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Article

Improving Stability and Absorption of Minerals in Pharmaceutical Formulations: A Review of Emerging Strategies

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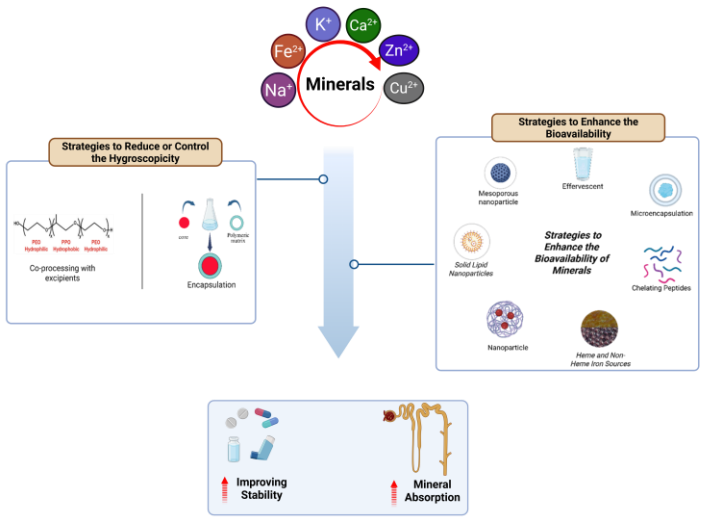
Abstract

Minerals are essential for numerous physiological functions. However, their application in pharmaceutical formulations is often limited by hygroscopicity and low bioavailability, which can diminish their therapeutic effectiveness. This article reviewa not only highlights these challenges but also provides an in-depth, up-to-date evaluation of various strategies designed to overcome these limitations, supported by quantitative data from recent literature. This review article emphasizes the role of co-processing with excipients and encapsulation technology, which improve mineral stability by creating an effective moisture barrier, thereby extending product shelf life. Effervescent formulations, through an acid-base reaction, generate gas that significantly enhances mineral solubility and contributes to increased bioavailability. Microencapsulation, using a polymer or protein layer, protects minerals from gastric degradation and allows for controlled release in the intestine, the primary site of absorption. Chelating peptides form stable complexes with mineral ions, improving their transport and uptake in the body. Meanwhile, advanced nanoparticle technologies like Solid Lipid Nanoparticles and liposomes increase the contact surface area, accelerate dissolution, and protect minerals from oxidative degradation. This review article offers a comprehensive overview of strategies that can significantly advance the development of more effective and stable mineral-based pharmaceuticals.

Keywords: *Bioavailability; hygroscopic; minerals; moisture barrier; stability.*

Graphical Abstract



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Introduction

Minerals are essential for human health, both as nutrients needed for the body to function properly and as key ingredients in the production of pharmaceutical and biomedical products [1,2]. For example, they are used to produce calcium supplements in the pharmaceutical [3] and serve as imaging agents in biomedical diagnostics [4]. Minerals are commonly classified into two categories: macrominerals and microminerals [5]. Macrominerals include calcium (Ca), magnesium (Mg), potassium (K), sodium (Na), chloride (Cl), phosphorus (P), and sulfur (S) whilemicrominerals include iodine (I), zinc (Zn), selenium (Se), iron (Fe), manganese (Mn), copper (Cu), cobalt (Co), molybdenum (Mo), fluoride (F), and chromium (Cr) [6,7]. These minerals are required for various physiological functions, including the formation of strong bones and teeth, nerve signal transmission, muscle contraction, and maintaining cardiovascular health [8–10]. For instance, macrominerals such as calcium, phosphorus, and fluoride are vital for bone and dental health, while magnesium, zinc, and copper serv e as cofactors in various enzymatic processes that regulate metabolism and cellular function [11,12]. Additionally, these minerals support normal heart rhythms, assist in hormone production, and play a crucial role in immune function [12]. Minerals have been used in the pharmaceutical industry as active ingredients in various applications, including nutritional supplements, imaging agents, advanced drug delivery systems, and as bioactives in regenerative therapy [13]. However, the integration of minerals in pharmaceutical formulations presents significant challenges, primarily due to issues with hygroscopicity and low bioavailability [4,14,15].

The challenge in formulating minerals lies in their hygroscopic nature and low bioavailability, which can negatively affect the effectiveness and stability of pharmaceutical preparations [16]. The hygroscopic of minerals, which is their ability to absorb moisture from the environment, can affect the physical and chemical stability of pharmaceutical preparations. Additionally, low bioavailability can limit the body's ability to efficiently absorb minerals, thereby reducing their therapeutic potential [17,18]. This approach must take into account various factors, including particle size, crystal form, and the use of excipients that can modify the physical and chemical properties of minerals for improved stability and absorption[19]. Various techniques such as encapsulation in nanoparticles, the use of binding compounds, and drug delivery technology based on liposomes can be used to enhance solubility and improve the bioavailability of minerals in pharmaceutical formulations [20,21]. This review article provides a comprehensive insight into various formulation methods applied to enhance the stability of minerals in pharmaceutical formulations, including microencapsulation, the use of complex minerals with carriers, and the utilization of advanced drug delivery technologies. Furthermore, this review highlights the key formulation challenges, particularly moisture sensitivity and low bioavailability, which can compromise the physical stability and therapeutic effectiveness of mineral-based products. Addressing these limitations is essential to ensure optimal delivery, sustained bioactivity, and overall therapeutic efficacy in clinical use.

Materials and Methods

The research methodology in this study is structured systematically to provide an in-depth literature review on formulation strategies aimed at enhancing the stability of minerals in pharmaceutical formulations. The methodology framework is designed to

explore key focus areas of mineral formulation, specifically how to maintain the stability of active ingredients, reduce detrimental interactions, and improve bioavailability. The methodology for this review involved a systematic approach to identify, analyze, and synthesize existing literature on mineral formulation strategies, providing a clear and detailed insight into this topic.

Tools and Materials

Literature search was conducted using two primary databases, namely PubMed and Google Scholar, which allow access to relevant and literature widely recognized in biomedical and pharmaceutical research. Keywords used in the article search included "Mineral Formulation AND Mineral Stability AND Hygroscopic Mineral AND Bioavailability Mineral" and "Mineral Formulation OR Mineral Stability OR Hygroscopic Mineral OR Bioavailability Mineral either individually or in combination. All articles found were managed using Mendeley reference management software to facilitate the organization and documentation of the literature.

Article Selection Criteria

The articles identified through the initial search were filtered based on predefined inclusion and exclusion criteria. Inclusion Criteria: The inclusion criteria cover articles published between 2018 and 2025, freely accessible, and original research discussing the application of formulation technology to improve mineral stability in pharmaceutical preparations. Articles focusing on strategies to address hygroscopicity and low mineral bioavailability in pharmaceutical products are of primary interest. Exclusion Criteria: The exclusion criteria include articles that are irrelevant to the topic of mineral stability, research conducted outside the context of pharmaceutical formulations, and duplicate articles. In addition, we excluded review articles, conference abstracts, non–peer-reviewed papers, and other forms of secondary publications. These restrictions ensured that all articles included in the analysis represented original primary research. The article selection process follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, designed to ensure transparency and quality in the collection and analysis of literature. Figure 1, illustrating the steps in article selection, from the initial literature search to the selection of articles that meet the research criteria (A PRISMA flowchart). As a result, 31 articles meeting the inclusion criteria were selected for further analysis.

Data Presentation and Conclusion Drawing

The analyzed data is presented in the form of tables, graphs, and descriptive narratives, as commonly done in systematic review research [22]. All stages of analysis are carried out independently by three researchers to ensure objectivity. The results of each analysis are then compared and discussed to ensure reliability and reduce potential bias in data interpretation.

Research Procedure.

This research procedure prioritizes validity through the selection of credible, high-quality articles. The establishment of inclusion and exclusion criteria aims to minimize potential bias and ensure the accuracy of the data to be analyzed. The data analysis process is carried out in four main stages.

Data Reduction: Each selected article is thoroughly read to understand its context and identify the key findings within [22]

Findings Recording: The key points from each article are recorded based on the conceptual framework established in this research. The conceptual framework for this research is based on two primary challenges in mineral formulation: hygroscopic nature and low bioavailability. Accordingly, the findings from each analyzed article were categorized and documented based on the formulation strategies that address these challenges. Additional findings that contribute to the formation of new insights are also documented [22].

Thematic Grouping: The notes collected from various articles are grouped into specific themes. These themes are then developed into thematic concepts that describe the mineral formulation [22].

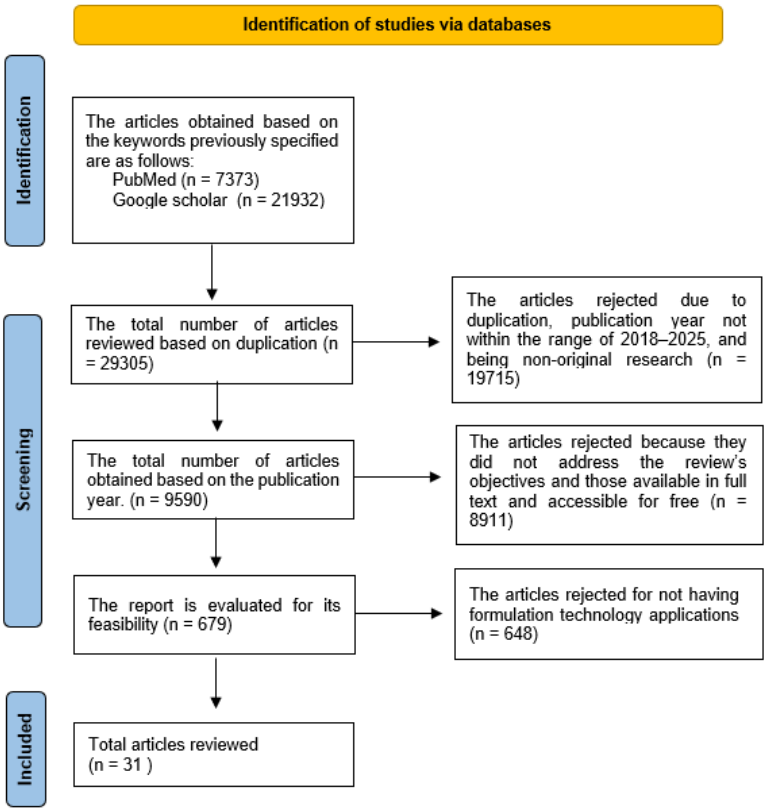

Figure 1. PRISMA Flowchart

Result and Discussion

Minerals play a vital role in the body, performing necessary functions ranging from building strong bones to transmitting nerve impulses - essential for sustaining physiological homeostasis and longevity [23]. The presence of a range of minerals is essential for various physiological processes, including acting as cofactors for enzymes involved in hormone synthesis and regulating normal heart rhythms. The role of macrominerals such as calcium (Ca), magnesium (Mg), potassium (K), sodium (Na), chloride (Cl), phosphorus (P), and sulfur (S) is required in larger amounts. Macrominerals are integral to bone health, muscle function, and metabolic processes [3]. For example, calcium intake has been investigated in relation to a reduced risk of obesity and certain cancers, though the evidence remains mixed[24]. Iodine (I), zinc (Zn), selenium (Se), iron (Fe), manganese (Mn), copper (Cu), cobalt (Co), molybdenum (Mo), fluoride (F), chromium (Cr), and boron (B) are essential for enzymatic functions and immune responses. For instance, iron is

crucial for oxygen transport and energy metabolism [25]. Mineral deficiencies can lead to health problems such as anemia, osteoporosis, and muscle weakness [26].

The formulation of minerals in the pharmaceutical industry faces several significant challenges, namely high hygroscopicity and low bioavailability. These two factors not only affect product stability but also its effectiveness in therapeutic applications. High hygroscopicity can lead to various issues in pharmaceutical formulations, including changes in the physicochemical properties of the substances, which result in difficulties in subsequent formulation processes, instability during storage, and negative effects on bioavailability [27,28]. Hygroscopicity is the ability of a substance to absorb moisture from the surrounding environment [29,30]. Minerals with high hygroscopic properties tend to undergo significant physical changes when exposed to moisture, such as changes in texture, particle size, or even undesirable chemical reactions. This is a major problem in pharmaceutical formulations, where product stability during storage and transport is crucial. When minerals absorb moisture, chemical degradation or changes in solubility can occur, ultimately reducing the effectiveness of the active ingredients. Moreover, improper storage conditions can accelerate this process, reduce shelf life, and make the product more prone to damage [31]. For example, mineral salts such as calcium and magnesium are highly affected by high humidity, which can influence chemical stability and reduce therapeutic potential [31,32]. In addition to hygroscopicity, low mineral bioavailability is also a significant challenge in pharmaceutical formulations. Bioavailability refers to the extent to which the body can absorb and utilize active ingredients once administered. Certain minerals, such as calcium, magnesium, and potassium, often have low bioavailability when consumed in conventional pharmaceutical formulations [34]. This can be due to various factors, including low solubility, binding with other components in the digestive system that hinder absorption, or the body's inability to efficiently metabolize the minerals [35]. Minerals that are poorly absorbed do not provide optimal therapeutic benefits [36], even when administered in sufficient doses. Therefore, efforts to enhance mineral bioavailability are crucial to ensure that mineral-based supplements or medications can provide significant therapeutic effects [37].

Strategies to Reduce or Control the Hygroscopicity of Minerals.

Common formulation strategies applied to reduce the hygroscopic properties of minerals include co-processing with excipients and encapsulation. Co-processing with excipients involves combining the active ingredient with hydrophobic excipients to reduce the mineral's ability to absorb moisture. Meanwhile, encapsulation refers to the process of coating a product with a wall material to shield it from environmental factors [38]. This method presents a promising approach for enveloping minerals, aiming to preserve their therapeutic function, control their release, and enhance their solubility. Furthermore, encapsulation can effectively reduce hygroscopicity, which facilitates preparation and extends shelf life. During this process, minerals are dispersed within a matrix of wall materials and subsequently encapsulated within a particulate structure. Common encapsulation techniques include spray drying, freeze drying, and coacervation [39]. Figure 2 illustrates strategies to reduce or control mineral hygroscopicity, while Table 1 summarizes specific formulation approaches.

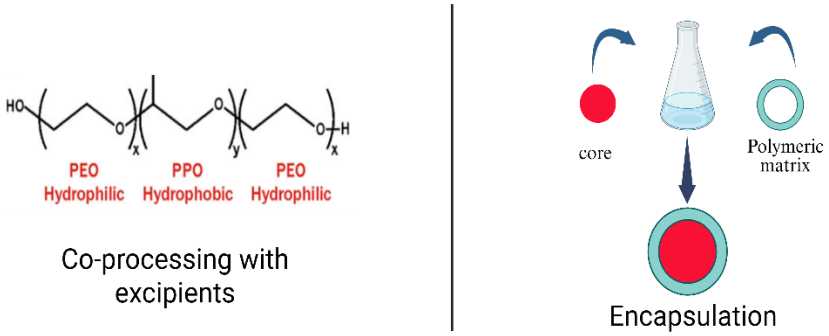

Figure 2. Strategies to Reduce or Control the Hygroscopicity of Minerals

Table 1. Application of Strategies to Reduce Hygroscopicity of Minerals

No	Active Ingredient	Strategy	Polymer	Findings	Ref.
1	Sodium chloride	Co-processing with excipients	Pluronic	Significant reduction in hygroscopic growth (>50%)	[32]
2	Sodium chloride	Encapsulation	$Si0_2$	Protects particles from air moisture and slows down deliquescence.	[40]

Pharmaceutical dosage forms generally consist of active ingredients combined with various excipients, which support the manufacturing process and ensure stability and effective delivery of the active ingredient. Most excipients used must be inert, meaning they do not affect the therapeutic effects of the active ingredient or cause unwanted changes such as phase changes or reduced stability during production and storage [41]. Excipients can be added to improve stability and reduce the hygroscopicity of pharmaceutical dosage forms by forming protective barriers or absorbing ambient moisture preferentially. co-processing with excipients to formulate the active ingredients with hydrophobic excipients to divert water away from the actives and encapsulation to envelop the active ingredients with polymers via spray-drying. Some commonly used co-processing techniques in pharmaceutical dosage form manufacturing include wet granulation, solution-based methods, and physical blending, followed by drying processes such as freeze-drying, oven drying, fluidized bed drying, or air drying [39]. Table 1 provides an example of co-processing strategies using excipients to reduce mineral hygroscopicity. For example, Haddrell et al [32] revealed that the addition of Pluronic F127, even at low concentrations (about 1% by weight), effectively reduced the hygroscopic growth of aerosols, which typically occurs when aerosols are exposed to environmental moisture. This finding indicates that F127 can be used to control or reduce the ability of aerosol particles to absorb moisture, which in turn can improve the stability of aerosol products and enhance drug delivery in nebulizer applications. Bermeo et al [40] showed that sodium chloride coated with

SiO_2 acts as an effective physical barrier against water vapor, protecting particles from environmental moisture and significantly slowing down the deliquescence process. This coating forms a relatively inert and stable structure, which not only prevents direct contact between particles and water vapor but also maintains the morphological integrity of the particles in high humidity conditions.

Strategies to Enhance the Bioavailability of Minerals

The chemical and physiological characteristics of the environment often hinder the optimal absorption and utilization of minerals in pharmaceutical and nutritional formulations. Therefore, various approaches have been developed and applied to significantly improve the bioavailability of active mineral ingredients. These methods carefully address common issues such as poor solubility, susceptibility to degradation, and adverse interactions within the gastrointestinal tract. Ultimately, this ensures improved absorption and clinical efficacy. Figure 3 illustrates the formulation strategies used to enhance mineral bioavailability, while Table 2 provides specific applications of these approaches.

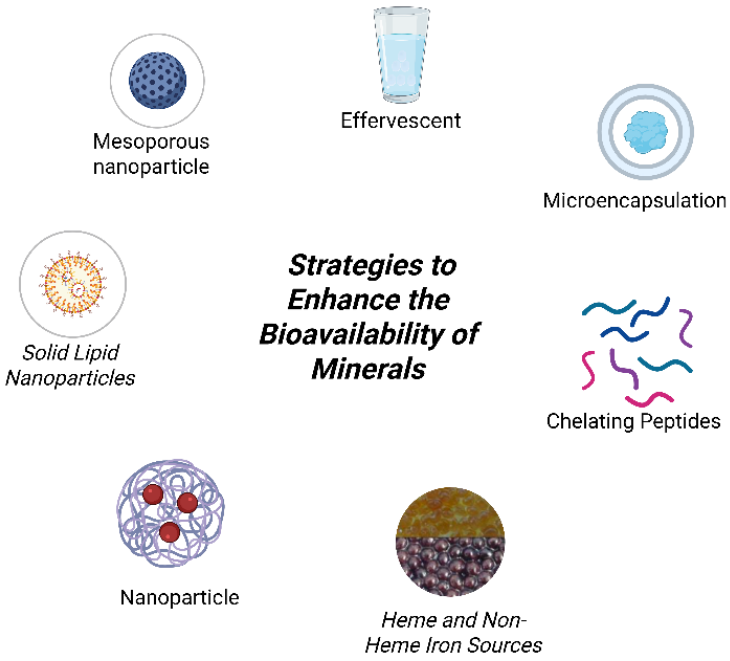

Figure 3. Strategies to Enhance the Bioavailability of Minerals

Enhancing the bioavailability of minerals is crucial for improving nutritional and pharmaceutical preparations, as physiological barriers often hinder optimal absorption [71], [72]. Innovative strategies to enhance mineral bioavailability include conventional formulation approaches (effervescent systems, microencapsulation, and chelating peptides) as well as advanced nanotechnology-based carriers (nanoparticles, solid lipid nanoparticles, mesoporous particles, and liposomes).

Table 2. Application of Strategies to Enhance the Bioavailability of Minerals

No	Active Ingredient	Strategy	Findings	Ref.
1	Ferro ascorbate	Formulated into effervescent	Bioavailability increased significantly (>70%) compared to IR tablets (15-30%).	[42]
2	Magnesium	Effervescent	Increased serum magnesium by 0.24 mM ($p < 0.0001$) and serum bicarbonate by 3 mM ($p = 0.015$).	[43]
3	Iron	Microencapsulation	Microencapsulation was most effective, achieving 29% bioaccessibility of iron.	[44]
4	Magnesium	Microencapsulation	10.3% increase in magnesium bioavailability.	[45]
5	Zinc and calcium	Microencapsulation	Microspheres released high amounts of calcium, phosphorus, and zinc, distributed throughout the defective region	[46]
6	Calcium	Microencapsulation	Enhances calcium bioavailability by improving the therapeutic performance	[47]
7	Calcium	Microencapsulation	Enhances calcium bioavailability, reaching up to 32%.	[48]
8	Zinc	Zinc-chelating peptide	40% increase in absorption rate.	[49]
9	Zinc	Zinc chelation	An oyster protein hydrolysates-zinc complex (OPH-Zn) showed antioxidant bioactivity and enhanced zinc bioaccessibility.	[50]
10	Iron	Zinc chelation	High iron content (31.3 ± 1.4 to 61.1 ± 4.4 mg Fe/g dried beads) and high EE% (57.6 ± 7.7% to 78.5 ± 2.9%). Ferrous bis-glycinate chelate increases iron bioavailability by 23%.	[51]
11	Calcium	Chelating peptides	Calcium solubility of the 65.27% ± 2.75% was significantly higher than that of calcium chloride (38.99% ± 5.77%).	[52]
12	Calcium	Chelating peptides	Calcium absorption rate in rats, reaching 42.47% for the Chelating peptides -Ca group, which was substantially higher than the 31.23% observed in the control group.	[53]
13	Calcium	Chelating peptides	Chelation rate of 78.38%, calcium transport increased significantly compared to $CaCl_2$ in the Caco-2 cell model and calcium retention: ~88.39% after 2 hours of simulated gastric digestion.	[54]

No	Active Ingredient	Strategy	Findings	Ref.
14	Ferrous iron	Chelating peptides	Enhancing the transport, cellular retention, and utilization of iron.	[55]
15	Iron	Chelating peptides	Enhancing iron absorption, bioavailability increased from 72.85% to 81.33%.	[56]
16	Calcium	Chelating peptides	The absorption rate for the control group was only 60.52% and chelating peptides group was 68-73%.	[57]
17	Zinc	Nanoparticles	64.5% increase in zinc bioavailability.	[58]
18	Zinc	Nanoparticles	The bioavailability of $ZnSO_4$ dropped sharply to only 28.71% whereas ZnPNPs remained comparatively stable at 44.72%.	[59]
19	Zinc	Nanoparticles	zinc solubility declined markedly to approximately 32% within 3 hours. By contrast, the nanoparticle-mediated system maintained zinc solubility at nearly 100% over the same period.	[60]
20	Zinc	Nanoparticles	The serum zinc concentration in rats receiving nanoparticle increased markedly to 3.67 ± 0.25 μg/mL, in the control group receiving no zinc supplementation (2.32 ± 0.22 μg/mL) and in the group administered S-ZnO at the same dosage (2.43 ± 0.14 μg/mL).	[61]
21	Zinc	Nanoparticles	The expression of the osteocalcin (OC) gene was significantly upregulated and strongly correlated with bone mineralization levels (r = 0.84),	[62]
22	Zinc	Nanoparticles	Significantly enhance zinc bioavailability, plasma zinc concentrations markedly increased to 1.78 μg/mL.	[63]
23	Iron	Solid Lipid Nanoparticles (SLN)	SLN protects encapsulated iron in gastric fluid and releases almost 80% of iron in intestinal fluid.	[64]
24	ferrous sulphate	Solid Lipid Nanoparticles (SLN)	Drug release from SLN structure and ferrous sulfate tablets in phosphate-buffered saline at pH = 7.4 show higher and sustained release, almost double the free drug.	[65]
25	Iron	Mesoporous iron particles	Superior bioavailability of MIP compared to commercial iron particles.	[66]

No	Active Ingredient	Strategy	Findings	Ref.
26	Ferrous sulphate	Liposomes	Encapsulation efficiency higher than 97%, optimal short-term and long-term stability, and excellent bioavailability in Caco-2 cell lines.	[67]
27	Cupric	Liposomes	pH-sensitive copper release, releasing 36/78% and 47/94% of copper at pH 6/4.5	[68]
28	Iron	Liposomes	About 9 mg of iron in liposomal form promotes longer and more consistent iron release compared to non-liposomal containing the same iron amount.	[69]
29	Zinc	Liposomes	The liposomal group showed an increase of +14.3 ± 18.5% after 4 hours, whereas the standard group experienced a decrease of −6.0 ± 13.1% (p = 0.0001). After 6 hours, the liposomal group maintained a slight increase of +1.0 ± 20.9%, while the standard group saw a more pronounced decrease of −21.0 ± 15.3%.	[70]

Effervescent

Effervescent formulations significantly increase the bioavailability of various drugs, especially those that are poorly soluble or unstable in acidic environments. This system uses effervescence generated from the reaction between an acid and a base to facilitate rapid dissolution and absorption of the drug [73]. For example, Singh et al [42] formulated an effervescent preparation with the active ingredient Ferrous Ascorbate (FA), which has low bioavailability, solubility, and stability at higher pH. Their study showed that the retention time in the stomach for the effervescent preparation increased significantly (6 hours) compared to conventional tablets (<1 hour). This prolonged retention is attributed to the effervescence, which generates carbon dioxide (CO_2) and causes the tablet to float, thereby delaying gastric emptying. This mechanism ensures that the drug remains in the optimal absorption site for a longer duration, ultimately improving its bioavailability. Additionally, the bioavailability of the effervescent formulation also increased significantly (>70%) compared to conventional tablets (15-30%). The bioavailability study was conducted in an animal model. The in vivo studies, including the gastroretentive study using X-ray radiography and the pharmacokinetic study, were carried out on healthy rabbits. This approach allowed us to demonstrate the prolonged gastric retention and enhanced bioavailability of the floating tablet formulation. These findings suggest that formulating the preparation into an effervescent form can enhance its bioavailability. Quinones et al [43] demonstrated that the effervescent formulation significantly increased serum

magnesium by 0.24 mM ($p < 0.0001$) and serum bicarbonate by 3 mM ($p = 0.015$) in patients with stage 5D chronic kidney disease compared with controls receiving calcium acetate, thereby confirming the effectiveness of the effervescent dosage form in enhancing mineral bioavailability.

Microencapsulation.

Microencapsulation significantly improves the bioavailability of minerals compounds by providing a protective layer that enhances stability and controlled release [74,75,76]. Cian et al [44] used a microencapsulation method to improve the bioavailability of iron. This research successfully developed a microencapsulation method for iron and ascorbic acid by utilizing protein concentrate from brewer's spent grain (BSG) and locust bean gum as the encapsulating material. This process used spray drying technology to enhance the bioaccessibility of iron, which is essential for ensuring the body can absorb it effectively. The study showed that the BSG protein concentrate had a high ability to chelate iron, helping to keep the iron dissolved and stable as it passed through the digestive tract. Microencapsulation was most effective, achieving 29% bioaccessibility of iron under simulated digestion, which represents more than a twofold increase compared to the unencapsulated control.

Pajuelo et al [45] showed that microencapsulation results in a more stable and prolonged increase in plasma concentrations compared to the non-encapsulated form, with bioavailability up to 10.3% higher. Zelaya et al [46] demonstrated that zinc-doped carbonated nanocrystalline hydroxyapatite (Zn-cHA), encapsulated in alginate microspheres, significantly enhanced the bioavailability of zinc and calcium in Wistar rats compared with controls (non-zinc hydroxyapatite and zinc sulfate solution). The nanocrystalline form possesses a very high surface area-to-volume ratio, thereby accelerating the dissolution of mineral ions (Zn^{2+} and Ca^{2+}) and enabling efficient release. Mi et al [47] demonstrated that microencapsulation enhances calcium bioavailability by improving the therapeutic performance of formulations for osteoporosis in animal models, as it protects calcium from gastric degradation and ensures improved mineral release and absorption in the intestine. Aquino et al [48] demonstrated that microencapsulated calcium exhibited significantly higher bioavailability, reaching up to 32%, compared to calcium chloride control in an in vitro study.

Chelating Peptides

Peptide chelation is a very effective and useful strategy for significantly increasing the bioavailability of essential minerals, especially iron and zinc [77,78]. This innovative process is based on the stabilization of the complex between certain peptides and metal ions, which increases mineral stability and solubility in the gastrointestinal tract [78,79]. The basic principle of chelation is the binding of a mineral ion with an organic molecule that acts as a chelating agent. This process forms a complex, ring-like structure where the chelating agent's functional groups (such as carboxyl or amino groups) donate a pair of free electrons to bond with the mineral ion [55–57]. By strengthening this soluble and often more permeable complex, chelating peptides can identify common inhibitors of absorption and facilitate more effective absorption across the intestinal barrier, which eventually affects more beneficial mineral utilization in the body. This study makes use of the inherent peptide biology compatibility and offers a suitable, safe, and effective method for maximizing mineral delivery and addressing deficiency [80]. For

example, Syahputra et al [49] used chelating peptides to enhance zinc bioavailability. These chelating peptides were synthesized by hydrolyzing collagen with the bromelain enzyme, which yielded peptides with high zinc-chelating ability. The peptides were then further purified using reverse-phase high-performance liquid chromatography (RP-HPLC), and their efficacy in enhancing zinc absorption was evaluated ex vivo. The study demonstrated that these zinc-chelating peptides have the potential to be a more effective alternative to current zinc supplements, increasing zinc bioavailability by 40%.

The research conducted by [50] demonstrated that zinc chelation with OPH (oyster protein hydrolysates) results in the formation of an OPH-Zn complex, which enhances zinc solubility under specific pH conditions and during gastrointestinal digestion simulations. Furthermore, the antioxidant activity of OPH remains preserved or even increases after chelation with zinc. The OPH-Zn complex has a nanoparticle structure, allowing for improved zinc bioaccessibility by reducing the potential for zinc precipitation and its interaction with other components in the digestive tract. The use of OPH-Zn shows great potential as a functional ingredient that can enhance zinc absorption, with the added benefit of improved antioxidant activity, which is important for human health, especially in the prevention of diseases related to oxidative stress.

Cui et al [52], after simulated gastrointestinal digestion, the calcium solubility of the NDEELNK–calcium complex (65.27%) was significantly higher than that of calcium chloride (38.99%). A substantial increase in calcium bioavailability has been demonstrated in vitro using the Caco-2 cell model, where the uptake of calcium ions was effectively improved by complexing them with the peptide NDEELNK and protein hydrolysates from sea cucumber egg yolk. Zhang et al [53] revealed that the complexation of peptides with calcium led to a significant increase in the apparent calcium absorption rate in rats, reaching 42.47% for the CBP-Ca group, which was substantially higher than the 31.23% observed in the control group. Wu et al [54] demonstrated that a pig bone collagen peptide-calcium chelate significantly enhances calcium bioavailability. The complex showed an optimal chelation rate of 78.38%, which is notably higher than that achieved with single enzymes (42–56%). The chelate was also proven to increase calcium transport in a Caco-2 cell model compared to a $CaCl_2$ control at all time points from 30 to 240 minutes. Furthermore, this chelate effectively resisted absorption inhibitors like phosphate and phytate and exhibited high stability during digestion, with calcium retention remaining at approximately 88.39% after 2 hr of simulated gastric digestion. These findings highlight its potential as an effective mineral supplement. Li et al [55] have successfully demonstrated that the complexation of peptides with ferrous iron (Fe^{2+}) significantly enhances its transport, cellular retention, and utilization in an in vitro study using the Caco-2 cell model. Patil et al [56] demonstrated that chelating with chickpea can significantly enhance iron binding efficiency and iron uptake in an in vitro study using Caco-2 cells. The results show that the non-fermented chickpea protein–iron complex (NCP-Fe) had a mineral bioavailability of 72.85 ± 1.45%. However, after 90 hours of solid-state fermentation with Aspergillus awamori (FCP90-Fe), this value increased significantly to 81.33 ± 1.23%. Yuan et al [57] demonstrated that supplementation with peptide–Ca complexes from sunflower seeds (SSP-Ca) and peanuts (PP-Ca) significantly improved

calcium bioavailability in female mice on a low-calcium diet. The absorption rate for the control group was only 60.52 ± 8.95%, while supplementation with $CaCO_3$ was slightly higher at 65.78 ± 10.30%. The most significant increase was observed in the L-SSP-Ca group, with an absorption rate of 75.96 ± 4.26%, followed by the H-SSP-Ca (73.10 ± 8.96%), and H-PP-Ca (68.31 ± 11.02%) groups.

Heme and Non-Heme Iron Sources.

The bioavailability of iron is crucial, and its absorption and utilization in the human body are significantly influenced by the differences between heme and non-heme iron sources. Heme iron, primarily derived from animal products such as meat, poultry, and fish, possesses a unique porphyrin ring structure. This structure allows for the absorption intact by the intestine through highly effective routes, bypassing the inhibitory effects of several food components that typically interfere with the absorption of non-heme iron [81]–[84]. In contrast, non-heme iron, which is prevalent in plant-based foods (such as legumes, leafy vegetables, fortified cereals) and animal products, must be released from food components before it can be absorbed. Churio et al [51], demonstrated that alginate beads containing a mixture of heme and non-heme iron had a high iron content and good encapsulation efficiency. These beads showed higher stability under simulated gastric conditions, with slower iron release compared to alginate beads containing only ferrous fumarate (FF) or ferrous bis-glycinate chelate (Ferrochel®) (FCH). Most of the iron release occurred under intestinal conditions, the site of iron absorption, with higher release efficiency in the mixed beads. This study suggests that a combination of heme and non-heme iron could be an effective alternative in iron supplementation or fortification strategies, as this approach addresses the limitations of both forms the poor stability of heme and the poor absorption of non-heme iron.

Nanoparticles

Nanoparticles represent a transformative advancement in drug delivery by simultaneously enhancing aqueous solubility, conferring physicochemical stability, and ultimately improving the bioavailability of diverse minerals [85]–[88]. These benefits are primarily achieved through the reduction of particle size to the nanometer scale (1–1000 nm), which markedly increases the surface area-to-volume ratio [89]. The resulting higher dissolution rate and saturated solubility are critical determinants for more efficient absorption. In addition, the nanoscale dimensions of these particles facilitate improved penetration across biological barriers and enable targeted delivery to specific sites [90,91]. Beyond solubility enhancement, nanoparticles provide a protective microenvironment that shields encapsulated or adsorbed compounds from enzymatic degradation, pH fluctuations, and oxidative stress [92], thereby preserving their structural integrity and prolonging their functional lifespan within complex biological systems [93,94]. Nanoparticle technology has become a fundamental basis for the development of contemporary pharmaceutical formulations, as it effectively addresses solubility and stability challenges, consequently enhancing bioavailability to maximize therapeutic potential [85,95].

Cheng et al [58] developed Zn-WPH-COS (zinc-whey protein hydrolysate-chitosan oligosaccharide) nanoparticles to enhance the bioavailability of zinc. Zn-WPH-COS was prepared by combining zinc with whey protein hydrolyzate (WPH) and chitosan oligosaccharide (COS) using transglutaminase (TGase) to generate

nanoparticles. The study found that Zn-WPH-COS significantly increased the solubility and dialyzability of zinc compared to Zn-WPH or $ZnSO_4 \cdot 7H_2O$, leading to improved zinc bioaccessibility. This was achieved thanks to the protection provided by COS on Zn-WPH, reducing the formation of zinc precipitates with phytic acid and enhancing zinc bioavailability. The materials used in our formulation, whey protein hydrolysate (WPH) and chitosan oligosaccharide (COS), are generally recognized as safe and have a history of use in food and biomedical applications. Feng et al [59] reported that the zinc bioavailability of zinc-enriched polyphosphate nanoparticles (ZnPNPs) reached 60.17 ± 3.95% relative to $ZnSO_4$ (100%) in rats. However, when calcium and phytate known strong inhibitors of zinc absorption—were present, the bioavailability of $ZnSO_4$ dropped sharply to only 28.71 ± 2.80%, whereas ZnPNPs remained comparatively stable at 44.72 ± 3.66%. These findings indicate that although ZnPNPs are slightly lower than $ZnSO_4$ under normal conditions, they are far more resilient against phytate inhibition, making them a more effective strategy for enhancing zinc bioavailability in phytate-rich cereal-based diets. Feng et al [60] reported that casein hydrolysate mediated the formation of Zn/CaP nanoparticles, which effectively prevented zinc precipitation in the intestinal environment. In the absence of these nanoparticles, zinc solubility declined markedly to approximately 32% within 3 hours. By contrast, the nanoparticle-mediated system maintaining zinc solubility at nearly 100% over the same period. This stabilization not only preserved zinc availability but also resulted in a significant enhancement of zinc transport across the mouse intestinal model, underscoring the potential of casein-derived nanoparticles to improve mineral bioavailability.

According to the findings of Olbert et al [61] zinc oxide nanoparticles (ZnO-NPs) demonstrated a significantly enhanced bioavailability compared to the standard form (S-ZnO) in an in vivo study conducted on rats. After two weeks of oral administration, the serum zinc concentration in rats receiving ZnO-NPs at a dose of 7 mg/kg increased markedly to 3.67 ± 0.25 μg/mL. This value was substantially higher than that observed in the control group receiving no zinc supplementation (2.32 ± 0.22 μg/mL) and in the group administered S-ZnO at the same dosage (2.43 ± 0.14 μg/mL). This pronounced difference confirms that nanoparticles, due to their extremely small size, are more efficiently absorbed by the body, thereby enhancing mineral levels in the bloodstream. Terova et al [62] demonstrated that administering a diet supplemented with nanoparticle forms of zinc, manganese and selenium to gilthead seabream (Sparus aurata) larvae over a 24-day period significantly increased total body length (9.00 ± 0.32 mm) and stress resistance (65.79 ± 3.72%) compared to the control group. Furthermore, the expression of the osteocalcin (OC) gene was significantly upregulated and strongly correlated with bone mineralization levels ($r = 0.84$), indicating enhanced absorption and utilization of minerals delivered in nanoparticle form.

Swain et al [63] demonstrated that zinc supplementation in the form of nanoparticles (NP-ZnO) significantly enhanced bioavailability compared to the conventional form (ZnO) in weaned piglets. After 14 days of treatment, plasma zinc concentrations markedly increased to 1.78 μg/mL in the NP-ZnO group (800 mg/kg), compared to 1.23 μg/mL in the control group and 1.33 μg/mL in the conventional ZnO group. These findings indicate that zinc

nanoparticles are more efficiently absorbed by the body.

Solid Lipid Nanoparticles (SLN)

Minerals essential to the human body often suffer from low bioavailability due to poor solubility [97]. Solid lipid nanoparticles (SLNs), owing to their nanometric size and lipid-based composition, enhance the surface area of encapsulated minerals, protect them from degradation processes such as oxidation, and facilitate improved absorption [98,99]. This delivery system offers promising applications in mineral supplementation, food fortification, and clinical nutrition [100,101]. Hong et al [64] developed solid lipid nanoparticles (Fe-SLNs) based on a W/O/W double emulsion coated with water-soluble chitosan (WSC) to enhance iron bioaccessibility and stability. The study showed that Fe-SLNs and WSC-Fe-SLNs protected encapsulated iron from lipid peroxidation under different pH and temperature conditions and could release nearly 80% of iron in a simulated intestinal fluid. Coating with WSC also reduced lipid peroxidation that occurred in pure iron.

Hatefi and Farhadian [65] demonstrated that the encapsulation efficiency reached 92.3% with a particle size of approximately 358 nm. The resulting solid lipid nanoparticles (SLNs) exhibited higher and more sustained drug release compared to conventional ferrous sulfate tablets. This study suggests that ferrous sulfate SLNs can be an attractive delivery system for oral iron therapy due to their ability to reduce oxidation and increase contact time with the mucosal membrane, ultimately enhancing iron absorption.

Mesoporous

Mesoporous materials offer a solution by encapsulating minerals within their nano-sized pores [102]–[105]. This mechanism works by increasing the surface area, reducing the crystallinity, and decreasing the particle size of the minerals [106–108]. This way, mesoporous materials make the minerals more soluble and, ultimately, more easily absorbed by the body [109, 110]. Lin et al [66] demonstrated that mesoporous iron particles (MIPs) had excellent potential to improve iron bioavailability. The study used Caco-2 cell models to measure iron absorption, and the results showed that MIPs had much higher bioavailability compared to commercial iron particles due to their high porosity and smaller particle size. In vivo tests on iron-deficient rats showed that supplementation with MIPs significantly increased hemoglobin levels and red blood cell regeneration.

Liposomes

Liposomes are encapsulation systems formed through surfactant interactions with an aqueous medium [111,112]. This structure encloses hydrophilic compounds in the core and hydrophobic compounds in the two layers. Surfactants used in liposomes are made from phospholipids, which carry an electrical charge [113,114]. Bochicchio et al [67] demonstrated that nanoliposomes enhance the bioavailability of ferrous sulfate compared to control formulations in Caco-2 cell models, while also exhibiting a high iron encapsulation efficiency (>97%), thereby maintaining stability and protecting the compound from degradation. Pinho et al [68] demonstrated that the use of pH-sensitive liposomes containing Cu(II) phenanthroline (Cuphen) complex can significantly enhance copper (Cu) bioavailability in colorectal cancer therapy.

Ko et al [69] demonstrated that nanoliposomes effectively enhance the bioavailability of ferrous sulfate and vitamin E. This is evidenced by a more prolonged increase in the blood levels of these

nutrients in the group consuming the liposomal formulation compared to the non-liposomal control. In the study by Tinsley et al [70], liposomes in a multivitamin/mineral (MVM) supplement significantly increased the bioavailability of iron. The mean area under the curve (AUC) for iron in the liposomal MVM was 33.22 mcg/dL × 6 hours, which was 50% higher than the standard MVM (19.84 mcg/dL × 6 hours; p = 0.02). When measuring the percentage change in serum iron levels from baseline, the liposomal group showed an increase of +14.3 ± 18.5% after 4 hours, whereas the standard group experienced a decrease of −6.0 ± 13.1% (p = 0.0001). After 6 hours, the liposomal group maintained a slight increase of +1.0 ± 20.9%, while the standard group saw a more pronounced decrease of −21.0 ± 15.3%, which was also statistically significant (p = 0.0002).

Conclusions

Minerals play a vital role in various physiological functions, but low bioavailability and hygroscopicity remain major challenges in pharmaceutical formulations. To overcome this, various innovative strategies have been developed. To prevent hygroscopicity, methods like co-processing with hydrophobic excipients and encapsulation have proven effective. To enhance bioavailability, research shows that chelating compounds improve mineral absorption, while effervescent formulations increase solubility. Modern technologies such as microencapsulation and nanoparticles (including solid lipid nanoparticles and liposomes) effectively enhance both the stability and absorption of minerals. While these technologies offer promising solutions, challenges related to safety evaluation, toxicity, and production scalability still need to be addressed. Therefore, future research must focus on developing delivery systems that are safer, more efficient, and scalable to maximize the therapeutic benefits of mineral supplements.

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Author Contributions

Conceptualization, PP and YWW; Methodology, PP; Software, PP; Validation, P, YWW and AHC; Formal Analysis, P; Investigation, P; Resources, P; Data Curation, P; Writing - Original Draft Preparation, P; Writing - Review & Editing, P; Visualization, P; Supervision, AYC; Project Administration, AYC; Funding Acquisition, AYC.

Conflict of Interest

The authors declare no conflict of interest.

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