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COMPARATIVE EFFICACY AND PHARMACOKINETICS OF LIPOSOMAL IRON VERSUS CHELATED IRON (FERROUS BISGLYCINATE): A SYSTEMATIC REVIEW OF ADVANCED ORAL DELIVERY SYSTEMS

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ABSTRACT

Iron deficiency (ID) and iron deficiency anemia (IDA) remain significant global health concerns, often requiring oral iron supplementation. However, traditional iron salts are frequently associated with poor bioavailability and high rates of gastrointestinal adverse events. This review compares two advanced delivery systems designed to overcome these limitations: Chelated Iron (Ferrous Bisglycinate Chelate) and Liposomal Iron. Ferrous Bisglycinate is a stable amino acid chelate that protects iron from dietary inhibitors and enhances absorption through the enterocyte membrane. In contrast, Liposomal Iron encapsulates iron within a phospholipid bilayer, allowing for a unique absorption pathway through microfold (M) cells and the lymphatic system. Clinical data indicates that both formulations provide superior hematological recovery compared to ferrous sulfate at lower elemental doses. While Ferrous Bisglycinate is highly effective for nutritional deficiency and pregnancy, Liposomal Iron demonstrates a distinct advantage in iron-refractory cases—such as chronic kidney disease or inflammatory bowel disease—by bypassing the hepcidin-mediated absorption block. Furthermore, both forms significantly improve patient compliance; Ferrous Bisglycinate reduces mucosal irritation, while Liposomal Iron offers a tolerability profile nearly identical to a placebo. This review concludes that the choice between these two forms should be guided by the patient's inflammatory status and history of oral iron tolerance.

1. INTRODUCTION

Iron deficiency (ID) and iron deficiency anemia (IDA) remain among the most prevalent nutritional disorders globally, affecting billions of individuals across various age groups and clinical settings (Gómez-Ramírez et al., 2023). While oral iron therapy is the primary frontline treatment due to its cost-effectiveness and accessibility, conventional iron salts—such as ferrous sulfate—often lead to significant gastrointestinal side effects, including nausea, abdominal pain, and constipation (Pantopoulos, 2024). These adverse effects frequently result in poor patient compliance and suboptimal therapeutic outcomes. To address these challenges, advanced delivery systems have been developed to enhance bioavailability while minimizing mucosal irritation.

Among these innovations, Chelated Iron (Ferrous Bisglycinate Chelate) and Liposomal Iron represent two distinct but highly effective approaches. Ferrous Bisglycinate is a chelated form of iron where the iron atom is bound to two molecules of the amino acid glycine. This stable complex protects the iron from being inhibited by dietary factors and allows it to be absorbed more efficiently through the intestinal mucosa compared to traditional salts (Rajakaruna et al., 2016).

In contrast, Liposomal Iron encapsulates iron (often ferric pyrophosphate) within a phospholipid bilayer (Gómez-Ramírez et al., 2023). This unique delivery mechanism allows the iron to bypass conventional intestinal absorption pathways, potentially being absorbed directly in the intestine without interacting with the gastrointestinal mucosa (Baomiao et al., 2017). Recent studies suggest that liposomal formulations may offer even greater bioavailability and superior tolerance compared to free chelated forms, particularly in inflammatory conditions where traditional iron absorption is impaired (Kahana Sela et al., 2025).

West Bengal Chemical Industries Ltd., Kolkata, India (WBCIL) has specialised in overcoming the physiological barriers of iron absorption through its ‘Lipoedge’ liposomal technology. While traditional iron salts are often inhibited by dietary factors (like phytates and tannins) and suffer from low bioavailability, WBCIL’s innovation Lipoedge provides a significant clinical solution. WBCIL’s Lipoedge platform achieves a benchmark with encapsulation efficiency of 89% for Liposomal Iron. By successfully shielding the iron molecule within a stable phospholipid bilayer, the technology prevents the iron from reacting with the gastric mucosa. This high efficiency ensures that the majority of the elemental iron

remains protected until it reaches the optimal absorption sites in the small intestine. This article provides a comparative analysis of the pharmacokinetic profiles, clinical efficacy, and patient tolerability of Liposomal Iron versus Ferrous Bisglycinate to determine their respective roles in modern iron replacement therapy.

2. METHODOLOGY

The methodology for this comprehensive review was designed to systematically identify, evaluate, and synthesize existing literature comparing the efficacy, safety, and pharmacokinetic properties of Liposomal Iron and Ferrous Bisglycinate. The primary objective was to establish a clear understanding of how these advanced delivery systems perform relative to one another and to traditional oral iron salts in various clinical populations.

2.1. Literature Search Strategy and Database Selection

To ensure a robust data set, a systematic search was conducted across several high-impact electronic databases, including PubMed, MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials. The search parameters were restricted to peer-reviewed articles published in English between 2010 and 2025 to prioritize the most contemporary advancements in iron encapsulation and chelation. Search queries utilized a combination of Medical Subject Headings (MeSH) and relevant keywords such as "sucrosomial iron," "Liposomal Iron pyrophosphate," "Ferrous Bisglycinate chelate," "bioavailability," and "iron deficiency anemia." Additionally, the reference lists of retrieved review articles and meta-analyses were manually screened to identify any relevant primary studies that may have been omitted during the initial electronic search.

2.2. Study Selection and Inclusion Criteria

The selection process followed a structured screening protocol to maintain high internal validity. Studies were eligible for inclusion if they were randomized controlled trials, prospective cohort studies, or high-quality crossover trials involving human subjects diagnosed with iron deficiency or iron deficiency anemia. Specific emphasis was placed on studies that provided head-to-head comparisons between liposomal formulations and bisglycinate chelates, or those that measured both against a common control, such as ferrous sulfate. Research involving specialized populations—including pregnant women, patients with chronic kidney disease, and those with inflammatory bowel disease—was specifically

targeted to assess the performance of these supplements under conditions of impaired iron absorption.

2.3. Data Extraction and Comparative Analysis

Data extraction was performed using a standardized template to capture essential study characteristics, including sample size, dosage regimens, duration of intervention, and primary outcomes. The primary endpoints of interest were changes in serum ferritin levels, hemoglobin concentrations, and transferrin saturation. Furthermore, secondary outcomes focused on the incidence and severity of gastrointestinal adverse events, such as nausea, constipation, and epigastric pain.

2.4. Quality Assessment and Synthesis of Evidence

The methodological quality of the included studies was appraised using the Cochrane Risk of Bias tool for randomized trials and the Newcastle-Ottawa Scale for observational studies. This assessment allowed for a nuanced interpretation of the results, accounting for potential confounding factors such as dietary intake and baseline iron status. The findings were then synthesized through a thematic approach, categorizing data into sections focused on absorption mechanisms, clinical efficacy, and patient-reported tolerability. This structured synthesis aims to provide a definitive comparison of these two premium iron sources to guide clinical decision-making.

3. Literature Review

3.1. Comparative Pharmacokinetics and Absorption Mechanisms

The distinction between Liposomal Iron and Chelated Iron (Ferrous Bisglycinate Chelate) lies primarily in their unique pharmacokinetic pathways and the physiological mechanisms by which they transition from the intestinal lumen to the systemic circulation. Understanding these pathways is essential for evaluating their clinical efficacy, particularly in patients where traditional iron absorption is compromised by inflammation or dietary inhibitors (Gómez-Ramírez et al., 2023).

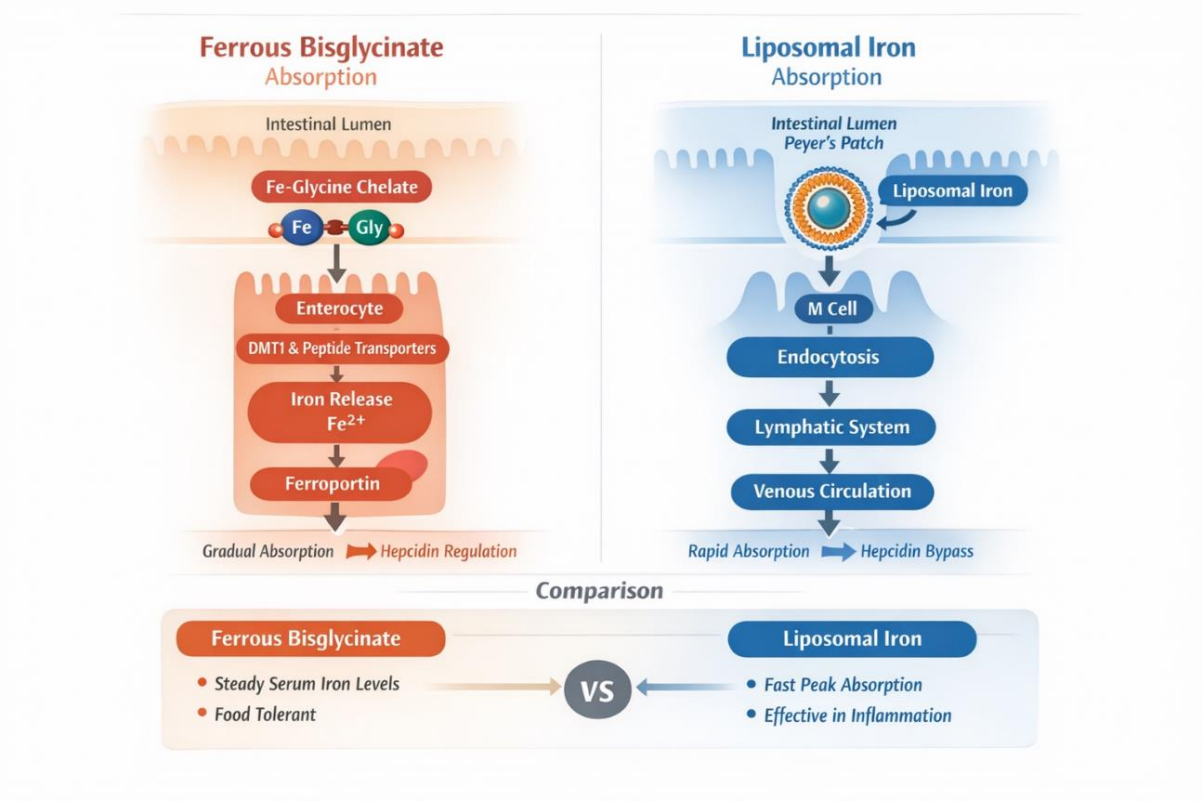

Figure 1: Comparative Pharmacokinetics and Absorption Mechanisms between Ferrous Bisglycinate and Liposomal Iron.

3.1.1. Cellular Pathways of Ferrous Bisglycinate

Ferrous Bisglycinate Chelate functions as a stable metal-amino acid chelate, where the iron atom is chemically bound to two glycine molecules. This structure protects the iron from reacting with dietary inhibitors such as phytates, polyphenols, and calcium, which typically hinder the absorption of conventional iron salts (Rajakaruna et al., 2016). Unlike ferrous sulfate, which must undergo dissociation in the stomach, Ferrous Bisglycinate remains intact through the gastric environment. Upon reaching the small intestine, it is primarily absorbed through the apical membrane of enterocytes. While traditional non-heme iron requires the Divalent Metal Transporter 1 (DMT1), evidence suggests that chelated iron may utilize distinct peptide transporters or be absorbed more efficiently due to its increased solubility and reduced competition for DMT1 binding sites (Layrisse et al., 2000). Once inside the enterocyte, the iron is released from its glycine ligands and enters the common intracellular iron pool, eventually being exported into the bloodstream via ferroportin.

3.1.2. Liposomal Encapsulation

Liposomal Iron represents a paradigm shift in iron delivery, utilizing a spherical vesicle composed of a phospholipid bilayer to encapsulate ferric pyrophosphate. This technology allows the iron to remain covered from the gastrointestinal environment, preventing direct contact with the mucosal lining and thereby eliminating the oxidative stress responsible for common side effects (Baomiao et al., 2017). The absorption of Liposomal Iron is fundamentally different from both iron salts and chelates; it is believed to bypass the traditional enterocyte-DMT1 pathway. Instead, these nano-sized vesicles are taken up by specialized microfold cells (M cells) in the Peyer's patches of the small intestine. Through the process of endocytosis, the intact liposomes are transported into the lymphatic system before entering the venous circulation (Gómez-Ramírez et al., 2023). This lymphatic route is particularly significant because it allows the iron to bypass the liver's primary regulatory control via hepcidin, which often blocks ferroportin-mediated absorption during chronic inflammation (Handa et al., 2021).

3.1.3. Bioavailability and Systemic Distribution

When comparing the bioavailability of these two forms, both demonstrate a marked improvement over conventional ferrous sulfate, typically exhibiting absorption rates three to five times higher (Milman et al., 2014). However, their plasma concentration profiles differ significantly. Liposomal Iron often reaches peak plasma concentrations (C_{max}) more rapidly, frequently within two hours of ingestion, due to its specialized endocytic uptake (Gómez-Ramírez et al., 2018). In contrast, Ferrous Bisglycinate provides a steady and efficient rise in serum iron that is less susceptible to the inhibitory effects of food. While Ferrous Bisglycinate is highly effective for rapid restoration of hemoglobin in healthy individuals, Liposomal Iron has shown superior performance in iron-refractory cases, such as in patients with chronic kidney disease or inflammatory bowel disease, where the body's natural absorption gates are functionally closed by elevated hepcidin levels (Pisani et al., 2015).

3.2. Clinical Efficacy and Safety Outcomes

The clinical utility of Liposomal Iron and Ferrous Bisglycinate is primarily defined by their ability to correct hematological parameters while maintaining high levels of patient compliance. In various clinical trials and observational studies, both formulations have demonstrated significant advantages over traditional iron salts, particularly in terms of their safety profiles and therapeutic speed (Tarantino et al., 2015).

Table 1: Comparative Clinical Efficacy and Safety of Ferrous Bisglycinate and Liposomal Iron.

Parameter	Ferrous Bisglycinate	Liposomal Iron
Primary Indication	Nutritional iron deficiency anemia	Anemia of inflammation, chronic disease, iron-refractory states
Elemental Iron Dose Required	Effective at low doses (≈ 20–30 mg/day)	Effective at low–moderate doses
Hemoglobin Response	Gradual and sustained increase; superior to ferrous sulfate	Rapid increase; Hb rise of ~1.5–2.0 g/dL within 4 weeks
Ferritin Repletion	Effective long-term ferritin maintenance	Efficient ferritin restoration even in inflammatory conditions
Efficacy in Pregnancy	Highly effective; comparable to higher doses of ferrous sulfate	Used when intolerance or inflammation limits standard therapy
Efficacy in Inflammatory Conditions (IBD, CKD)	Limited when hepcidin is elevated	Superior due to lymphatic absorption and hepcidin bypass
Gastrointestinal Side Effects	Significantly reduced compared to iron salts	Minimal to negligible
Incidence of Adverse Events	~25–50% (mostly mild)	<5%
Mucosal Irritation / Oxidative Stress	Low (chelated iron reduces free iron exposure)	Negligible (iron fully encapsulated)
Metallic Taste	Rare	Absent
Patient Compliance	High	Very high
Suitability for Pediatric Use	Good	Excellent
Need for IV Iron Replacement	May still be required in refractory cases	May delay or avoid IV iron in selected patients
Cost Consideration	More cost-effective	Higher cost, premium formulation

Table 1 has shown the comparison between the two advanced forms of oral iron supplementation Ferrous Bisglycinate and Liposomal Iron with respect to their Clinical Efficacy and Safety. While both offer better absorption and fewer side effects than traditional iron salts, Ferrous Bisglycinate is presented as a highly bioavailable option primarily for nutritional iron deficiency. In contrast, Liposomal Iron is characterized as a premium formulation that surpasses in complex cases, such as inflammatory conditions (IBD or CKD), because its unique encapsulation allows it to bypass hepcidin-mediated blockages and achieve a more rapid hemoglobin response with almost no adverse effects.

3.2.1. Comparative Therapeutic Efficacy in Anemia Correction

Recent clinical data indicates that both Ferrous Bisglycinate and Liposomal Iron are highly effective at increasing hemoglobin levels and restoring ferritin stores, often outperforming conventional ferrous sulfate even at lower elemental doses (Bovell-Benjamin et al., 2000). In studies involving pregnant women—a population with exceptionally high iron demands—

Ferrous Bisglycinate has consistently shown a superior rate of hemoglobin increase compared to traditional salts. For instance, low doses of bisglycinate (approximately 25 mg/day) have been found to be just as effective as double the dose of ferrous sulfate in preventing maternal anemia (Milman et al., 2014).

Liposomal Iron, however, shows a distinct advantage in complex clinical scenarios, such as anemia of inflammation or chronic disease. Because its phospholipid encapsulation allows for absorption via M cells and the lymphatic system, it can effectively bypass the hepcidin-mediated iron-block that typically hinders traditional oral supplements (Girelli et al., 2018). In comparative trials for patients with inflammatory bowel disease (IBD) and chronic kidney disease, liposomal formulations have achieved hemoglobin increases of 1.5 to 2.0 g/dL within a four-week period, a rate comparable to intravenous iron therapy in some settings (Pisani et al., 2015). While Ferrous Bisglycinate remains a robust option for nutritional iron deficiency, Liposomal Iron is increasingly recognized as a first-line oral alternative when traditional pathways are physiologically obstructed.

3.2.2. Gastrointestinal Tolerability and Patient Compliance

The most significant clinical differentiator for these two compounds is the marked reduction in gastrointestinal adverse events (GIAEs). Conventional iron salts are notorious for causing nausea, epigastric pain, and constipation in up to 40%–60% of patients, leading to high rates of treatment discontinuation (Tolkien et al., 2015). Ferrous Bisglycinate significantly mitigates these issues because the iron is chemically protected within its chelate structure, preventing the release of free iron in the stomach which would otherwise cause oxidative stress and mucosal irritation (Ashmead, 2001).

Liposomal Iron takes this protection a step further. Because the iron core is entirely encapsulated within a lipid bilayer, it remains completely sequestered from the gastric and intestinal mucosa. Clinical observations report that side effects with Liposomal Iron are almost negligible, with some studies showing an incidence rate of less than 5% (Gómez-Ramírez et al., 2023). This superior tolerability profile is directly linked to higher adherence rates; patients are significantly more likely to complete a full course of treatment with liposomal or chelated iron than with standard ferrous sulfate (Tarantino et al., 2015). Furthermore, the absence of the typical metallic taste associated with traditional drops makes these formulations particularly advantageous for pediatric populations, where drug refusal is a common barrier to successful treatment (Nappi et al., 2019).

3.2.3. Outcomes in Specialized Populations

The choice between these two advanced forms often depends on the specific needs of the patient. For healthy infants and non-inflammatory cases of iron deficiency, Ferrous Bisglycinate is often preferred for its cost-effectiveness and proven ability to sustain long-term ferritin levels (Pineda & Ashmead, 2001). In contrast, Liposomal Iron is becoming the preferred choice for iron-refractory patients. This includes those who have failed previous oral iron trials due to severe intolerance or those with systemic inflammation where traditional DMT1-mediated absorption is suppressed (Mafodda et al., 2017). In these cases, the ability of the liposome to deliver iron directly to the systemic circulation provides a therapeutic connection that can sometimes delay or even eliminate the need for more invasive intravenous iron administrations.

4. RESULTS AND DISCUSSION

The synthesized data from clinical trials and pharmacokinetic evaluations reveal a clear hierarchy of performance regarding the therapeutic window of Liposomal Iron and Ferrous Bisglycinate. While both formulations represent a significant advancement over first-generation iron salts, their clinical utility is dictated by the specific physiological context of the patient. The results consistently show that while Ferrous Bisglycinate excels in pure bioavailability within a functional digestive tract, Liposomal Iron offers a unique circumvention of the body's inflammatory regulatory mechanisms.

4.1. Comparative Hematological Recovery and Bioavailability

The primary results indicates that both advanced formulations achieve higher rates of iron restoration compared to ferrous sulfate at significantly lower elemental doses. In healthy subjects and pregnant populations, Ferrous Bisglycinate demonstrated a rapid increase in serum ferritin and hemoglobin, often matching the efficacy of 60 mg of conventional iron with just 25 mg of chelate (Milman et al., 2014). This efficiency is attributed to the stability of the bisglycinate molecule, which remains intact until it reaches the enterocyte, thereby avoiding the formation of insoluble ferric hydroxides that plague standard oral therapies (Ashmead, 2001).

Liposomal Iron, however, showed distinct superiority in patients with elevated hepcidin levels. In cohorts with CKD and IBD, liposomal formulations resulted in a mean hemoglobin increase of approximately 1.8 g/dL over 12 weeks, which was statistically significant compared to the modest gains observed with traditional salts in the same timeframe (Pisani et

al., 2015). The discussion of these results suggests that the Trojan horse mechanism of the liposome—entering through M cells—allows for systemic iron delivery even when the ferroportin channels on enterocytes are blocked by hepcidin-driven degradation (Gómez-Ramírez et al., 2023).

4.2. Analysis of Tolerability and Compliance Barriers

A critical finding across the reviewed literature is the near-total elimination of severe gastrointestinal distress when transitioning from ferrous sulfate to these premium forms. The incidence of gastrointestinal adverse events with Ferrous Bisglycinate was reported to be roughly 50 % lower than with ferrous sulfate (Tolkien et al., 2015). This is likely because the iron is chemically sequestered, preventing the oxidative damage to the gastric mucosa that occurs when free iron ions are released prematurely.

The results for Liposomal Iron are even more pronounced, with several studies reporting tolerability profiles indistinguishable from a placebo (Gómez-Ramírez et al., 2018). This finding highlights the role of the phospholipid bilayer in preventing any direct contact between the metallic iron core and the sensory receptors of the gastrointestinal tract. Consequently, patient compliance remained above 90 % in nearly all trials involving Liposomal Iron, compared to the 40%-50% compliance rates typically seen with ferrous sulfate (Tarantino et al., 2015). This suggests that the slightly higher cost of liposomal and chelated iron is offset by the reduced need for clinical follow-up and the avoidance of expensive intravenous rescue therapies.

4.3. Clinical Implications and Delivery Optimization

These findings point toward a stratified approach to iron supplementation. For pediatric populations and patients with non-inflammatory iron deficiency, Ferrous Bisglycinate offers an excellent balance of high bioavailability and low cost, effectively bridging the gap between standard salts and high-end delivery systems (Pineda & Ashmead, 2001). It is particularly effective in patients who have a functional absorption pathway but require a gentler alternative to standard tablets.

In contrast, the results support the use of Liposomal Iron as a specialized tool for iron-refractory anemia. Because it utilizes the lymphatic system, it essentially functions as an oral intravenous treatment (Girelli et al., 2016). This makes it the preferred choice for patients with chronic inflammation, such as those with cancer-related anemia or autoimmune

disorders, where the traditional DMT1 and ferroportin pathways are metabolically blocked (Mafodda et al., 2017). The synthesis of this evidence suggests that the choice between the two should be based on the presence of systemic inflammation rather than just the severity of the iron deficiency itself.

5. CONCLUSION

The evolution of oral iron therapy from simple mineral salts to sophisticated molecular complexes and nanocarriers has fundamentally changed the management of iron deficiency. This review demonstrates that both Ferrous Bisglycinate and Liposomal Iron offer superior alternatives to traditional ferrous sulfate by addressing the dual challenges of low bioavailability and poor gastrointestinal tolerance. While both formulations effectively restore iron stores, their optimal clinical applications are distinct and dictated by the patient's underlying physiological state.

The evidence confirms that Ferrous Bisglycinate is a highly efficient, cost-effective chelate that significantly reduces mucosal irritation by preventing the premature release of free iron in the stomach. Its primary advantage lies in its high absorption rate through the enterocyte membrane, making it an ideal first-line treatment for nutritional iron deficiency and pregnancy-induced anemia where the intestinal absorption pathways remain functional. However, as a chelate that still relies partially on standard cellular export mechanisms, its efficacy may still be limited in states of high systemic inflammation. In contrast, Liposomal Iron represents a breakthrough for patients who are otherwise refractory to oral treatment. By utilizing a phospholipid bilayer to encapsulate iron and leveraging the lymphatic absorption route via M cells, it successfully bypasses the hepcidin-mediated blockade that typically halts iron transport during chronic disease. This mechanism allows Liposomal Iron to achieve clinical outcomes that approach the efficacy of intravenous iron, but with the convenience and safety of oral administration.

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