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Optimizing Iron Compounds And Bioavailability

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Stages in the Development of an Iron Fortified Food

For several reasons, iron is the most difficult mineral to add to foods while ensuring adequate bioavailability by the body. Iron compounds that are highly bioavailable, such as ferrous sulfate, can cause color and flavor changes. These organoleptic problems raise issues of consumer acceptance. On the other hand, iron compounds that do *not* cause organoleptic problems, such as elemental iron, are not as bioavailable and are poorly absorbed. Finally, major vehicles for iron fortification contain potent inhibitors of iron absorption, such as phytic acid in cereals, or are often consumed along with foods that contain powerful inhibitors such as polyphenols in tea. Even highly absorbable iron compounds, such as ferrous sulphate, may be poorly absorbed unless food manufacturers protect the iron or remove the inhibitors from the food.

A three-stage process of development for iron fortified food products may help overcome these difficulties. The first stage, *optimizing the iron compound*, involves selecting an iron compound, which offers the highest potential absorption while causing no organoleptic problems. Optimizing the iron compound also involves organoleptic trials in order to identify problems with color or taste that may arise during storage or preparation. The second stage, *optimizing iron absorption*, involves assessing nutritional needs of the consumer; determining the target level of iron to be provided by a food product; and finally estimating or measuring actual iron absorption to determine whether those consumer needs are met. With these findings in hand one can evaluate options including the addition of enhancers, removing inhibitors or simply modifying the level of added iron. The third and final stage is *to demonstrate improved iron status* by monitoring a decrease in iron deficiency anemia among consumers.

Selecting the Iron Compound

The relative bioavailability of iron compounds is determined by their solubility in the stomach's gastric juice. The highly absorbable compounds, such as ferrous sulphate, gluconate and ferric ammonium citrate, are water soluble and dissolve instantaneously in the dilute acid of the gastric juice. Compounds such as ferrous fumarate, ferrous succinate and ferric saccharate, dissolve poorly in water but dissolve over time in the presence of dilute HCL. These can also be highly absorbable. On the other hand, the body has difficulty absorbing water insoluble compounds that are poorly dissolved in dilute acid. This category includes different forms of elemental iron, such as electrolytic, carbonyl and reduced iron, as well as the phosphate iron compounds, ferric pyrophosphate and orthophosphate. (See Figure 3a).

The relative bioavailability of iron compounds is standardized on a comparison to ferrous sulfate. Ferrous sulphate is given a relative absorption (RBV) of 100 in both rats and humans. Freely water soluble compounds also have a relative absorption of 100. Compared to ferrous sulfate, the iron compounds soluble in dilute acid indicate a relatively high RBV in humans: 100 for ferrous fumarate, 92 for ferrous succinate and 74 for saccharate. Compounds that are poorly soluble in dilute acid have low and variable RBV, varying from RBV of 21-75 for ferric pyrophosphate or 25-32 for ferric orthophosphate. RBV for the various forms of elemental iron varies more extremely from RBV of 5 to 148.

Relative Absorption Common Iron Compounds

(Hurrell, 1997)

	rat	man	approx.relative cost
water soluble			
ferrous sulphate	100	100	1.0
soluble in dilute acid			
ferrous fumarate	95	100	1.3
ferrous succinate	119	92	4.1
ferrous saccharate	92	74	5.2
poorly soluble in dilute acid			
ferric pyrophosphate	45-58	21-75	4.1
ferric orthophosphate	6-46	25-32	2.3
elemental iron: electrolytic	44-48	5-100	0.5
carbonyl	39-66	5-20	1.0
reduced	24-54	13-148	0.2

Figure 3a

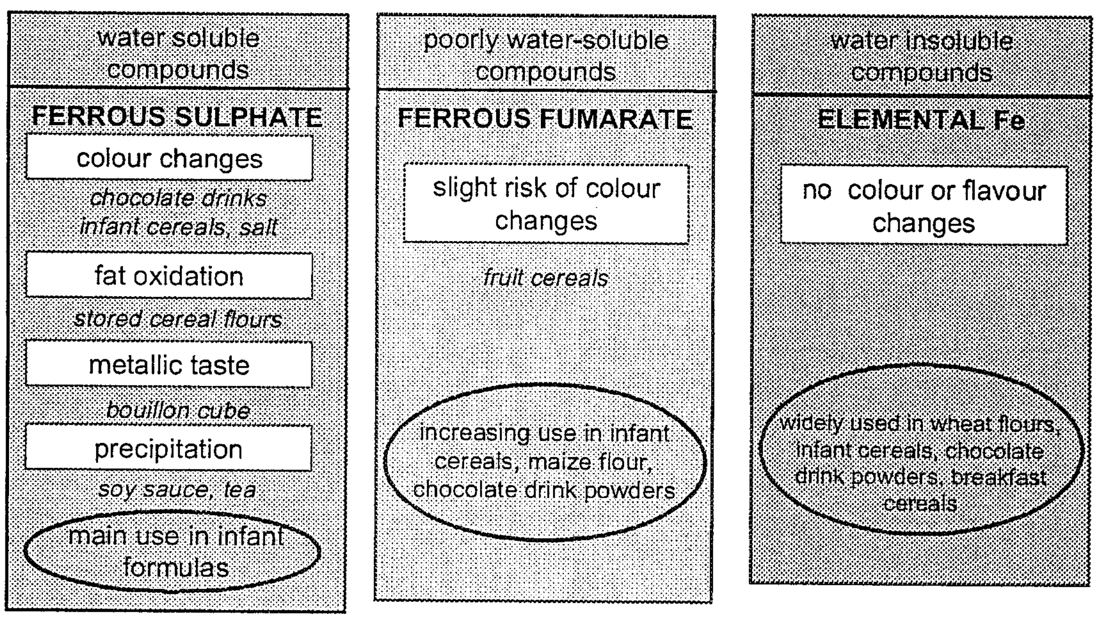
There are several explanations for this wide range of findings. Different batches of the same compound have somewhat different physiochemical properties and thus different solubility in the gastric juice. Although some experimental elemental iron compounds have shown higher absorption, it is highly unlikely that the higher values for elemental iron would occur in a commercial product. Commercial compounds that have been tested in rat assays all indicate an absorption about half of ferrous sulphate. Generally, relative cost factors for the various iron compounds are also standardized using ferrous sulphate. With the relative cost of ferrous sulphate at one, costs range from 4-5 for ferrous succinate to 0.5 for electrolytic and 0.2 for reduced iron.

Organoleptic Issues

There are a number of organoleptic problems associated with adding highly absorbable water soluble iron compounds to food products. Ferrous sulphate causes some unacceptable color changes. For example, chocolate drinks become gray, infant cereal with banana turns blue and salt can change to brown. Ferrous sulphate causes metallic off-flavors in bouillon cubes. It catalyzes fat oxidation reactions and consequently, cereal flours stored over a period time become rancid. When added to soy sauce, soluble peptides will precipitate. Ferrous sulphate in sugar causes a flocculation on the surface whenever the sugar is added to tea—as the polyphenols in the tea combine with the iron. In short, it is very difficult to add ferrous sulfate to foods without changing their organoleptic quality and threatening consumer acceptance. It is usually used only in infant formulas, short shelf life bread and some pastas.

As a result of these organoleptic difficulties, the poorly water-soluble compounds such as ferrous fumarate are increasingly used in fortification. Although there is a slight risk of color change, particularly in slightly acid products such as fruit cereals, it can be used in infant cereals, in maize flour and chocolate drink powders. The least absorbable iron forms, such as water insoluble compounds like elemental iron, produce no color or flavor changes. As a result these compounds are very widely used in fortifica-

Organoleptic Problems Associated With Iron Fortification
(Hurrell, 1998)

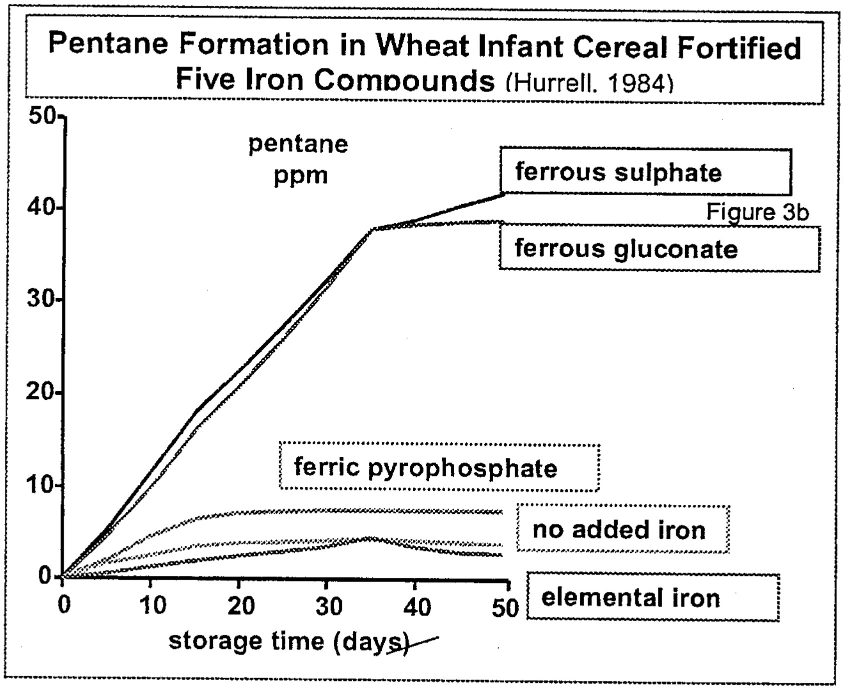


tion of wheat flours, infant cereals, chocolate drink powders and breakfast cereals. (See Figure 3b).

The impact of various iron compounds on rancidity in wheat flour can be measured using pentane as an indicator. Formation of pentane correlates with rancid off-flavors in flour. Ferrous sulphate, ferrous gluconate, ferric pyrophosphate and elemental iron were added to infant cereals made of pre-cooked roller-dried wheat flour and stored in aluminum cans at 37° C for up to one year. Pentane in the headspace of the cans was measured by gas chromatography. Pentane tests have demonstrated that cereals with water soluble iron compounds reached 30-40 ppm pentane within 30-40 days. On the other hand, the formation of pentane in cans of cereal with water insoluble compounds such as elemental iron was negligible and similar to the content with no added iron. (See Figure 3c).

Optimizing Absorption by Encapsulation

There are several alternatives to maximizing absorption while minimizing unacceptable organoleptic changes. These include encapsulating the iron, utilizing novel iron compounds, adding absorption enhancers, and the removal of absorption inhibitors.



Encapsulation, which prevents fat oxidation during storage of the cereal flours, involves coating the iron with a protective layer that does not affect its ability to dissolve in the gastric juice. In rat assays, coating with hydrogenated oil such as soy bean oil or with ethyl cellulose or maltodextrin had little effect on the RBV. However, the hydrogenated oils are not heat stable and melt at about 65° C while ethyl cellulose and maltodextrin are water soluble. When the coating is removed, unacceptable color changes follow. When adding hot water or milk to infant cereal, the fat capsulation melts and, if there are bananas in the cereal, the cereal turns blue. If a manufacturer is drying chocolate milk powder that includes an encapsulated iron compound, the dried powder turns gray. This lack of heat stability is a key barrier to iron encapsulation.

More research needs to be undertaken in order to identify a capsule which is stable to heat and insoluble in water and can be removed during digestion so that the iron is bioavailable.

Optimizing Absorption with Iron EDTA

New or novel iron compounds such as Iron EDTA should be considered. Iron EDTA was accepted by JECFA 1993 for use in government sponsored food fortification programs. Although it is a soluble iron compound, and consequently can cause unwanted color reactions in certain situations, EDTA does not provoke fat oxidation during storage in cereal flours. No rancidity was reported in a number of studies with several different cereal flours, including wheat flour.

The superior relative absorption of EDTA has been demonstrated in many studies over the past 20 years. EDTA consistently indicates 2-3 times better absorption than ferrous sulphate, which is the best of the ordinary compounds. In an unpublished study in collaboration with Cook (1992, Kansas University Medical Center), it was found that adding iron EDTA to infant cereals resulted in a fourfold increase in absorption compared to ferrous sulphate and ferrous fumarate.

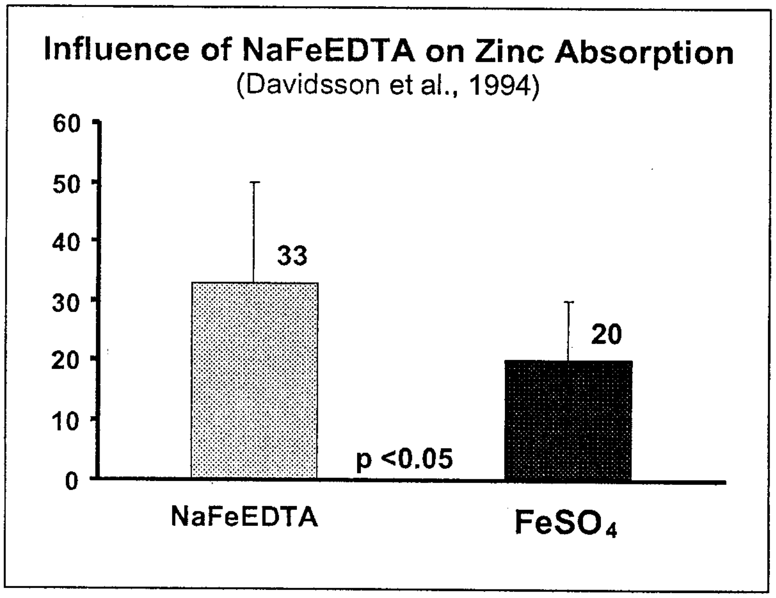


Figure 3a

This markedly superior absorption, however, is limited to high phytate meals because EDTA chelates the iron thus protecting it from phytates. When there is no phytate present, EDTA is similar or displays even less absorption than ferrous sulfate. In a sugar syrup for example, ferrous sulfate would be better absorbed than iron EDTA. But in a high phytate cereal, iron EDTA has an advantage of 2-4 times. Consequently, iron EDTA fortification of wheat and corn flours offers an opportunity to deliver iron to the at-risk populations in developing countries. However, cost remains an issue with EDTA as it is approximately six times more expensive than ferrous sulfate.

EDTA offers increased zinc absorption as well. In a 1994 study using stable isotopes, 10 women consumed high phytate wheat flour baked into bread rolls. The rolls contained either 5 mg iron as ferrous sulphate or as iron EDTA. Zinc absorption was 33% with iron EDTA and 20% with ferrous sulfate. It is noteworthy that urinary excretion of zinc did increase slightly with iron EDTA but was nevertheless less than 1% of intake. (See Figure 3d).

Optimizing Absorption with Ferrous Bisglycinate

It has been suggested that another novel compound, ferrous bisglycinate, offers superior relative absorption because the glycine binds iron and protects it from inhibitors in a similar way to EDTA. However, this superior absorption has not been convincingly demonstrated in published literature. Fox et al. (1998) compared iron absorption in a vegetable puree and a whole grain infant cereal in two studies, one with ferrous sulphate and one with ferrous bisglycinate. The results are limited by the fact that the comparisons are not strictly between the iron compounds but rather paired within each study of vegetable and grain meals. Given this limitation, the study indicates 9% absorption from ferrous sulphate in the vegetable meal versus 9.8% for the glycinate. In the higher phytate grain meal, Fox et al. report 3.8% absorption from ferrous sulphate and 5.2% from ferrous bisglycinate, slightly higher but not significant. While the gain in absorption is minor, ferrous bisglycinate is a soluble iron compound, and like other soluble iron compounds, can cause color reactions and provoke fat oxidation. (See Figure 3e).

Comparative Absorption: Ferrous Bisglycinate and Ferrous Sulphate
(Hurrell, 1998)

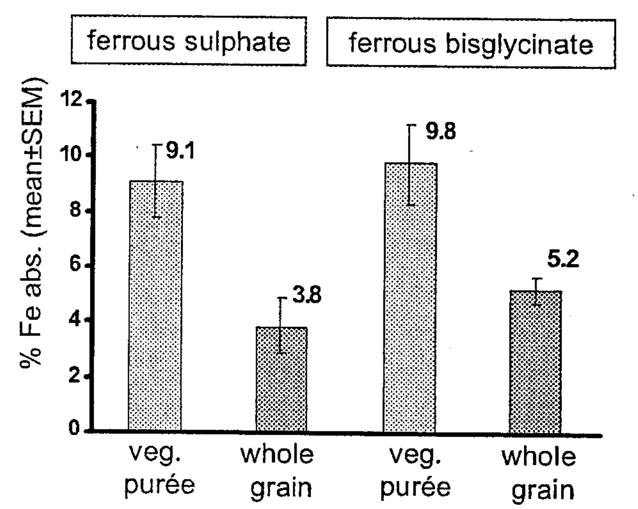


Figure 3e

Optimizing Absorption with Ascorbic Acid

From the food manufacturer's point of view, adding ascorbic acid offers the easiest approach to optimizing absorption. A number of studies have shown that ascorbic acid increases absorption of all fortification iron compounds in humans. Using two iron compounds, Derman et al. (1980) reported significant increases in iron absorption from infant cereals. The increase was dependent on the level of added ascorbic acid and iron. In an infant cereal meal containing 6.9 mg iron from ferrous sulfate, absorption increased from 1% to 3.7% after adding 24 mg ascorbic acid. Absorption rose from 0.8% to 10.3% when 50 mg ascorbic acid was added to infant cereal meal containing 5 mg iron as ferrous ammonium citrate.

Increased Absorption of Iron from Cereals with Addition of Ascorbic Acid with various Fortification Compounds

(Hurrell, 1998)

			% Iron absorption		
Study/Meal	Iron compound	(mg)	Without ascorbic acid	With ascorbic acid	(mg)
Derman et al. (1980)/ Infant cereal	ferrous ammonium citrate ferrous sulphate	5 6.9	0.8 1.0	10.3 3.7	50 24
Forbes et al. (1989)/ Farina with milk	ferric orthophosphate ferrous sulphate electrolytic iron	3 3 3	0.8 4.5 3.4	3.3 15.4 8.0	100 100 100

Figure 3f

Working with 3 different iron compounds, an INACG study by Forbes et al. (1989), demonstrated significant increases in absorption from a meal of farina and milk containing 3 mg iron. After the addition of 100 mg ascorbic acid, absorption of ferric orthophosphate rose from 0.8% to 3.3%, ferrous sulphate from 4.5% to 15.4% and electrolytic iron from 3.4 to 8%. These increases range from about two- to four-fold. (See Figure 3f).

Ascorbic acid is a very effective enhancer of iron absorption. It is thought to reduce iron from the ferric to the ferrous state and chelate the iron into an absorbable form. The disadvantage is that ascorbic acid is unstable under the stresses of heat and humidity found in food processing and in storage, especially in the climates of the developing world. This lack of stability means large overages must be added and that packaging needs to be relatively sophisticated. Consequently, ascorbic acid becomes a fairly expensive option to optimize absorption.

Optimizing Absorption by Phytic Acid Removal

Phytic acid, a powerful inhibitor of iron absorption present in cereal and legume products can be removed by various approaches. Most commonly the enzyme *phytase* is used to "dephytinize." In an unpublished study conducted with Cook (Kansas University Medical Center), iron absorption from a high phytate wheat soy cereal was compared under 4 conditions—no optimization, addition of 25 mg ascorbic acid, phytate removal with phytase, and both ascorbic acid addition and "de-phytinization." Iron absorption by 9 adult subjects was 1% with no optimization. There was no significant increase with the addition of 25 mg ascorbic acid. Absorption rose to 4% with phytate removal and 8% when both optimization techniques were used together. Less phytic acid and more vitamin C clearly will increase iron absorption.

The effect of phytic acid removal and ascorbic acid addition in a commercial soy formula product was studied by Davidsson et al (1994). Each liter of the product contained 20 mg iron from ferrous sulphate, 400 mg phytate and 100 mg ascorbic acid. The study design incorporated two optimization alternatives. One formulation degraded the phytate to 1.3 mg from 400 per liter while leaving the original level of ascorbic acid. The other alternative doubled the level of ascorbic acid to 220 mg per liter while leaving the phytate at the original level. Using stable isotopes, iron absorption was compared for each infant fed the same two meals. Absorption more than doubled, from 3.9% to 8.8%, with phytate removal and rose from 5.7% to 9.5% with increased vitamin C. Either optimization option was feasible for the manufacturer. (See Figure 3g).

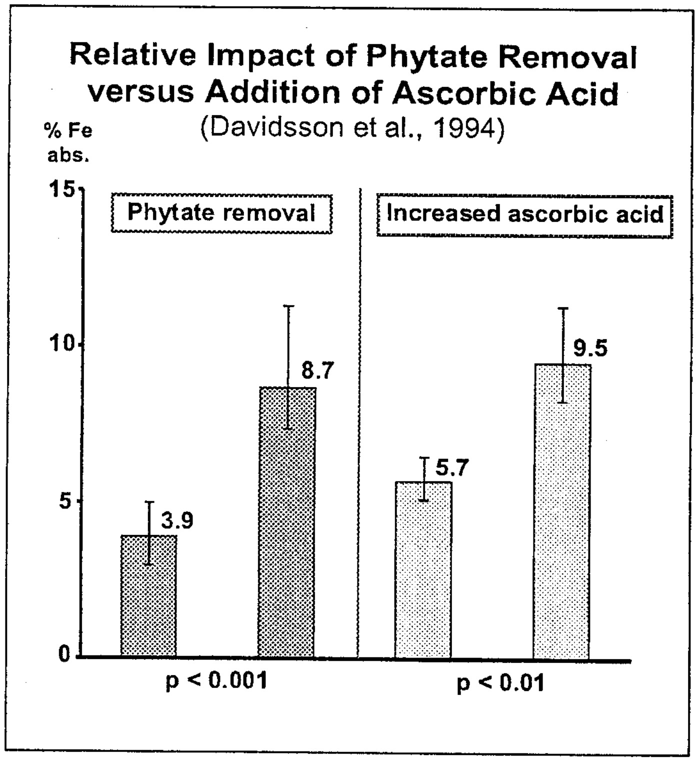


Figure 3g

When considering phytate removal, it is important to note that a substantial amount of the phytate, about 95%, must be removed before achieving a useful increase in iron absorption. It is not sufficient to remove half the phytate. In a study in which adults were fed a liquid formula meal of soy protein isolate in a medium of maltodextrin and corn oil, we found that when the phytic acid content was decreased in the soy protein isolate from 1000 mg to 400 mg per 100g, there was no improvement in iron absorption. However, when the phytate level was taken down below 200 mg per 100g, absorption began to increase and rose to about three-fold the original value when the phytic acid level reached level zero. (See Figure 3h).

Effect of Phytic Acid Removal/Degradation on Fe Absorption by Adults from Soy Protein Isolates Fed in a Liquid Formula Meal

(Hurrell et al., 1992)

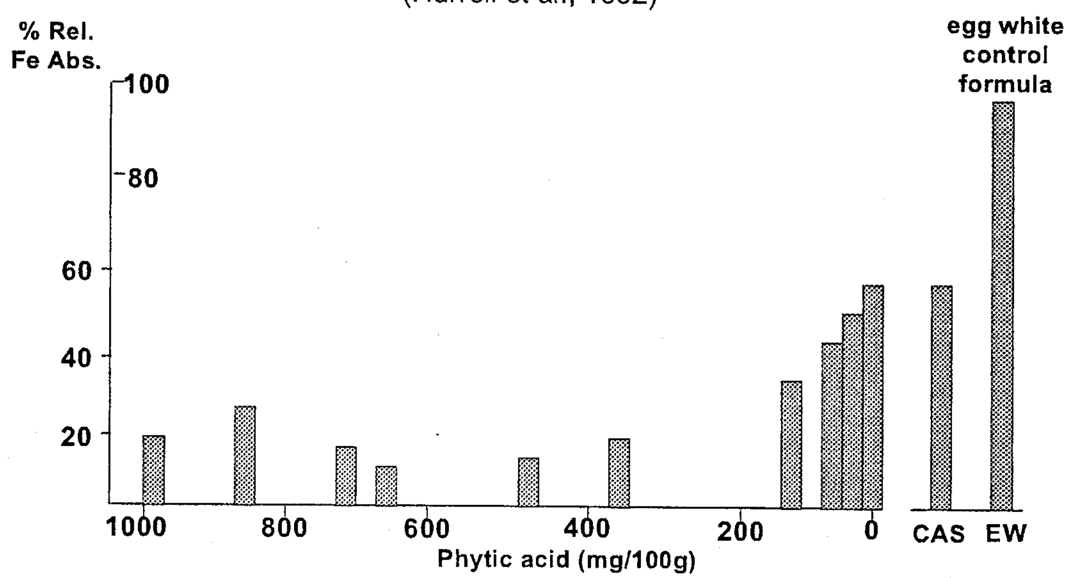


Figure 3h

Optimizing Absorption with Sodium EDTA

Sodium EDTA is a permitted additive in many countries, albeit in specified foods only. It is much more stable to processing and storage than vitamin C. When foods with added sodium EDTA are consumed, iron EDTA will be created from iron present in the common pool. This is because at pH-1, iron has the strongest binding constant to EDTA.

The impact of the addition of sodium EDTA alone has been shown in an unpublished radio iron absorption study (Hurrell, Reddy & Cook, 1992). In this study, adult subjects were fed two different infant cereals, one a high phytate soy based cereal, and the other a lower phytate wheat cereal. The meals included 50 g infant cereal with 300 ml water, 5 mg iron as ferrous sulfate with varying concentrations of EDTA (at Fe:EDTA ratios of 1:0, 1:0.33, 1:0.67 and 1:1). Without the addition of sodium EDTA, the absorption of ferrous sulphate from the wheat cereal was only about 1%. With the addition of increasing concentrations of EDTA, absorption improved gradually up to a maximum of up to 6%. The same procedure with a higher phytate soy based product showed absorption rising from about 0.5% with no added EDTA to over 3% as the concentration of the sodium EDTA was increased. The study shows an increased absorption of ferrous sulfate with sodium EDTA of about six-fold, and demonstrated that sodium EDTA can be a useful alternative to ascorbic acid for enhancing iron absorption (Hurrell, R.F., Reddy M. and Cook, J.D., unpublished).

Recommendations

It is clear that absorption of even highly absorbable iron compounds may be unacceptably low from high phytate containing foods, which contain no ascorbic acid or other enhancers. After optimizing the iron compound and obtaining the maximum level and bioavailability with no organoleptic problems, absorption can still be improved via a number of methods.

The best way to optimize absorption from iron compounds depends on the facilities available. In industrialized countries, adding ascorbic acid or removing the phytate is usually the most effective approach. In developing countries, after optimizing the iron compound, the use of sodium EDTA as an enhancer may provide a useful alternative.

Sodium EDTA is more stable than ascorbic acid and is more realistic considering the less sophisticated packaging and storage found in developing countries. Sodium EDTA itself may also be used to enhance iron absorption.

Finally, in many developing countries, there are traditional processes which can activate the native phytates present in cereals and legumes. The phytates then degrade and lower levels of phytic acid. Soaking, germination and fermentation will degrade phytic acid. Fermentation is the most effective since the acid pH generated favors phytase action. However it should be stressed that iron absorption is only improved after phytic acid has been more or less completely degraded.

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