

Determination of Ferrous Iron in Ferric Chloride Hexahydrate

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Abstract: Objective: As a pharmaceutical raw material, ferric chloride hexahydrate has been included in the British Pharmacopoeia, the European Pharmacopoeia (2008) and the United States Pharmacopoeia (2015), and there are detailed discussions on quality standards and testing methods. Ferric chloride hexahydrate has not been included in the Chinese Pharmacopoeia. This study is the part of research to establish a spectrophotometric method for the determination of ferrous iron in ferric chloride hexahydrate. In this study, the two methods were discussed in detail, and the spectrophotometric method for detecting the content of ferrous iron in ferric chloride hexahydrate was proposed. Methods: The detection method on ferrous iron in ferric chloride hexahydrate among European pharmacopoeia, United States pharmacopoeia and Chemical Reagent Ferric Chloride Hexahydrate (HG/T3474-2014) of China's Chemical Industry were compared. The last two methods were not easy to operation. On the basis of the European pharmacopoeia, a method was proposed that after Fe^{3+} were screened with H_3PO_4 , Fe^{2+} was measured by spectrophotometry, and the method was verified by experiments. Results and Conclusion: The spectrophotometry method is easy to operate and has good reproducibility. The content of ferrous iron can be calculated semi-quantitatively by masking ferric iron with H_3PO_4 and spectrophotometric determination of ferrous ion content. Therefore, the method established in this study can more clearly detect whether the ferrous content in ferric chloride hexahydrate is up to standard.

Keywords: Ferrous Ion, Ferric Chloride Hexahydrate, Spectrophotometry, Quality Control

1. Preface

As a pharmaceutical raw material, ferric chloride hexahydrate has been included in the British Pharmacopoeia, the European Pharmacopoeia (2008) and the United States Pharmacopoeia (2015) [1-5], and there are detailed discussions on quality standards and testing methods. Ferric chloride hexahydrate has not been included in the Chinese Pharmacopoeia [6], but it has been widely used as a pharmaceutical raw material by many domestic pharmaceutical companies. Regarding its quality indicators and testing methods, domestic pharmaceutical companies have their own corporate standards, but they vary according to the understanding of the quality inspection personnel of each enterprise, and the testing methods are not the same. The method for determining the content of ferrous iron in ferric chloride hexahydrate is

basically divided into two types at home and abroad: one is the direct color development method of potassium ferricyanide represented by American Chemical Society (ACS); The second is the phosphate masking represented by the European Pharmacopoeia - potassium ferricyanide coloring method. In this study, the two methods were discussed in detail, and the spectrophotometric method for detecting the content of ferrous iron in ferric chloride hexahydrate was proposed.

2. Instruments and Reagents

2.1. Instruments

722 spectrophotometer (Shanghai Jinghua Technology Instrument Co., Ltd.).

2.2. Reagents

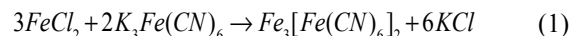
Potassium ferricyanide (Shanghai Qianshun Chemical Reagent Co., Ltd., batch number 1401107), 5% potassium ferricyanide solution prepared on the test day; phosphoric acid (Shanghai Lingfeng Chemical Reagent Co., Ltd., batch number 20151009); sulfuric acid heptahydrate Yatie (Shenzhen Pharmaceutical Group Chemical Reagent Co., Ltd., batch number 10012118) Fe^{2+} concentration of 0.1mg/mL stock solution (weigh 0.250g $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, add H_2SO_4 5mL dissolved and diluted into 500mL volumetric flask); Fe^{2+} concentration of 0.01mg/mL solution (take 10m Fe^{2+} concentration 0.1mg /mL stock solution, diluted to 100mL volumetric flask, ready for use) Ferric chloride solution of hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, Sinopharm Chemical Reagent Co., Ltd., batch number 10011918); hydrochloric acid, Sinopharm Chemical Reagent Co., Ltd., batch number 10011018).

3. Methods and results

3.1. Principle of the Method

$\text{K}_3\text{Fe}(\text{CN})_6$ solution and the divalent iron salt immediately form the Teng's blue precipitate, and its composition is $\text{Fe}^3[\text{Fe}(\text{CN})_6]_2$ [7-9]. At this time, the ferric iron does not interfere, because Fe^{3+} and $\text{K}_3\text{Fe}(\text{CN})_6$ only produce a light

green-brown solutio [10-12], and the Fe^{3+} complex was masked with H_3PO_4 to make it colorless. The chemical reaction formula is as follows:



3.2. Method Establishment

3.2.1. ACS Detection Method

Method: Weigh 0.5g of sample, dissolve it in 20mL hydrochloric acid (1→19), and add 0.05mL of newly prepared 5% $\text{K}_3\text{Fe}(\text{CN})_6$. If there is no blue-green color in 1min, the Fe^{2+} content of the sample is considered no more than 0.002%.

Exploratory test 1: Take different amounts of Fe^{2+} , add different amounts of hydrochloric acid, add 2 drops of 5% $\text{K}_3\text{Fe}(\text{CN})_6$, and measure the absorbance after color development at 1min and 10min. The wavelength of the incident light was yellow ($\lambda=570 \mu\text{m}$), and the length of the cuvette was 5 mm, which was measured with a 722 spectrophotometer. The results are shown in Table 1 and Table 2. It can be seen that when 1mL hydrochloric acid is added to the 25mL test solution, the color is basically not developed, especially when the Fe^{2+} content is as low as 10 μg , the absorbance is lower. In this case, it is impossible to distinguish by visual inspection

Table 1. Absorbance at different iron contents at 1 minute.

HCL \ Fe^{2+} content	10 μg	20 μg	30 μg	40 μg	50 μg	60 μg
0 mL	0.093	0.186	0.283	0.366	0.458	0.562
0.5 mL	0.005	0.013	0.049	0.059	0.183	0.408
1mL	0.005	0.009	0.007	0.011	0.015	0.017
1.5mL	0.010	0.009	0.019	0.008	0.007	0.012

Table 2. Absorbance at different iron contents at 10 minute.

HCL \ Fe^{2+} content	10 μg	20 μg	30 μg	40 μg	50 μg	60 μg
0 mL	0.106	0.193	0.287	0.374	0.465	0.570
0.5 mL	0.005	0.014	0.123	0.237	0.417	0.574
1mL	0.005	0.010	0.010	0.009	0.016	0.029
1.5mL	0.010	0.005	0.019	0.006	0.012	0.012

Table 3. Absorbance comparison of ferrous iron under different conditions.

Time	(1)	(2)	(3)	(4)	(5)
1min	0.093	0.005	0.015	0.059	0.187
2min	0.099	0.005	0.014	0.058	0.186
3min	0.101	0.005	0.015	0.058	0.188
4min	0.102	0.006	0.013	0.059	0.196
5min	0.104	0.004	0.013	0.059	0.198
6min	0.105	0.004	0.013	0.059	0.207
7min	0.105	0.005	0.014		0.223
8min	0.106	0.005	0.016		0.239
9min	0.106	0.003	0.016		0.251
10min	0.107	0.003	0.022		0.254
11min	0.107	0.003	0.023		0.252
12min	0.107	0.005	0.021		0.251
13min	0.108	0.005	0.023		0.251
14min	0.108	0.004	0.018		0.251
15min	0.108	0.005	0.020		0.251

Exploratory Test 2: The test was carried out under the following conditions. Condition A, take 10 μg Fe^{2+} standard solution without adding hydrochloric acid, dilute to 25mL, add 1 drop of 5% $\text{K}_3\text{Fe}(\text{CN})_6$; condition B, take 10 μg Fe^{2+} standard solution, add 1mL hydrochloric acid, dilute to 25mL, add 1 drop of 5% $\text{K}_3\text{Fe}(\text{CN})_6$; Condition C, take 50 μg Fe^{2+} standard solution, add 1mL hydrochloric acid, dilute to 25mL, add 1 drop 5% $\text{K}_3\text{Fe}(\text{CN})_6$; condition D, take 0.5g $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, add 1mL hydrochloric acid, dilute to 25mL without adding $\text{K}_3\text{Fe}(\text{CN})_6$; Condition E, take 0.5g $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, add 1mL hydrochloric acid, dilute to 25mL, add 1 drop of 5% $\text{K}_3\text{Fe}(\text{CN})_6$. The absorbance of the solution was measured using a Model 722 spectrophotometer. The results are shown in Table 3. It can be seen that in the presence of 1 mL of hydrochloric acid, not only the absorbance of 10 μg of

Fe^{2+} is extremely low, but the absorbance of 50 μg of Fe^{2+} is also less than 0.02, but how the absorbance (>0.2) of the sample solution (Condition E) is generated. This is the biggest problem with the ACS method. In addition, without blue-green is not certain that the Fe^{2+} content is not more than 0.002%. Such a small amount of Fe^{2+} (10 μg) relies on visual inspection; the randomness is too large. This is the second problem of the ACS method. Moreover, since the color of the ferric iron is too dark, the detection sampling volume should not be too large.

3.2.2. Test Methods for China's Chemical Industry

Method: The quality index and detection method of ferric chloride hexahydrate in China's chemical industry standard [13] is basically derived from the ACS method. Weigh 0.5g sample, dissolve it in 20mL anaerobic water, add 1mL hydrochloric acid and 1 drop of freshly prepared 5% $\text{K}_3\text{Fe}(\text{CN})_6$, shake it and let it stand for 10min. The solution should be dark blue-green and not deeper than the standard colorimetric solution. Among them, the standard colorimetric solution is prepared by weighing 0.5 g of ferrous iron-free ferric chloride hexahydrate (the solution does not appear blue-green according to the above method) and 0.01 mg Fe^{2+} (analytical grade) or 0.025 mg Fe^{2+} (chemical purity) the ferrous (Fe^{2+}) standard solution, is treated the same as the sample.

Problem: There are three disadvantages of this method: first, that 1 mL of hydrochloric acid is used in the ACS method; second, the sample volume is too little, and the third is to use ferrous-free ferric chloride hexahydrate. Ferrous-free ferric chloride hexahydrate is hard to find. According to the ACS method, no blue-green color indicates that the ferrous content is not more than 0.002%, and it is not meaning free of ferrous iron. Moreover, the author's test shows that the content of ferrous iron in the sample may still be greater than 0.002% or even higher without blue-green color, but it is just visually undetectable.

3.2.3. European Pharmacopoeia Detection Method

Method (phosphoric acid masking - potassium ferricyanide coloring method): To 10mL sample solution (containing 1g sample), add 1mL H_2O and 1 drop of 5% $\text{K}_3\text{Fe}(\text{CN})_6$ solution, then add 4mL H_3PO_4 . After 10min, the blue color in the test solution should not be deeper than the standard solution. The standard solution was 1 mL freshly prepared ferrous sulfate solution (0.25 g/L $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$) and 10 mL H_2O , it treated simultaneously with the sample. Analysis of the detection method of the European Pharmacopoeia, masking the ferric chloride with H_3PO_4 , the method is simple and clear. However, if a spectrophotometer is used for the detection, a sample blank solution should be prepared, that is, the sample ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) solution is mixed with the same H_3PO_4 . When calculating the ferrous content, the absorbance of the sample blank solution should be subtracted from the absorbance of the sample solution.

3.2.4. H_3PO_4 Masking Fe^{3+} Test

Add 1g of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and 25mL of H_2O to each of the 4

colorimetric tubes, and then add 4, 6, 8, 10mL of H_3PO_4 , shake well, and measure the absorbance. The results are shown in Table 4. It can be seen that 10mL H_3PO_4 has the best masking effect. In order to save H_3PO_4 and to be as consistent as possible with the European Pharmacopoeia method, I chose 8mL H_3PO_4 (solution volume before adding H_3PO_4 is 25mL) and the volume of solution of the European Pharmacopoeia method before adding 4mL H_3PO_4 is 11mL.

Table 4. H_3PO_4 Masking Fe^{3+} test= $570\mu\text{m}$, $h=50\text{mm}$.

Time	4mL	6mL	8mL	10mL
2min	0.043	0.041	0.035	0.002
3min	0.041	0.040	0.034	0.002
4min	0.042	0.040	0.033	0.001
5min	0.041	0.042	0.033	0.001
6min	0.042	0.041	0.036	0.001

3.2.5. Spectrophotometric Detection of Ferrous Iron

According to the European Pharmacopoeia method, the method for detecting ferrous iron in ferric chloride hexahydrate is to take four 50 ml colorimetric tubes, numbered A, B, C, and D. Add 50 μg of Fe^{2+} standard solution to the tube A and D. Add 1 gram of sample to each of the B tube, C tube, and D tube, and dissolve with a small amount of H_2O ; dilute the 4 tube solutions to 25 ml with H_2O , shake well; go to tube A, tube C, and tube D, Add 2 drops of 5% $\text{K}_3\text{Fe}(\text{CN})_6$ solution, shake well; add 8mL H_3PO_4 to each of the 4 tubes, shake well [where the D tube only plays the role of supervising the sample, its color must be deeper than the A tube, otherwise the sample may contain an oxidant (such as Cl_2). If knowing there is no oxidant in the sample, the tube D may not be used. After 10 minutes, the absorbance is determined by the 722 spectrophotometer= $570\mu\text{m}$, $H=50\text{mm}$, calculate the content of ferrous iron in the sample using the following formula

$$x = 50(C - B) / A \quad (2)$$

Table 5. Verify test results (absorbance).

Time	50 μg Fe^{2+}	1gSample Blank	1gSinopharm Sample
01min	0.208	0.054	0.106
2min	0.199	0.050	0.109
3min	0.194	0.049	0.113
4min	0.192	0.049	0.117
5min	0.189	0.049	0.121
6min	0.187	0.049	0.124
7min	0.186	0.048	0.126
8min	0.185	0.049	0.129
9min	0.184	0.050	0.132
10min	0.183	0.049	0.134
11min	0.181	0.048	0.135
12min	0.182	0.049	0.138
13min	0.181	0.050	0.139
14min	0.180	0.048	0.140
15min	0.179	0.049	0.141
16min	0.178	0.048	0.143
17min	0.178	0.048	0.144
18min	0.178	0.048	0.146
19min	0.177	0.048	0.146
20min	0.177	0.048	0.147

3.3. Experimental Verification

Take the $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ sample of Sinopharm Chemical Reagent Co., Ltd. and measure according to the method of 2.2.5. The results are shown in Table 5. Since the absorbance of $50\mu\text{g Fe}^{2+}$ standard solution and sample solution changes with time, therefore, the time limit should be specified, and still take the European Pharmacopoeia 10min as the standard. Calculated according to formula 1, the content of ferrous iron in the sample is obtained.

4. Discussion

When the content of Fe^{2+} in the sample is under very strict requirement, such as Fe^{2+} not more than 50×10^{-6} , or even no more than 20×10^{-6} , it should be considered that ferric chloride hexahydrate is not very stable. Ferric chloride hexahydrate is a very strong oxidant, and it is very active and has obvious disproportionation. When the aqueous solution is directly heated on an electric furnace, and even the hot solution is filtered by a filter paper filter cloth or a PP microporous membrane, it can generate Fe^{2+} [14-15]. Ferric chloride hexahydrate is especially sensitive to light, and disproportionation is easy to occur under illumination, and ferrous iron is automatically generated. For example, ferric chloride hexahydrate having a Fe^{2+} content of 0.002% is placed in a test tube, and after being placed outdoors for 10 days, the Fe^{2+} content becomes 0.22%, which can be increased by 100 times. Therefore, the packaging and storage of its products is very important. Only to be absolutely protected from light, the ferrous iron will no longer be produced or the growth rate will slow down. When testing the ferrous content of the product, the package should be opened newly. Do not take samples from the product that has been opened for a long time. If the ferrous test requirements are very strict during production, try not to use ferric chloride hexahydrate when the package is opened for a long time.

The detection method of the European Pharmacopoeia takes $50\mu\text{g Fe}^{2+}$ standard solution, which is 5 times of the ACS method ($10\mu\text{g}$). The blue-green color is clear, and there is no plausible and ambiguous feeling when visually observed. It is also reliable to measure the absorbance with a spectrophotometer. The European Pharmacopoeia's detection method subtly uses H_3PO_4 to mask the color of ferric iron, eliminating the background color of FeCl_3 , which is basically at the same color level as the standard solution without FeCl_3 . It is easier, more clear, and more reasonable. The content of ferrous iron can be calculated semi-quantitatively by masking ferric iron with H_3PO_4 and spectrophotometric determination

of ferrous ion content. Therefore, the method established in this study can more clearly detect whether the ferrous content in ferric chloride hexahydrate is up to standard.

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