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Iron Absorption and Bioavailability in Rats of Micronized Dispersible Ferric Pyrophosphate

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Abstract: Unlike commercial ferric pyrophosphate, micronized dispersible ferric pyrophosphate (MDFP: SunActive Fe™) does not precipitate and is completely dispersible in liquid form. MDFP shows a sharp particle size distribution at a nanometer level, which is several times smaller than that of commercial ferric pyrophosphate. The bioavailability of MDFP was compared to ferric pyrophosphate, sodium ferrous citrate, and ferrous sulfate by three bioavailability tests in rats; namely the serum iron concentration curve, the hemoglobin regeneration efficiency, and Association of Official Analytical Chemists' hemoglobin repletion test. The high area under curve value, a lag in peak time, and continued high serum iron concentration by MDFP over the other iron compounds indicates a sustained release of iron in the serum iron concentration curve method. MDFP showed the highest hemoglobin regeneration efficiency among all the iron compounds tested. The relative biological value of MDFP per unit of ferrous sulfate in each bioavailability test showed a high value as compared to other iron compounds. The above results suggest that MDFP is an ideal compound with high bioavailability for iron fortification in various liquid applications.

Key words: Bioavailability, iron absorption, iron fortification, micronized dispersible ferric pyrophosphate, relative biological values

Introduction

Iron deficiency anemia is especially prevalent in young children, women of childbearing age, and pregnant and lactating women [1, 2]. Iron deficiency may impair development of children and may affect their later performance in schools [3, 4]. Anemia during pregnancy may also lead to the risk of premature labor or increased perinatal morbidity and may even cause mortality [5, 6]. Iron fortification in food is one strategy to combat iron deficiency. Several soluble and insoluble iron compounds such as ferrous sulfate, ferrous fumarate, sodium ferrous citrate, reduced iron, and ferric pyrophosphate have been used to fortify foods such as cereals, rice, soy sauce, salt, sugar, and wheat flour [7, 8]. Although the soluble iron compounds have high bioavailability, they often cause unacceptable color and flavor [9, 10, 11]. Nonreactive iron compounds such as ferric pyrophosphate or reduced iron are often preferred sources for fortification in foods as they have less "iron taste" compared to soluble iron; however

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they have low to medium bioavailability [8] and they are insoluble or precipitate in liquids. We have developed a micronized dispersible ferric pyrophosphate formulation (MDFP), commercially known as SunActive Fe™ (Taiyo Kagaku Co. Ltd., Japan), which completely disperses, without precipitation, insoluble iron in liquid formulations.

In this study, we examined in rats the absorption and bioavailability of MDFP compared to commercial ferric pyrophosphate, sodium ferrous citrate and ferrous sulfate.

Materials and Methods

Iron compounds

Micronized dispersible ferric pyrophosphate (MDFP, SunActive Fe™) is an aqueous suspension containing 12 mg Fe/g, and prepared by Taiyo Kagaku Co., Ltd (Yokkaichi, Japan) by mixing ferric chloride, sodium pyrophosphate, and emulsifiers [12]. Reagent grade ferric pyrophosphate, sodium ferrous citrate, and ferrous sulfate were purchased from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan).

Particle size distribution of basic iron compounds

Particle size distribution of MDFP and ferric pyrophosphate was measured using laser diffraction particle size distribution analyzer (Helos Sympatec Co. Ltd., USA). For the measurement, MDFP and ferric pyrophosphate were dispersed in 50 and 1250 mL of distilled water, respectively.

Animal diets

The standard rat diet was prepared from a commercial grade diet (MF powder, Oriental Yeast Co. Ltd. Japan) supplemented with a 45 mg Fe/kg diet. The low-iron diet had the following composition: corn starch 33% w/w; corn oil 5.0% w/w; casein 2.0% w/w; cellulose powder 5.0% w/w; sucrose 30.0% w/w; AIN-76 vitamin 4.0% w/w, and mineral mixture 1.0% w/w. The composition of mineral mixture (g/kg) was 343.1 KH_2PO_4; 292.9 $CaCO_3$; 250.6 NaCl; 200.2 ZnCl; 48.764 $MgSO_4$; 4.3 $CaHPO_4$-$2H_2O$; 1.21 $MnSO_4$-$5H_2O$; 0.025 $(NH_4)_6Mo_7O_{24}$-$4H_2O$; and 0.005 KI.

Iron absorption and bioavailability studies in rats

Four- to ten-week-old male weanling Sprague-Dawley rats (Charles River Japan Inc. Japan) were used in all the studies. During the experimental period, the rats were individually housed in stainless steel metabolic cages under the conditions of 22 ± 2°C temperature, 50% relative humidity, and a 12-hour light-dark cycle (light exposure from 8:00 am to 8:00 pm).

Bioavailability of iron from different iron compounds was determined by the serum iron concentration curve (SIC) method [13, 14], the hemoglobin regeneration efficiency (HRE) method [15, 16], and the modified hemoglobin repletion method from the Association of Official Analytical Chemists (AOAC) [17].

1. Iron absorption by SIC

This method was based on plotting the serum iron concentrations after oral administration of iron compounds to rats [14]. Prior to the start of the experiment, the ten-week-old rats were fed with a standard diet and distilled water *ad libitum* for five days. Then all the rats were fasted for 18 hours and randomly distributed into five groups having 10 rats each. The average weights of the rats among the groups were similar. MDFP, ferric pyrophosphate, sodium ferrous citrate, and ferrous sulfate were dissolved or dispersed in 5 mL distilled water and orally administrated to the rats to provide 2 mg Fe/kg body weight. For the control treatment, distilled water alone was orally administered to the rats. After 0, 0.5, 1, 2, 4, 8, and 12 hours of oral administration, blood samples were drawn from the carotid artery of the rat for the measurement of serum iron concentration. The serum iron concentration was measured by the colorimetric method following the standard method of the International Committee for Standardization in Hematology [18]. The "area under the curve" (AUC) values for various iron compounds were calculated as the total amount of serum iron content. The difference between the AUC of various iron compounds and of the control was calculated, and the relative biological value (RBV) for each iron compound was calculated relative to ferrous sulfate.

2. Iron bioavailability by HRE

This method was based on hemoglobin repletion in anemic rats after iron supplementation [15, 16]. Iron-deficient anemic rats were prepared by feeding four-week-old rats a low iron diet for five weeks. At the same time, control rats were fed the standard diet. The anemic rats were randomly separated into four groups of eight rats with each group having approximately equal body weight. Experimental diets were prepared by adding 35 mg Fe/kg as MDFP, ferric pyrophosphate, and ferrous sulfate to the low-iron diets. Experimental diets were fed *ad libitum* to the anemic rats for four weeks. The control rats were similarly fed the standard diet *ad libitum.* The daily intake of feed was registered during the experimental period. After 0, 4, 7, 11, 14, 18, 21, and 28 days, the body weights were

registered and blood samples were taken from the tail of each rat. The hemoglobin content in each blood sample was determined by the hemoglobin cyanide method [19].

The iron content in all the experimental diets was measured after ashing at 550°C in the presence of 1N nitric acid for 24 hours. Ash samples were digested in concentrated HCl and diluted with ionized water. The iron content in the digested sample was determined by atomic absorption spectrophotometer (Hitachi, Japan). The HRE value of various iron sources was calculated as below [15, 16].

Hb Fe (mg) = body wt (kg) × [0.075 L blood/body wt (kg)] × [Hb (g)/blood (L)] × [3.35 mg Fe/Hb (g)]
HRE = $[(\text{Hb Fe (mg)})_{\text{final}} - (\text{Hb Fe (mg)})_{\text{initial}}]$ / Fe consumed (mg)

The RBV for various iron compounds was calculated as the percentage ratio of HRE of MDFP, ferric pyrophosphate, and sodium ferrous citrate with that of ferrous sulfate.

3. Iron bioavailability by modified AOAC method

The anemic and control rats were prepared using the same conditions as described in the HRE method. The iron-deficient anemic rats were randomized into 11 groups with six rats in each group. The iron-deficient anemic rats were fed with different iron compounds providing 0, 6, 12, 18, 24, or 36 mg Fe/kg as MDFP, ferric pyrophosphate, or ferrous sulfate *ad libitum* for two weeks. The blood sample was taken from the tail of the rat at the beginning and end of intake of the experimental diet to measure hemoglobin content. The hemoglobin content in blood samples and the iron content in the experimental diets was measured according to the method described in the HRE method. The slope value for various iron sources was calculated as the ratio between the gain in hemoglobin content in the blood and the iron content in the experimental diet. The RBV for various iron sources was calculated as the percentage ratio between the slope value of the test iron compound and ferrous sulfate.

Statistical analysis

All results were subjected to one-way analysis of variance and expressed in terms of mean and standard error. Differences in the mean values between the groups were analyzed by Duncan's multiple range test and considered significant at $p < 0.05$.

Results

Particle size distribution of base iron compounds

The particle size distribution for MDFP was within the range of 0.1 to 2.6 μm and the average particle size was 0.3 μm. Whereas the particle size distribution of ferric pyrophosphate was between 0.5 to 60 μm and the average size was 5.2 μm (Fig. 1). MDFP showed a sharp and narrow particle size distribution compared to wide distribution of ferric pyrophosphate. Also MDFP particles did not aggregate, unlike ferric pyrophosphate, and its particle size remained constant for six months.

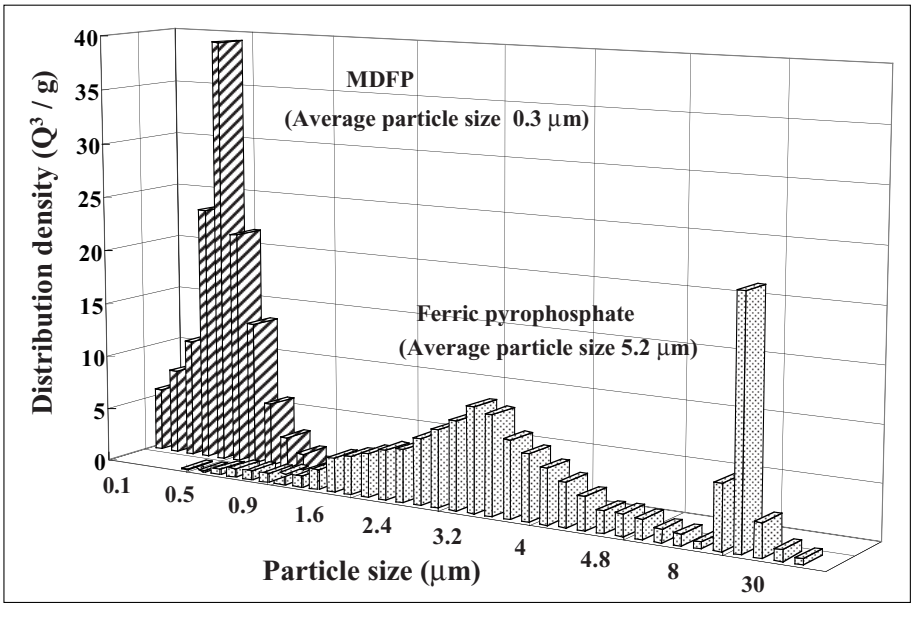

Figure1: Particle size distribution of MDFP and ferric pyrophosphate. The particle size distribution was measured with the laser diffraction particle size distribution analyzer.

Bioavailability studies

1. Measurement of iron bioavailability by SIC method

The changes in serum iron concentrations after oral administration of various iron compounds are shown in Figure 2. In the control group, an average value of 113.4 µg/dL of SIC was observed and it was nearly unchanged during the experimental period. In the iron-fortified groups, the SIC rapidly increased to peak level and then gradually decreased. The SIC reached a peak of 340.0 µg/dL in the ferric pyrophosphate group and 441.2 µg/dL in the sodium ferrous citrate group after 30 minutes of iron administration, and 444.4 µg/dL in the ferrous sulfate group after 60 minutes of iron administration. The SIC in these iron groups rapidly decreased and reached the level of the control group within 8 hours, whereas in the MDFP group, the SIC reached a peak of 388.8 µg/dL after 2 hours of oral administration, with a continuous high SIC even after 8 hours of oral administration.

The average values of AUC for various iron compounds are shown in Table I. MDFP showed the highest AUC value, followed by ferric pyrophosphate, sodium ferrous citrate, ferrous sulfate, and control. The RBV of iron compounds relative to ferrous sulfate was 1.20, 0.61, and 1.10 for MDFP, ferric pyrophosphate, and sodium ferrous citrate, respectively.

2. Measurement of iron bioavailability by HRE method

The initial mean value of hemoglobin levels in anemic rats was in the range of 3.79–4.06 g/dL, compared to 13.90 g/dL in normal control rats. The hemoglobin levels in control rats were unchanged in the four weeks of the experimental period. In the anemic rats, the iron supplementa-

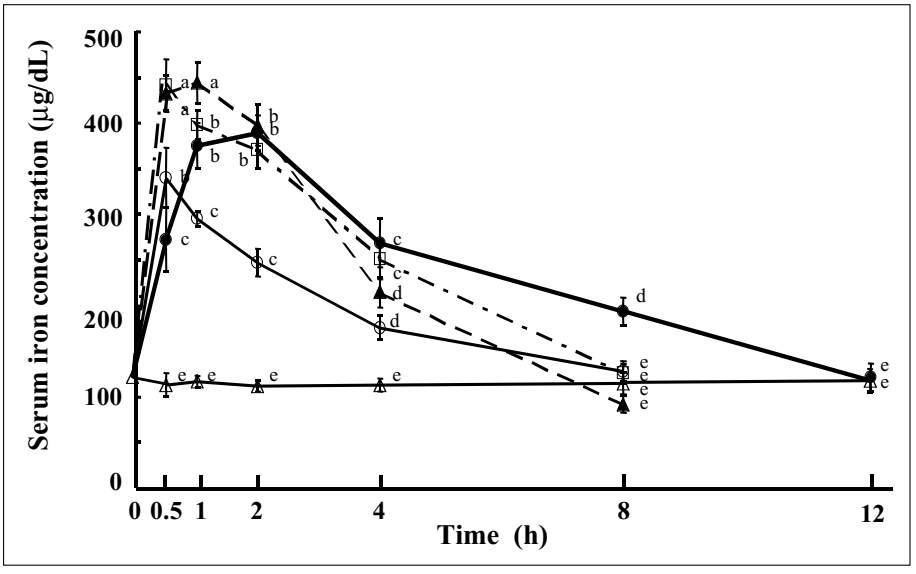

Figure 2: Serum iron level curves after oral administration of 2 mg Fe/kg body weight as MDFP (●), ferric pyrophosphate (○), sodium ferrous citrate (□) and ferrous sulfate (▲) or distilled water as control (△) in normal rat. Error bars indicate the standard error of ten replications. Differences in mean values between the groups were analyzed by Duncan's multiple range test and considered significant at $p < 0.05$.

Table I: Relative biological values (RBV) of various iron compounds as measured by the serum iron concentration method

Iron compound	Maximum (µg/dl)	AUC (µg/dl)	RBV
MDFP	388.8 ± 6.0[a]	2838.9 ± 39.0[a]	1.20 ± 0.03[a]
Ferric pyrophosphate	340.0 ± 10.3[b]	1572.6 ± 25.2[b]	0.61 ± 0.02[b]
Sodium ferrous citrate	441.2 ± 9.0[c]	2107.5 ± 29.5[c]	1.10 ± 0.03[c]
Ferrous sulfate	444.4 ± 7.1[c]	2000.7 ± 30.9[d]	1.00 ± 0.03[d]
Control	116.8 ± 2.0[d]	909.4 ± 12.9[e]	——

Various iron compounds were orally administered at 2 mg Fe/kg body weight to fasted normal rats.
Data are expressed as means ± SE of ten rats in each group.
Differences in mean values between the groups were considered significant at $p < 0.05$.
Maximum is the peak serum iron concentration achieved by each iron compound.
AUC is calculated as the total serum iron concentration for each iron compound.
RBV is the relative AUC value of each iron compound to that of Ferrous sulfate.

tion with MDFP, sodium ferrous citrate, and ferrous sulfate increased the hemoglobin concentrations up to normal levels after 3 weeks. In ferric pyrophosphate however, the hemoglobin level did not reach normal levels even after 4 weeks (data not shown). After 2 weeks of iron fortification, the HRE values were significantly higher for all iron compounds than control treatment (Table II). The RBV of iron compound relative to ferrous sulfate was 1.05 for MDFP, 1.00 for sodium ferrous citrate, and 0.78 for ferric pyrophosphate. MDFP showed the highest values of HRE and RBV among the iron compounds tested.

3. Measurement of iron bioavailability by modified AOAC method

Body weights increased in proportion to hemoglobin content in blood and the amount of iron in diet. The slope value between hemoglobin content and iron content in the diet was 0.270, 0.145, and 0.259 for MDFP, ferric pyrophosphate, and ferrous sulfate, respectively. The RBV of iron compounds relative to ferrous sulfate was 1.04 and 0.56 for MDFP and ferric pyrophosphate, respectively (Table III).

Discussion

Iron fortification in foods is a challenging task because both the soluble and insoluble iron compounds have advantages and disadvantages. Soluble iron compounds are highly bioavailable but they can produce a typical iron taste and may react with food components to change color or flavor of the food. On the other hand, the insoluble iron compounds have the advantage of being nonreactive with food components and have less iron taste, but their insolubility prevents their use in liquid products and they have a low to medium bioavailability. We have developed a micronized, dispersible ferric pyrophosphate (MDFP; SunActive Fe™), which, with the coating of emulsifiers, disperses the insoluble iron in liquid formulations and thus overcomes the major disadvantage of insoluble iron compound.

In the reported bioavailability studies, the MDFP has a bioavailability equivalent to ferrous sulfate and significantly higher than regular ferric pyrophosphate. Earlier studies have indicated a RBV of 39–58% for regular fer-

Table II: Relative biological values (RBV) of various iron compounds as measured by the HRE method

	Body wt. gain (g)	Iron intake (mg/g)	Hb gain (g/dl)	HRE ratio (%)	RBV ratio (%)
Control	87.7 ± 5.2[a]	10.64 ± 0.21[a]	0.60 ± 0.39c	30.41 ± 3.54[c]	
MDFP	86.3 ± 2.4[a]	10.10 ± 0.08[a]	6.85 ± 0.26[a]	55.36 ± 1.69[a]	1.05 ± 0.03[a]
Ferric pyrophosphate	73.7 ± 3.5[b]	10.41 ± 0.24[a]	5.37 ± 0.23[b]	41.11 ± 1.47[b]	0.78 ± 0.03[b]
Sodium ferrous citrate	91.0 ± 3.2[c]	10.42 ± 0.14[a]	6.64 ± 0.43[a]	52.97 ± 2.37[a]	1.00 ± 0.05[a]
Ferrous sulfate	78.9 ± 2.9[f]	10.65 ± 0.14[a]	7.04 ± 0.18[a]	52.81 ± 1.47[a]	1.00 ± 0.03[a]

Iron deficient anemic rats were fed the experimental diet containing 35 mg fortification Fe/kg low iron diet.
Data are expressed as means ± SE of six anemic rats of each group.
Differences in mean values between the groups were considered significant at $p < 0.05$.
RBV is the relative HRE value of each iron compound to that of Ferrous sulfate.

Table III: Relative biological values (RBV) of various iron compounds as measured by the Modified AOAC method

Iron compound	Supplemental iron mg /Fe/kg diet	Body weight gain (g)	Hb gain (g/dl)	Slope	RBV
Ferrous sulfate	0	32.2 ± 5.9	–0.73 ± 0.10		
	6	66.2 ± 7.8	0.56 ± 0.25		
	12	77.9 ± 7.7	2.83 ± 0.24	0.259	1.00
	18	103.9 ± 6.9	3.85 ± 0.21		
	24	116.6 ± 7.4	5.41 ± 0.34		
MDFP	12	72.7 ± 8.0	2.24 ± 0.24		
	24	97.0 ± 5.7	5.22 ± 0.30	0.270	1.04
	36	102.3 ± 5.2	9.06 ± 0.19		
Ferric pyrophosphate	12	65.2 ± 4.2	0.45 ± 0.13		
	24	93.6 ± 2.7	2.74 ± 0.15	0.145	0.56*
	36	102.1 ± 6.4	4.32 ± 0.27		

Six iron deficient anemic rats were fed with supplemental iron diet for 14 days.
Data are expressed as means ± SE. Mean values were significantly different from ferrous sulfate value at $*p < 0.05$.
Slope is the regression slope between hemoglobin gain and level of supplementation.
RBV is the relative slope values of MDFP and ferric pyrophosphate to that of ferrous sulfate.

ric pyrophosphate compared to ferrous sulfate [20,21]. The reason for the high absorption and bioavailability of iron from MDFP could be its micronized particle size and relatively sharp particle size distribution over regular ferric pyrophosphate (Fig. 1). Particle size has previously been shown to have positive influence on iron absorption. Motzok *et al* [22] found about a three-fold increase in bioavailability of reduced iron by reducing the particle size from 24–40 μm to 7–10 μm. Similar observations were also reported for electrolytic iron powder [23] and ferric orthophosphate [24]. Iron absorption is dependent on the solubility of iron compounds in gastric juices [25], as well as their ability to cause precipitation or molecular aggregation [26, 27]. The higher iron absorption from MDFP compared to regular ferric pyrophosphate might be due to an enhanced solubility in gastric juices.

Several iron bioavailability studies have been carried out by the SIC method after oral administration of ferrous sulfate, sodium ferrous citrate, or ferric pyrophosphate [13, 14, 28] and have shown serum iron concentration curves similar to those found in the study. By contrast, the SIC curve after oral iron administration of MDFP showed a lag in peak time and a lengthy period of continued high concentration, which suggest sustained release of iron in the serum (Fig. 2). Further, the high AUC value for MDFP confirmed the high absorption and bioavailability (Table I). The lag in peak time and the sustained release of iron from MDFP is probably a consequence of encapsulation with emulsifiers.

The micronized dispersible ferric pyrophosphate (MDFP) commercially known as SunActive Fe™, offers new possibilities for iron fortification of milk products, soft drinks, yogurt, yogurt drinks, ice cream, soups, and salad dressings. MDFP disperses insoluble iron in liquid formulations without affecting the color and flavor of the product and, unlike regular ferric pyrophosphate, it has equivalent bioavailability to ferrous sulfate.

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