate whether this four-source strategy could achieve stronger formulation performance than simpler comparator systems while remaining scientifically aligned with published oral iron literature. To that end, we integrated the formulation and preclinical data with current evidence on oral iron therapy, heme versus nonheme administration, chelated iron, and vitamin C-assisted absorption.

2. MATERIALS AND METHODS

We evaluated a four-source iron matrix composed of heme iron, glycine chelated iron, ferrous gluconate, and ferrous lactate, together with a natural cofactor fraction derived from camu camu and acerola cherry. We prepared the natural cofactor powder through low-temperature activity-preserving processing and produced the glycine chelated iron fraction by controlled chelation and purification. Three comparator systems were used to separate the contributions of iron-source diversity and natural cofactor replacement.

Our analytical and biological evaluation program included accelerated stability testing of vitamin C under 40 C ± 2 C and 75% ± 5% relative humidity, paddle-method dissolution in pH 4.5 acetate buffer, rat in situ intestinal perfusion to determine iron absorption, and a 28-day rat iron-deficiency anemia model with hemoglobin, hematocrit, serum iron, and serum ferritin as key outcomes.

Table 1. Selected published evidence relevant to a multi-pathway oral iron platform

Published source	Study type	Key result	Relevance to this platform
WHO 2025 anaemia estimates [1]	Global surveillance	Anaemia remains highly prevalent in women, pregnant women, and young children.	Supports the clinical need for improved oral iron delivery.
NIH ODS iron fact sheet [2]	Official guidance	Ferrous forms are more bioavailable than ferric forms; high-dose supplemental iron can cause GI side effects.	Supports the use of soluble ferrous components while motivating lower-burden formulations.
Fischer et al. 2023 [5]	Systematic review and meta-analysis of 17 RCTs	Ferrous bisglycinate increased hemoglobin in pregnant women and reduced GI adverse events relative to other iron supplements.	Supports inclusion of amino acid-chelated iron logic.
Gallo Ruelas et al. 2024 [6]	Systematic review and meta-analysis of 13 RCTs	Heme iron produced a 38% relative risk reduction in total side effects and improved hemoglobin in children with low iron status, although certainty was very low.	Supports adding a heme-associated uptake route.
Teucher et al. 2004; Fidler et al. 2003 [7, 10]	Human absorption studies and review	Ascorbic acid consistently enhances nonheme iron absorption.	Supports natural vitamin C-rich cofactor strategy.

Table 2. Functional roles of the NVTIA component system

Component	Formulation role	Mechanistic contribution
Heme iron	Anchor iron source	Supports uptake through a heme-associated intestinal pathway.
Glycine chelated iron	Chelated iron fraction	Adds an amino acid-chelate transport route and may improve tolerance.
Ferrous gluconate	Rapidly soluble ferrous salt	Supports early luminal availability of absorbable ferrous iron.
Ferrous lactate	Complementary soluble ferrous salt	Extends soluble iron presence and balances release behavior.
Camu camu extract	Natural vitamin C-rich cofactor	Provides reducing capacity and a polyphenol-rich antioxidant matrix.
Acerola cherry extract	Natural vitamin C-rich cofactor	Augments redox support and cofactor stability logic.

3. RESULTS

Beyond the core tablet used for direct comparison, we also generated chewable, film-coated, and oral-solution prototypes, indicating that the platform can be translated across age groups and swallowing preferences without changing the central four-source design.

Under accelerated storage, the natural cofactor system maintained a clear stability advantage. Vitamin C retention in Embodiment 1 remained 93.25% after 6 months, whereas the comparator using synthetic vitamin C substitution fell to 65.17%. The widening gap over time supports the view that the natural cofactor matrix improved preservation of redox-active components.

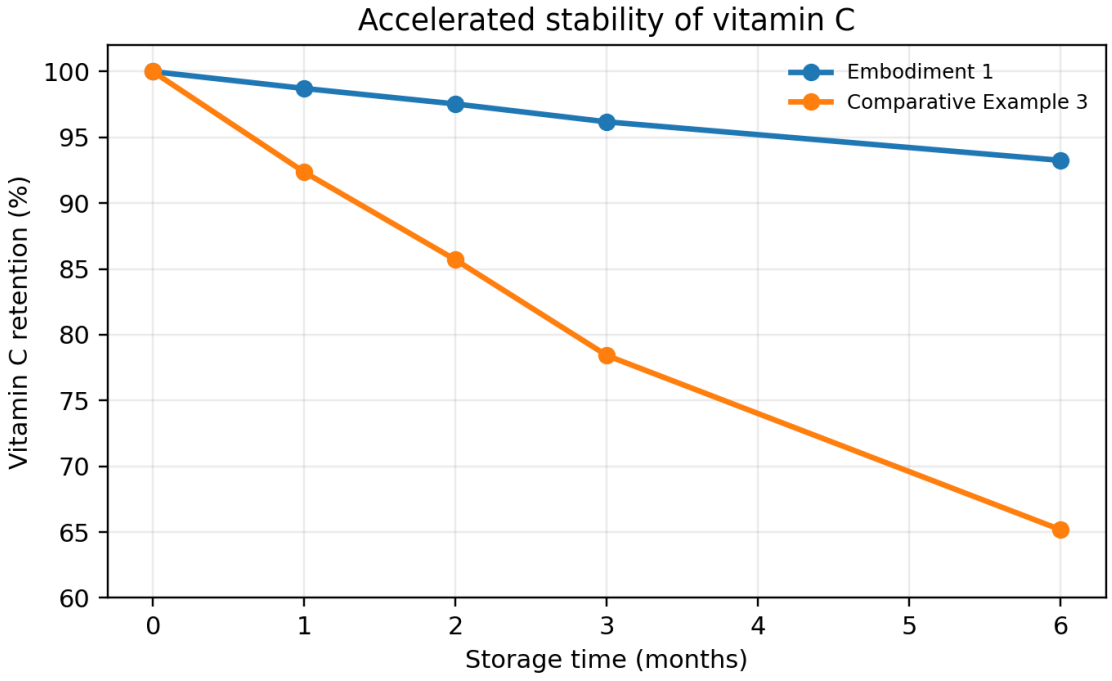

Figure 1. Accelerated stability comparison of the natural cofactor system and a synthetic vitamin C substitution control

Dissolution testing also favored the full NVTIA platform. We observed 38.65% cumulative ferrous dissolution at 5 min and 72.38% at 15 min, both higher than the comparator systems. By 60 min, cumulative dissolution reached 98.26%, indicating near-complete release under the disclosed test conditions.

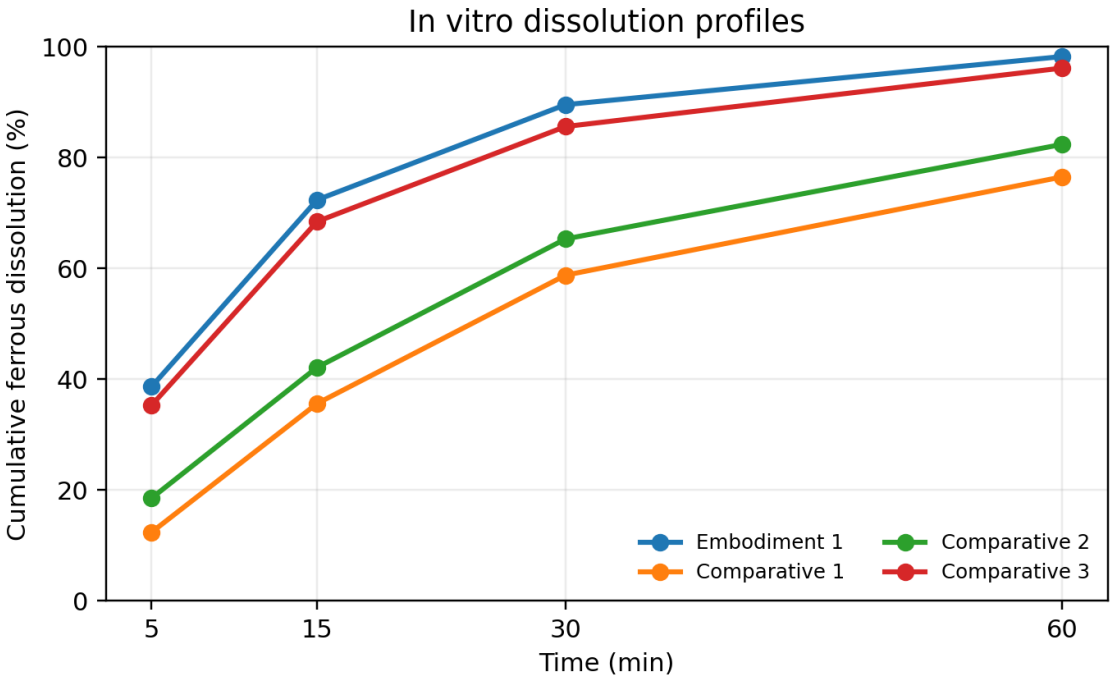

Figure 2. In vitro dissolution profiles of Embodiment 1 and comparator formulations

In the rat in situ intestinal perfusion model, iron absorption reached 38.72% for Embodiment 1, compared with 8.64%, 22.58%, and 29.43% for the three comparator groups. This pattern suggests that both the diversified iron-source strategy and the natural cofactor complex contributed to improved intestinal uptake.

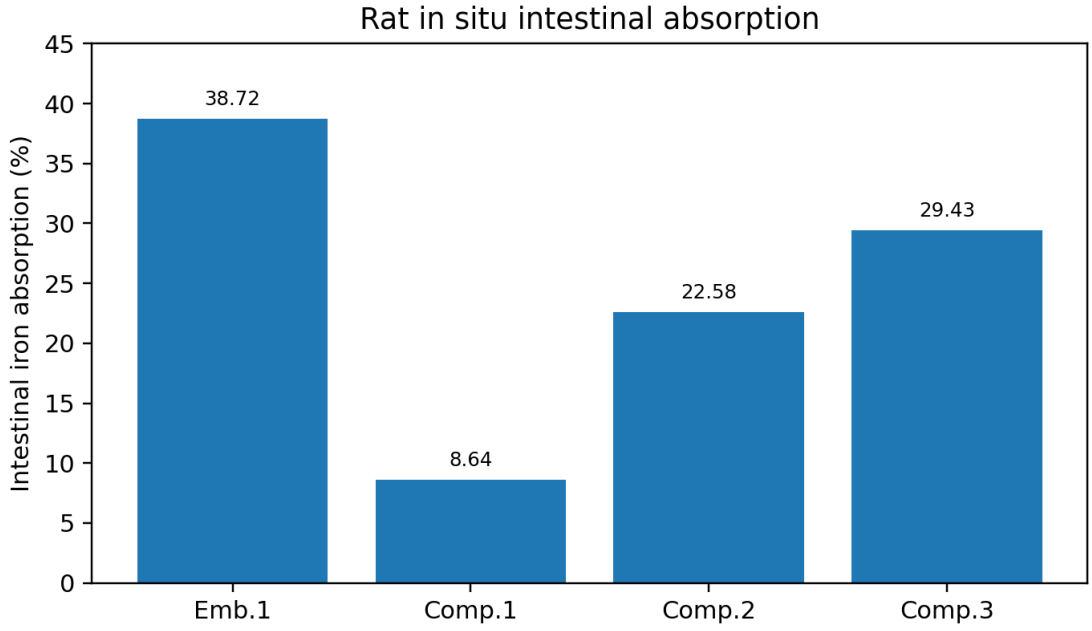

Figure 3. Rat intestinal iron absorption rates across tested formulations

After 28 days in the rat iron-deficiency anemia model, the NVTIA group approached normal-control values more closely than all comparator groups. Hemoglobin rose to 139.76 g/L and serum ferritin to 112.58 microg/L in the NVTIA group, outperforming the three comparator systems across both circulating and storage-associated markers.

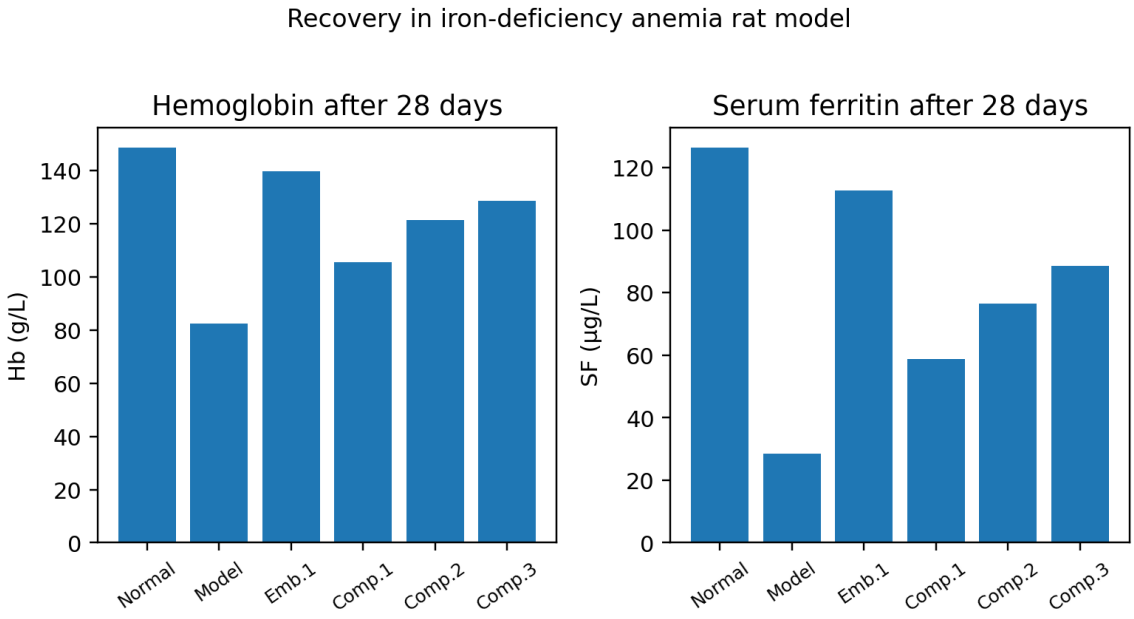

Figure 4. Recovery of hemoglobin and serum ferritin in the rat iron-deficiency anemia model after 28 days

Table 3. Key outcome summary for the NVTIA prototype and comparator formulations

Metric	NVTIA Emb.1	Comp.1	Comp.2	Comp.3
Vitamin C retention at 6 months (%)	93.25	-	-	65.17
Cumulative ferrous dissolution at 60 min (%)	98.26	76.54	82.41	96.18
Intestinal iron absorption in rats (%)	38.72	8.64	22.58	29.43
Hemoglobin after 28 days (g/L)	139.76	105.63	121.47	128.59
Serum ferritin after 28 days (microg/L)	112.58	58.72	76.39	88.46

4. DISCUSSION

The central strength of this platform is not simple ingredient stacking but alignment of multiple absorption logics in one dosage form. The heme fraction broadens intestinal uptake beyond conventional nonheme transport alone, the glycine chelated fraction maps onto a literature-supported amino acid-chelate strategy, and the soluble ferrous salts provide rapid dissolution that can improve early luminal availability [2-6].

Our cofactor design is equally important. Public literature consistently shows that ascorbic acid is one of the most reliable enhancers of nonheme iron absorption [7, 10]. Camu camu and acerola are both described as rich sources of vitamin C and other antioxidant phytochemicals [8, 9]. In our system, these matrices were associated with substantially higher vitamin C retention during accelerated storage than synthetic vitamin C substitution alone, suggesting that the natural matrix contributed both biochemical and formulation-level advantages.

The preclinical findings are also directionally concordant with recent oral iron reviews, which stress that better absorption and fewer gastrointestinal complaints are key determinants of adherence and real-world efficacy [3, 4]. In that context, the current results support the view that a four-source iron strategy can outperform simpler formulations without relying on a single transport mechanism. At the same time, the published evidence base for heme iron in humans remains limited and the certainty of comparative benefits is still low in several populations [6].

We therefore interpret the present results as strong formulation and translational evidence rather than as definitive clinical proof. The next logical step is a rigorously reported human trial with ferritin, hemoglobin, transferrin saturation, tolerability, and adherence as co-primary or hierarchical outcomes.

5. CONCLUSION

We found that a four-source oral iron platform combined with natural vitamin C-rich cofactors achieved favorable stability, dissolution, intestinal absorption, and anemia-model repletion profiles. By integrating heme-associated uptake, amino acid-chelate transport, rapidly soluble ferrous salts, and a redox-supporting natural cofactor layer, the NVTIA system provides a coherent formulation basis for next-stage clinical validation.

DATA AVAILABILITY

All quantitative data analyzed in this article are presented within the main text, tables, figures, and cited references.

CONFLICTS OF INTEREST

The authors declare no competing interests for the purpose of this manuscript.

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