ABSTRACT

Background: Iron deficiency anemia (IDA) is a common nutritional disease worldwide. Iron supplementation is an efficient method for treating patients with IDA. Polysaccharide iron complex is an oral iron supplement that is associated with generally good tolerability and good bioavailability.

Objective: The aim of this study was to evaluate the bioequivalence of 2 branded formulations of polysaccharide iron complex in healthy adult male Chinese volunteers by determining the pharmacokinetic parameters after single-dose oral administration.

Methods: This sequence-randomized, double-blind, 2-way crossover study was carried out in the Affiliated Hospital, Institute of Medical Sciences of Qingdao University, Qingdao, China. Healthy adult male Chinese volunteers were enrolled and evenly randomized to receive 1 of 2 formulations on day 1. Subjects received an oral dose of 150 mg (1 capsule) of polysaccharide iron complex with 150 mL of warm water in the morning. Capsules were of similar size, shape, and color to ensure blinding. Four hours after administration, the subjects were given standardized meals. After a 1-week washout period, the subjects were crossed over to receive the other formulation in a similar manner. The serum iron concentration 12 hours after study drug administration was determined using atomic-absorption spectrometry. The pharmacokinetic parameters $C_{\text{max}}$, $T_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were obtained and analyzed using the Schuirmann 2 one-sided $t$ test. The 2 formulations were considered bioequivalent if the test/reference ratios of $C_{\text{max}}$, $AUC_{0-t}$, and their 90% CIs were within the range of 70% to 143% for $C_{\text{max}}$ and within 80% to 125% for $AUC_{0-t}$. Tolerability was monitored by inquiring whether the subjects had experienced adverse events (AEs), with a focus on gastrointestinal AEs, during the clinic visits during the 24-hour period after drug administration and subsequently via telephone throughout the study.

Results: Thirty adult male Chinese volunteers were assessed for inclusion. Twenty healthy male volunteers (10 in each group) (mean [SD] age, 21.5 [2.9] years...
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(range, 19–23 years); weight, 66.2 [5.8] kg (range, 56–80 kg); height, 172.5 [5.1] cm (range, 162–180 cm) were enrolled and completed the study. The pharmacokinetic parameters of the test and reference formulations were as follows: AUC$_{0-t}$, 6.58 (2.09) and 6.58 (1.91) μg/mL · h$^{-1}$; C$_{max}$, 1.10 (0.28) and 1.07 (0.25) μg/mL; T$_{max}$, 3.93 (0.37) and 3.93 (0.37) hours; t$_{1/2}$, 8.33 (0.36) and 8.38 (0.41) hours; and AUC$_{0-\infty}$, 6.93 (2.23) and 6.95 (2.13) μg/mL · h$^{-1}$, respectively. There were no statistically significant differences in AUC$_{0-t}$ or T$_{max}$ by formulation, period, or subject between the test and reference formulations. Similarly, there were no statistically significant differences in C$_{max}$ by period; however, a significant difference was found in C$_{max}$ by formulation ($P = 0.012$). No clinically significant AEs were reported with either formulation.

**Conclusions:** In these healthy adult male Chinese volunteers, the test formulation of polysaccharide iron complex was found to be bioequivalent to the reference formulation according to the Chinese regulatory definition. A significant difference by formulation was found in C$_{max}$. The sample size was smaller than that recommended by the US Food and Drug Administration for a bioequivalence study, and additional studies with larger sample sizes are needed. (Curr Ther Res Clin Exp. 2009;70:104–115) © 2009 Excerpta Medica Inc.

**Key words:** polysaccharide iron complex, Hongyuanda™, Niferex™, bioequivalence, healthy male volunteers.

**INTRODUCTION**

Iron is important in many bodily functions, especially for the transport of oxygen in the blood.$^1$ Iron deficiency anemia (IDA) is a common nutritional disease worldwide.$^2$ Using anemia as an indicator, the World Health Organization has estimated that 39% of the children 0 to 4 years of age in nonindustrialized countries and 20% of those in industrialized countries have iron deficiency.$^3$ Iron supplementation is an efficient method for treating patients with IDA.$^4$ Traditional iron supplements, such as ferrous sulfate, are associated with serious adverse events (AEs) including abdominal pain, heartburn, nausea, vomiting, constipation, and diarrhea, probably owing to production of hydroxyl free radicals.$^5$ Polysaccharide iron, a form of the mineral iron, is the complex of ferric iron and a low-molecular-weight polysaccharide. This polysaccharide is produced by extensive hydrolysis of starch.$^6$,$^7$ As a ferric supplement, polysaccharide iron has been used to prevent and to treat iron deficiencies and IDA in clinical practice.$^6$,$^7$ Polysaccharide iron can increase concentrations of serum iron and hemoglobin.$^8$,$^9$ It also can be combined with other antianemia drugs, such as recombinant human erythropoietin, to reduce the degree of anemia.$^{10}$,$^{11}$ The absorption of polysaccharide iron complex is comparable to that of a ferrous salt, but it has been associated with fewer gastrointestinal AEs.$^{12}$,$^{13}$ These clinical observations suggest that polysaccharide iron complex, which is associated with generally good tolerability and good bioavailability, might be used as an oral iron supplement.$^{14}$ Because polysaccharide iron is an organic complex without free ions, it may not be associated with AEs common to free ferrous ion: tension, diarrhea, motion sickness, and gastritis.$^4$ Polysac-
charide iron complex can be absorbed at the molecular level in the gastrointestinal tract, and its absorption is not affected by a reduction of hydrochloric acid in gastric fluids or by food. Therefore, polysaccharide iron complex may be regarded as a reliable, effective iron supplement.

According to the bioequivalence standards of the Chinese State Food and Drug Administration (SFDA), 2 formulations are considered bioequivalent if the test/reference ratios of C max, AUC 0–t, and their 90% CIs are within the range of 70% to 143% for C max and within 80% to 125% for AUC 0–t. The bioequivalence standards of the SFDA are consistent with those of the US FDA.

The aim of this study was to evaluate the bioequivalence of 2 branded formulations of polysaccharide iron complex in Chinese volunteers by determining the pharmacokinetic parameters after single-dose oral administration.

SUBJECTS AND METHODS

Subjects

Healthy adult male volunteers were recruited via posters placed at a local university campus. Volunteers were selected after passing a clinical screening procedure that included a physical examination and laboratory tests (blood chemistry, urinalysis, and liver and kidney function studies). Exclusion criteria were a history of drug or alcohol abuse, allergy or AEs with iron therapy, and use of any other investigational medication within 1 month of enrollment. Volunteers were also excluded if they had a history of any illness of the gastrointestinal tract; hepatic, renal, neural, or cardiovascular systems; or a metabolic abnormality; or any other type of coexisting anemia. This was done to ensure that the existing degree of variation would not be due to an influence of illness or other medications.

The study was conducted according to the revised Declaration of Helsinki for biomedical research involving human subjects and the rules of Good Clinical Practice (China). Accordingly, subjects were informed of the aim and risks of the study by the clinical investigator. Subjects were free to withdraw at any time. All participants provided written informed consent after they had been informed of the nature and details of the study. Subjects were compensated for their participation. Investigators were paid their usual salaries and additional money for participating in this study.

Medications and Apparatus

A test formulation* (lot no. 070201; expiration date, July 2, 2009) and a reference formulation† (lot no. 10920507; expiration date, November 15, 2008) of polysaccharide iron complex 150-mg capsules were studied. Formulations used were of similar size, shape, and color to ensure blinding.

Iron criteria solution (National Steel Material Test Center, Beijing, China; 1000 μg/mL in 10% hydrochloric acid) and blood serum standard samples (standard calf serum, 106

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*Trademark: Hongyuanda™ (Guofeng Pharmaceutical Co., Ltd., Qingdao, China).
†Trademark: Niferex™ (Central Pharmaceuticals, Inc., Seymour, Indiana).
National Standard Substance Research Center, Beijing, China) were used. The mean (SD) iron content of the standard serum samples was 1.57 (0.22) μg/mL.

An atomic-absorption spectroscopy (AAS) spectrometer (model AA7003, East & West Analytical Instruments, Inc., Beijing, China) was used for analysis (wavelength, 248.33 nm).

**Study Design**

This sequence-randomized, double-blind, 2-way crossover study was carried out in the Affiliated Hospital, Institute of Medical Sciences of Qingdao University, Qingdao, China. The study protocol was approved by the institutional review board of the Institute of Medical Sciences of Qingdao University.

Each subject received 1 of 2 formulations of an oral dose of 150 mg (1 capsule) of polysaccharide iron complex on the morning of day 1. A pseudorandomization test was done according to the randomization table pregenerated using SAS software version 8.0 (SAS Institute Inc., Cary, North Carolina). The capsules were taken in the morning with 150 mL of warm water. Four hours after administration, all subjects were given standardized meals (2500 kcal). After a 1-week washout period, the subjects were crossed over to the other formulation, in a similar manner. All subjects were instructed to refrain from smoking and from consumption of beverages containing alcohol or coffee, carbonated beverages, syrup, and foods containing large amounts of iron during the study period.

Subjects were instructed to report if they had experienced rheum or bacterial infection at any time during the study. Subjects who experienced rheum or bacterial infection during the study were to be withdrawn. Clinical investigators examined the subjects during the 24-hour period after drug administration and subsequently via telephone throughout the study.

**Blood Sample Collection**

Five-milliliter blood samples were collected via an indwelling cannula from the median cubital vein at 0, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 9, and 12 hours after study drug administration. The blood samples were withdrawn into heparinized glass tubes (Vacutainer, Heraeus, Hanau, Germany) and were stored for 30 minutes in water at 37°C. The blood samples were centrifuged at 3000 rpm for 5 minutes at 4°C, and a 2-mL aliquot of each sample was collected and stored frozen at −20°C until AAS analysis.

**Iron Content Assay**

Each serum sample was diluted with 0.15% deionized water solution (Triton™ X-100, The Dow Chemical Company, Midland, Michigan) at a ratio of 1:3, as explained further. The iron concentration in each sample was analyzed using an AAS method. The serum samples were diluted before AAS analysis to reduce the viscosity to a level that could be tested using AAS. To identify the optimum dilution ratio, iron concentrations in the serum samples were tested at ratios of 1:3, 1:4, 1:9, and 1:10. Five duplicate tests were carried out at each dilution ratio. F and t tests were
used to determine the differences in iron concentration at the different dilution ratios.

Precision (intraday and interday) tests were carried out at nominal iron concentrations of 0.2, 0.5, and 0.9 μg/mL. Recovery experiments were done at nominal iron concentrations of 0.2, 0.4, and 0.9 μg/mL. The standard curve of the serum was established using standard calf serum.

**Methodology**

Because the viscosity of serum is too high to assay iron content by AAS analysis, it was necessary to reduce the viscosity by diluting with deionized water and surfactant, such as Triton X-100. The *F* test (*α* = 0.05) indicated that there were no significant differences in iron content between the data groups with different dilution ratios (1:3, 1:4, 1:9, and 1:10, respectively). The *t* test (*α* = 0.05) found that there were significant differences in serum iron concentration between the dilution ratios of 1:3 or 1:4 and the other dilution ratios when the serum samples were diluted by deionized water; no significant differences were found between the dilution ratios of 1:3, 1:4, and the other dilution ratios when the serum samples were diluted by deionized water containing Triton X-100 (0.15%, W/W). According to the results of the *F* and *t* tests, the optimum dilution ratio of the serum samples was 1:3 with deionized water containing Triton X-100 (0.15%, W/W); therefore, the above optimum dilution ratio was used in testing.

Under the described analytical conditions, the lower limit of quantification (LLOQ) for polysaccharide iron was 0.2 μg/mL. The relationship between the concentration and peak area ratio was shown to be linear from 0.05 to 2.0 μg/mL (*r* > 0.998) (*n* = 5), and was represented as the following equation:

\[ Y = 9.2491X, \]

where *Y* was the iron content of the serum and *X* was the amount of absorption of light.

Quality control samples used to evaluate interassay and intra-assay precision were prepared by spiking control human serum with 0.2 (LLOQ), 0.5, and 0.8 μg/mL of iron.

The intraday precision ranged from 2.03% to 6.33% (all, relative standard deviation [RSD] < 15%), while the interday precision ranged from 1.88% to 6.15% (all, RSD < 15%) (*n* = 15). Recovery was in the range of 85% to 115% (*n* = 15) when the concentration was 0.2, 0.4, and 0.9 μg/mL.

**Tolerability Assessment**

Tolerability was monitored by inquiring whether the subjects had experienced any AEs, but especially gastrointestinal AEs, during the clinic visits during the 24-hour period after drug administration and subsequently via telephone throughout the study. Subjects were followed up for one week after the second administration.
The severity of the symptoms was assessed using the Treatment Emergent Symptoms Scale (scale: 0 = absent; 1 = slight; 2 = mild; 3 = moderate; and 4 = severe).

**Statistical Analysis**

All statistical analyses were performed using the CRFB Bioavailability Statistical Program (Mathematics and Pharmacology Institute, Beijing, China). The data analysis plan was developed a priori. AUC$_{0-t}$ was calculated using the trapezoidal method. C$_{\text{max}}$ and T$_{\text{max}}$ were obtained directly from the serum concentration–time curves of iron.

AUC$_{0-t}$, T$_{\text{max}}$, and C$_{\text{max}}$ were considered to be the primary end points to assess the bioequivalence between the test and reference formulations. Analysis of variance (ANOVA) ($\alpha = 0.1$) using logarithmically transformed AUC$_{0-t}$, C$_{\text{max}}$, and T$_{\text{max}}$ for the randomized 2-way crossover design was used to assess the effect of formulation, period, and subject on these parameters. The 2 formulations were considered bioequivalent if the test/reference ratios of C$_{\text{max}}$, AUC$_{0-t}$, and their 90% CIs were within 70% to 143% for C$_{\text{max}}$ and within 80% to 125% for AUC$_{0-t}$.

Differences between 2 related parameters were considered statistically significant at $P \leq 0.05$. The Schuirmann 2 one-sided $t$ test for logarithmically transformed data was conducted to test the bioequivalence of the pharmacokinetic characteristics of the 2 formulations.

**RESULTS**

**Subjects**

Thirty volunteers were assessed for inclusion. Twenty healthy adult male Chinese volunteers (10 in each group) (mean [SD] age, 21.5 [2.9] years [range, 19–23 years]; weight, 66.2 [5.8] kg [range, 56–80 kg]; height, 172.5 [5.1] cm [range, 162–180 cm]) were enrolled and completed the study. The demographic characteristics of the subjects are shown in Table I.

**Pharmacokinetic Characteristics**

AEs were measured individually through evaluation of the following 6 adverse gastrointestinal events: abdominal pain, heartburn, nausea, vomiting, constipation, and diarrhea. The clinical measurement was the proportion of subjects who reported

<table>
<thead>
<tr>
<th>Table I. Demographic characteristics of healthy male Chinese volunteers (N = 20).* Data are mean (SD).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Height, cm</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
</tbody>
</table>

*No significant between-group differences were found.
†Trademark: Hongyuanda™ (Guofeng Pharmaceutical Co., Ltd., Qingdao, China).
‡Trademark: Niferex™ (Central Pharmaceuticals, Inc., Seymour, Indiana).
any AE (gastrointestinal or otherwise). Clinical tolerability was good for both formulations. No clinically relevant AEs occurred during or after the study.

At the first sampling time (1 hour) after study drug administration, mean (SD) serum iron concentration was detectable in both the test and reference groups (test, 0.20 [0.08] μg/mL; reference, 0.23 [0.11] μg/mL) (Figure 1). The mean (SD) T_max for the test and reference formulations were both 3.93 (0.37) hours and C_max was 1.10 (0.28) and 1.07 (0.25) μg/mL, respectively. No statistically significant differences in these 2 parameters were found between the 2 formulations. Serum iron concentrations then gradually declined, with a mean (SD) terminal t_1/2 of 8.33 (0.36) hours and 8.38 (0.41) hours for the test and reference formulations, respectively (Figure 1 and Table II).

The bioavailability parameters AUC_0–t, C_max, and T_max of the polysaccharide iron complexes were obtained and compared by noncompartmental model analysis. The mean AUC_0–t values were similar for the test and reference formulations (6.58 [2.09] and 6.58 [1.91] μg/mL · h⁻¹, respectively), and the mean AUC_0–∞ values were also similar (6.93 [2.23] and 6.95 [2.13] μg/mL · h⁻¹) (Table II). The relative bioavailability of the test formulation to the reference formulation was 101.0%.

**Standard Bioequivalence Analysis**

The results of the ANOVA test for AUC_0–t, C_max, and T_max are shown in Table III. No statistically significant formulation, period, or subject effects were found in

![Figure 1](image-url). **Figure 1.** Mean serum concentration–time profiles after administration of a single oral dose (150 mg) of test (Hongyuanda™ [Guofeng Pharmaceutical Co., Ltd., Qingdao, China]) and reference (Niferex™ [Central Pharmaceuticals, Inc., Seymour, Indiana]) formulations of polysaccharide iron complex in healthy adult male Chinese volunteers.
AUC0–t or \( T_{\text{max}} \). A statistically significant formulation effect was found in \( C_{\text{max}} \) (\( P = 0.012 \)); the effects of period were not significant.

The 90% CIs of AUC0–t, \( C_{\text{max}} \), and \( T_{\text{max}} \) (natural-log transformed) were 0.986 to 1.031, 0.964 to 0.992, and 0.999 to 1.000, respectively (Table IV). The differences between AUC0–t, \( T_{\text{max}} \), and \( C_{\text{max}} \) were not significant.

**DISCUSSION**

Figure 2 shows the dissolution rates of test and reference formulations. The test formulation was completely dissolved at 25 minutes with a dissolution rate of 100.67%, while the reference drug was not completely dissolved until 40 minutes.

**DISCUSSION**

In this study of 20 healthy male Chinese subjects, two 150-mg polysaccharide iron complex formulations were found to be bioequivalent in all the pharmacokinetic parameters except \( C_{\text{max}} \) when analyzed using ANOVA.

Table II. Bioavailability parameters after administration of test and reference formulations of polysaccharide iron complex in healthy male Chinese volunteers (N = 20).* Data are mean (SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Formulation† (n = 10)</th>
<th>Reference Formulation‡ (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( AUC_{0-t} ), μg/mL ⋅ h(^{-1} )</td>
<td>6.58 (2.09)</td>
<td>6.58 (1.91)</td>
</tr>
<tr>
<td>( C_{\text{max}} ), μg/mL</td>
<td>1.10 (0.28)</td>
<td>1.07 (0.25)</td>
</tr>
<tr>
<td>( T_{\text{max}} ), h</td>
<td>3.93 (0.37)</td>
<td>3.93 (0.37)</td>
</tr>
<tr>
<td>( MRT_{0-t} ), h</td>
<td>5.35 (0.17)</td>
<td>5.39 (0.19)</td>
</tr>
<tr>
<td>( t_{1/2} ), h</td>
<td>8.33 (0.36)</td>
<td>8.38 (0.41)</td>
</tr>
<tr>
<td>( MRT_{0-\infty} ), h</td>
<td>5.85 (0.34)</td>
<td>5.89 (0.40)</td>
</tr>
<tr>
<td>( AUC_{0-\infty} ), μg/mL ⋅ h(^{-1} )</td>
<td>6.93 (2.23)</td>
<td>6.95 (2.13)</td>
</tr>
</tbody>
</table>

MRT = mean residence time.

*No significant between-group differences were found.
†Trademark: Hongyuanda™ (Guofeng Pharmaceutical Co., Ltd., Qingdao, China).
‡Trademark: Niferex™ (Central Pharmaceuticals, Inc., Seymour, Indiana).

The 90% CIs of AUC0–t, \( C_{\text{max}} \), and \( T_{\text{max}} \) (natural-log transformed) were 0.986 to 1.031, 0.964 to 0.992, and 0.999 to 1.000, respectively (Table IV). The differences between AUC0–t, \( T_{\text{max}} \), and \( C_{\text{max}} \) were not significant.

### DISCUSSION

In this study of 20 healthy male Chinese subjects, two 150-mg polysaccharide iron complex formulations were found to be bioequivalent in all the pharmacokinetic parameters except \( C_{\text{max}} \) when analyzed using ANOVA.

Table III. Analysis of variance test (\( \alpha = 0.1 \)) for natural–log-transformed AUC0–t, \( C_{\text{max}} \), and \( T_{\text{max}} \) in healthy male Chinese volunteers (N = 20).

<table>
<thead>
<tr>
<th>Source of Variance</th>
<th>( AUC_{0-t} )</th>
<th>( P^* )</th>
<th>( C_{\text{max}} )</th>
<th>( P^* )</th>
<th>( T_{\text{max}} )</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>0.001</td>
<td>0.521</td>
<td>0.005</td>
<td>0.012</td>
<td>&lt;0.001</td>
<td>0.331</td>
</tr>
<tr>
<td>Period</td>
<td>0.001</td>
<td>0.548</td>
<td>0.002</td>
<td>0.073</td>
<td>&lt;0.001</td>
<td>0.331</td>
</tr>
<tr>
<td>Subject</td>
<td>3.567</td>
<td>&lt;0.001</td>
<td>2.298</td>
<td>&lt;0.001</td>
<td>5.275</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*F test.
Clinical tolerability was good with both formulations. Almost identical serum iron concentration profiles were obtained with both formulations. Both formulations appeared to be readily absorbed in the gastrointestinal tract; measurable concentrations of polysaccharide iron were present at the first sampling time (1 hour postadministration).

**Table IV. Results of the Schuirmann 2 one-sided t tests on pharmacokinetic parameters of healthy adult male Chinese volunteers who received a single-dose administration of 2 formulations of polysaccharide iron complex (N = 20).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\text{AUC}_{0-t}$</th>
<th>$C_{\text{max}}$</th>
<th>$T_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test, * mean</td>
<td>1.844</td>
<td>0.045</td>
<td>3.925</td>
</tr>
<tr>
<td>Reference, † mean</td>
<td>1.835</td>
<td>0.067</td>
<td>3.925</td>
</tr>
<tr>
<td>Mean error</td>
<td>0.041</td>
<td>0.025</td>
<td>0.007</td>
</tr>
<tr>
<td>$t^{†}$</td>
<td>1.734</td>
<td>1.734</td>
<td>1.734</td>
</tr>
<tr>
<td>$t_1$</td>
<td>17.929</td>
<td>24.929</td>
<td>351.063</td>
</tr>
<tr>
<td>$t_2$</td>
<td>16.606</td>
<td>30.502</td>
<td>351.063</td>
</tr>
<tr>
<td>90% CI</td>
<td>0.986–1.031</td>
<td>0.964–0.992</td>
<td>0.999–1.000</td>
</tr>
</tbody>
</table>

*Trademark: Hongyuanda™ (Guofeng Pharmaceutical Co., Ltd., Qingdao, China).
†Trademark: Niferex™ (Central Pharmaceuticals, Inc., Seymour, Indiana).
‡$\alpha = 0.05$, df = 18.

**Figure 2.** Dissolution rate curve of a single oral dose (150 mg) of test (Hongyuanda™ [Guofeng Pharmaceutical Co., Ltd., Qingdao, China]) and reference (Niferex™ [Central Pharmaceuticals, Inc., Seymour, Indiana]) formulations of polysaccharide iron complex in deionized water at 37°C in healthy adult male Chinese volunteers.
tion) in all subjects. Serum profiles of polysaccharide iron concentration versus time after the oral administration of a single dose of both formulations exhibited similar patterns. All of the bioavailability parameters studied (AUC$_{0-t}$, C$_{max}$, T$_{max}$, t$_{1/2}$, and AUC$_{0-\infty}$) were found to be similar for the 2 formulations. No significant difference was found between the 2 formulations in AUC$_{0-t}$ or T$_{max}$ using ANOVA; however, a significant difference was found in C$_{max}$ by formulation (P = 0.012).

With regard to dissolution rates, the test formulation was completely dissolved at 25 minutes, while the reference formulation was completely dissolved at 40 minutes; significant differences were found in dissolution rates between test and reference formulations. Although the test formulation had a more rapid dissolution than that of the reference formulation, bioavailability was equivalent between the 2 formulations. This implies that the dissolution rate has little influence on the bioavailability of the formulations. This may be caused by the differing composition and preparation techniques of the formulations.

No clinically relevant AEs were reported during or after the study. Both formulations were well tolerated; no patient withdrew from the study due to an AE. This finding coincides with the findings of another study that a ferric polysaccharide product was associated with fewer AEs than a ferrous product. Ferrous products, such as ferrous sulfate, are associated with serious AEs. The 90% CIs for AUC$_{0-t}$ were completely contained within the predefined bioequivalence acceptance range of 80% to 125%. Bioequivalence was also demonstrated for C$_{max}$ with the 90% CI within the range of 70% to 143%. These findings both meet the standards required by the SFDA. However, a statistically significant difference was found by formulation in C$_{max}$ (P = 0.012).

This difference in C$_{max}$ has less effect on bioequivalence between the 2 formulations than AUC$_{0-t}$. For iron supplementation therapy, AUC$_{0-t}$ is more important than C$_{max}$ because it is more indicative of the serum iron content on which the effectiveness of iron supplementation depends. Moreover, the iron absorbed after dosing is less closely related to C$_{max}$ than to AUC$_{0-t}$. This relationship is different from that of other drugs (eg, antibiotics) whose C$_{max}$ determines whether the drug concentration reaches therapeutic levels. A statistically significant between-formulation difference was not found in AUC$_{0-t}$. Therefore, the 2 formulations were considered bioequivalent despite a significant difference in C$_{max}$ by formulation.

All pharmacokinetic parameters derived using the noncompartmental method were found to be similar for both formulations. The oral polysaccharide iron complex was cleared from the serum with a t$_{1/2}$ of ~8.33 and 8.38 hours for the test and reference formulations, respectively, which were in accordance with published results for polysaccharide iron complex.

According to SFDA guidance for bioavailability and bioequivalence studies for chemical drug products in humans, a sample size of 18 to 24 subjects is sufficient for a bioequivalence study. The sample size used in this study (20 subjects) had a power of 90% to detect a scientifically meaningful difference in AUC$_{0-t}$ between the 2 formulations.

Based on the US FDA guidelines, the sample size used in this study was smaller than that recommended for a bioequivalence study. Therefore, the results of the
present study require further confirmation by larger studies. Additional limitations of this study were the use of only a single dose of polysaccharide iron complex and the fact that all the subjects were healthy volunteers.

CONCLUSIONS
In these healthy male Chinese volunteers, the test formulation of polysaccharide iron complex was found to be bioequivalent to the reference formulation according to the Chinese regulatory definition. A significant difference by formulation was found in C\text{max}. The sample size was smaller than that recommended by the US FDA for a bioequivalence study, and additional studies with larger sample sizes are needed.

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REFERENCES


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