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A New FAAS Method for the Determination of Iron Content in Drugs Using SPME

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ABSTRACT

Objective: This study is based on the determination of iron, which is found in iron-containing drugs, by a simple, precise, and economical method.

Methods: In our study, Flame Atomic Absorption Spectroscopy (FAAS) was used for measurements due to its ease of use and low cost. The disadvantage of FAAS in terms of insufficient precision was turned into an advantage by adding a slotted quartz tube (SQT) to the device and using an enrichment method. Accordingly, a solid-phase microextraction (SPME) method interconnected with slotted quartz tube-flame atomic absorption spectrometry (SQT-FAAS) was developed.

Results: While the LOD value for Fe^{3+} ions measured by FAAS was 108.0 mg/L, the LOD value was determined to be 1.12 mg/L with the method developed using CoMNP-SPME-SQT. This indicates a 96.43-fold improvement in the LOD.

Conclusion: The developed Co-MNP-DSPE-SQT-FAAS method has been successfully and easily applied for the determination of iron in iron-containing drug samples. These results indicate that the method can also be applied to different samples.

Keywords: Atomic Absorption Spectroscopy (FAAS), Drug, Flame, Iron, Magnetic Nanoparticle-Solid Phase Microextraction (MNPSPME)

INTRODUCTION

The symbol for iron, "Fe," is derived from the Latin word "ferrum." It is a metal with an atomic number of 26 and an atomic weight of 55.847 amu. Between 3000 and 1700 BCE, iron of meteoric origin, along with silver and gold, was used to craft ornamental objects. Around 2000 BCE, the Hittites utilized iron obtained from iron ores to manufacture weapons.[1] Iron has been a fundamental element in human history from the dawn of civilization to the present day. In ancient times, it was used to shape tools, create weapons, and even as a dietary supplement. Iron is an essential inorganic nutrient for the human body. It plays a crucial role in DNA synthesis and repair, ATP (energy) production, oxygen transport, cognitive functions, enzymatic reactions, and various biological processes. Therefore, it must be maintained within specific levels in the body.[2-6] Iron is a trace element required for the structural and functional roles of the body, such as oxygen transport and storage, electron transport, oxidative metabolism, cell growth, and proliferation.[7,8] The amount of iron in the human body varies between 3 to 5 grams, with the majority found in the form of hemoglobin molecules.

Iron deficiency, also known as anemia, occurs when the body's need for iron cannot be met due to various reasons. In this condition, iron levels in the blood decrease, red blood cell production declines, and the amount of oxygen transported to cells is reduced. In iron deficiency, there is an imbalance between the iron intake through diet and the iron required for growth, development, and metabolic functions.[9] Iron is vital for almost all living organisms. However, both low and high iron levels are harmful to living beings and can lead to a wide range of diseases.[10] In cases of iron deficiency, various pathological and physiological disorders may occur in the body. If left untreated, iron deficiency anemia can result in complications such as irregular heartbeat, angina and heart attack, heart enlargement and failure, low birth weight, increased risk of infections, delayed growth (in children), diabetes, liver and kidney damage.[2,11,12]

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Flame atomic absorption spectrometry (FAAS) enables easy and cost-effective measurements at low concentrations. However, due to the short residence time of analyte atoms in the measurement zone, its sensitivity can be low. This issue has been largely minimized with the development of atom traps.[13,14] By using a glass tube called a slotted quartz tube (SQT), the residence time of analyte atoms in the measurement zone is extended, thereby enhancing sensitivity. It is an accessory designed to be used as an atom trap in the burner head of a conventional flame atomic absorption system.[15,16]

In this study, a sensitive, accurate, and environmentally friendly analytical method was developed. To determine the Fe^{3+} content in iron-containing drugs, the method was optimized by adjusting parameters such as the pH of the medium, the amount of buffer, the type and duration of mixing, and the amount of magnetic nanoparticles. Initially, FAAS was used, followed by optimization with SQT-FAAS and preconcentration using magnetic nanoparticles. Subsequently, the study focused on iron-containing drugs, yielding satisfactory results.

METHODS

Chemicals and reagents

Iron standard stock solution (1000mg/L) obtained from High Purity Standards was used for the preparation of the different concentrations of iron. All the dilutions and rinsing processes were done with ultrapure water which was produced by a Milli-Q® Reference Ultrapure Water Purification System. Sodium hydroxide, sodium bicarbonate, potassium dihydrogen phosphate, hydrochloric acid and di-sodium tetraborate decahydrate were used for the preparation of buffer solutions ranging from pH 1.0 to 9.0. Sigma-Aldrich brand oleic acid ($C_{18}H_{34}O_2$) was used as coating material and all the other chemical including ammonia, sodium hydroxide, sodium bicarbonate, potassium dihydrogen phosphate, hydrochloric acid, di-sodium tetraborate decahydrate, ethanol, nitric acid, ammonium iron(II)sulfate hexahydrate and iron(III) chloride were obtained from Merck, Germany.

Apparatus

Shimadzu Model –AA- 7000 series atomic absorption spectro meter was used throughout this study. The SQT used to lower the FAAS detection limit was a specially cut quartz tube with 18 mm inner diameter, 20 mm outer diameter, 10 cm inlet slit and 6 cm outlet slit. Heidolph model hot plate was used for all the heating processes. An OHAUS Pioneer PA214C precision scale and METTLER TOLEDO pH Meter were used for weighing and pH measurement purposes. For the separation of MNP from aqueous solution, a neodymium magnet was used. An Iron hollow cathode lamp operating at 248.3 nm was used as line source. In addition, a deuterium (D2) lamp was used as background correction tool. All the devices were calibrated to ensure that accurate measurements were performed.

Preparation of Magnetic Nanoparticles (MNP)

7.109 g $FeCl_3 \cdot 6H_2O$ and 5.883 g $(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$ are weighed and placed in a round-bottom flask. Then, 300 mL of distilled water is added to dissolve the compounds. The solution is heated at 80°C for 30 minutes. Subsequently, 30 mL of NH_3 and 3 mL of oleic acid are added simultaneously while nitrogen gas is passed through the solution to create an inert atmosphere. The mixture is heated for 2 hours. After 2 hours, nanoparticles begin to form in the solution.[17]

After the nanoparticles are formed, the particles are filtered using a magnet and washed five times with distilled water and ethanol. They are then dried in an oven under vacuum at 70°C. The dried MNPs are crushed in a mortar to form a powder. In this way, the MNPs to be used in the experiment are prepared.

Preparation of Solutions Used

Initially, 1000 mg/L stock iron solutions were prepared using iron standard for the experiments. Solutions with concentrations of 100, 150, 200, 250, 300, 350, 400, 500, 600, 700, 800, and 900 µg/L were prepared by diluting the stock solutions with distilled water and were used in the experiments. In addition, buffer solutions with pH values ranging from 1 to 9, measured with a pH meter, were used for pH adjustments.

Factors Affecting the Analysis Result

Liquid-phase microextraction experiments were conducted to remove iron ion using MNPs. During the experiment, the effects of metals that could potentially be present in the environment on the experimental results were examined.

Work with Real Samples

The iron content in commercially purchased iron-containing drugs was measured by determining the concentrations of the analyte in FAAS. The developed method was used to quantitatively measure the iron content in the iron-containing drugs.

Experimental Study to Be Conducted

The experimental design for the iron ion to be extracted is shown in Figure 1 below.

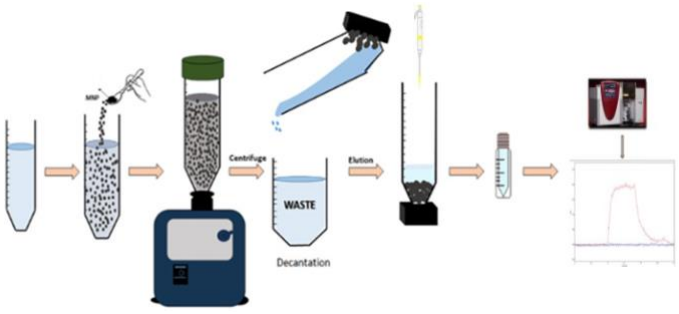

Figure 1. Schematic representation of the experimental study conducted.[18]

RESULTS and DISCUSSION

In the studies, we attempted to apply our method to iron-containing drugs. For this purpose, Fe-MNP was prepared. However, when we conducted experiments using Fe-MNP, inconsistencies were detected in the data obtained from the device analysis results. The same inconsistencies were observed in repeated experiments. The reason for this was determined to be the very high iron content of Fe-MNP.

In the study, the amount of iron added to the environment was 0.5 µg/L, and this value was very low compared to the MNP. Since the goal of the study was to analyze very low amounts of iron, Fe^{3+} determination studies were continued with Co-MNP instead of Fe-MNP. Co-MNP was purchased commercially.

Effect of pH on Microextraction for Fe^{3+}

In our work with iron, the effect of pH on microextraction was initially investigated. For this, 1 mL of buffer solutions with pH values of 3, 4, 5, 6, 7, 8, and 9 were added to 30 mL of 500 µg/L Fe^{3+} solution. After shaking by hand for 10 seconds, 0.1 g of Co-MNP was added and shaken again for 10 seconds. Then, the MNPs were held with a magnet, and the top liquid was discarded. Finally, 1 mL of concentrated nitric acid was added, and the solution was diluted to 50% before being measured with AAS.

In the experimental studies conducted with iron, it was observed that microextraction increased with pH changes in the acidic region, with the best retention occurring at pH = 5. The results are shown in Figure 2.

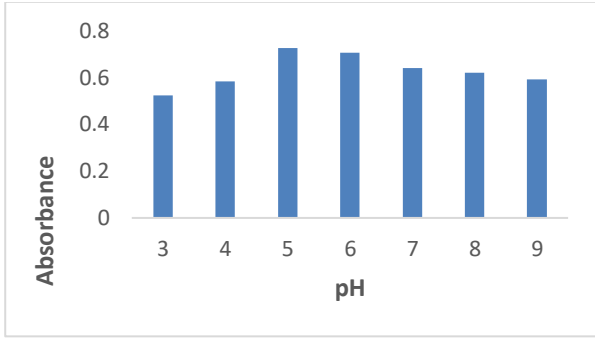

Figure 2. Retention of Fe^{3+} ions on the MNP surface at different pH values (N=4).

Metal Adsorption in Acidic and Basic Regions

In acidic regions, the capacity for metal adsorption from aqueous solutions decreases. As a result, at low pH, an electrostatic repulsion force is generated between the metal ion and the adsorbent, which prevents the metal from adhering. Metals are basic in nature. Therefore, at low pOH, the retention is low. In addition, in basic regions, the electrostatic repulsion force between the metal ion and the complex prevents metal adsorption. As a result, the capacity for metal absorption from aqueous solutions decreases in basic regions.

Effect of Buffer Amount on Microextraction for Fe^{3+}

After determining the optimum pH for Fe^{3+} as 5, the optimum buffer amount was studied. For this, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 mL of pH 5 buffer were added to 30 mL of 500 µg/L Fe^{3+} solution. The mixture was shaken by hand for 10 seconds, followed by the addition of 0.05 g of Co-MNP, which was shaken for an additional 10 seconds. The MNP portion was then held with a magnet, and the top liquid was discarded. 1 mL of concentrated nitric acid was added, and the solution was diluted to 50% before being measured with FAAS. Upon examining the effect of buffer amount on microextraction, it was observed that the highest adsorption occurred with 1 mL of pH 5 buffer, after which it decreased. The results are shown in Figure 3.

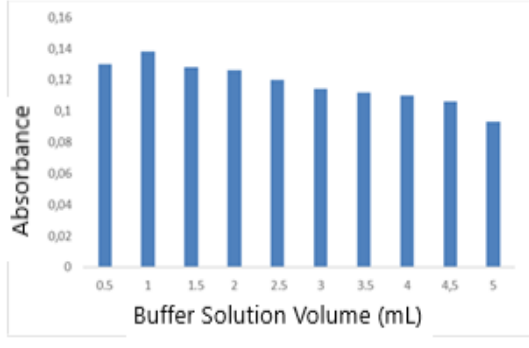

Figure 3. Fe^{3+} retention on MNP at different buffer amounts (N=4).

Effect of Magnetic Nanoparticle Amount on Microextraction for Fe^{3+}

After optimizing pH and buffer amount, the retention of Fe^{3+} ions on the adsorbent was investigated with varying amounts of magnetic nanoparticles. To do this, 1 mL of pH 5 buffer was added to 30 mL of 500 µg/L Fe^{3+} solution and shaken for 10 seconds. Then, Co-MNP was added in amounts of 0.01, 0.02, 0.03, 0.04, 0.05, and 0.06 g, and the mixture was shaken for another 10 seconds. The MNPs were held with a magnet, and the top liquid was discarded. Finally, 1 mL of nitric acid was added, and the solution was diluted to 50% before measurement. The results are shown in Figure 4.

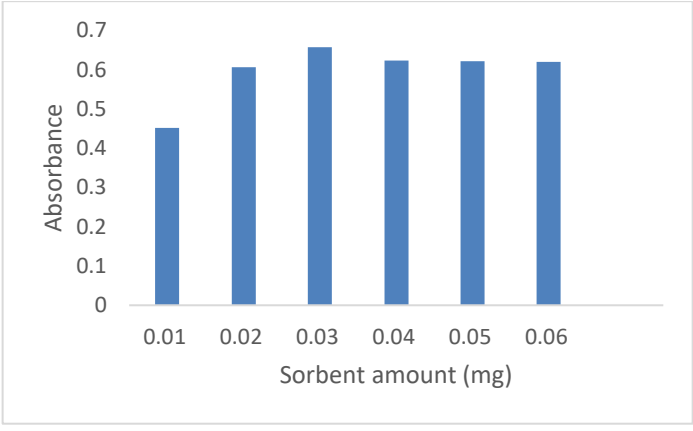

Figure 4. Retention of Fe^{3+} metal with different amounts of MNP (N=4).

As the amount of Co-MNP used increased, the adsorption showed a tendency to decrease after reaching a certain point. The reason for this is that as the amount of MNP increases, the surface area increases, but the forces on the surface overlap, leading to a reduction in the surface area, which in turn causes a decrease in adsorption. In our study, the optimum Co-MNP amount was found to be 0.03g.

Effect of shaking method on microextraction for Fe^{3+}

In order to investigate which type of shaker provides the best MNP adsorption for Fe^{3+} ions, five different shakers were used. 1 mL of pH 5 buffer was added to 30 mL of 500 µg/L Fe^{3+} solution, followed by shaking for 10 seconds by hand. Then, 0.03 g of optimized Co-MNP was added. Afterward, the mixture was shaken for 60 seconds using sonic, mechanical, rotator, manual (hand), and vortex methods. The MNP-containing portion was held with a magnet, and the top liquid was discarded. 1 mL of concentrated nitric acid was added, and the solution was diluted to 50% before measurement. As shown in Figure 5 the highest absorbance value was obtained using the mechanical stirrer.

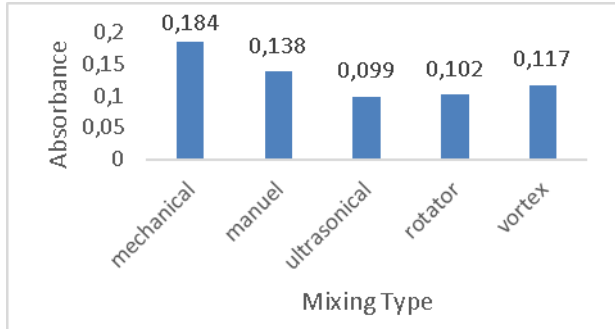

Figure 5. Fe^{3+} adsorption by MNP in different shakers (N=4).

Effect of shaking time on microextraction for Fe^{3+}

After deciding to use the mechanical shaker for shaking in the experimental studies, shaking time experiments were conducted. For this, 1 mL of the optimized pH 5 buffer was added to 30 mL of 500 µg/L Fe^{3+} solution, followed by shaking for 10 seconds by hand. Then, 0.03 g of Co-MNP was added and the mixture was shaken in the mechanical shaker for 15, 30, 45, 60, 90, 120, and 150 seconds. Afterward, the MNP-containing portion was held with a magnet and the top liquid was discarded. 1 mL of concentrated nitric acid was added, and the solution was diluted to 50% before measurement. The results are shown in Figure 6.

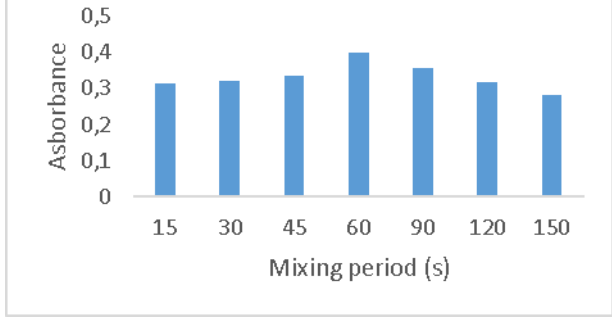

Figure 6. Effect of shaking time on Fe^{3+} adsorption (N=4).

The best absorbance values were observed at 60 seconds and 150 seconds. Since the absorbance difference between 60 seconds and 150 seconds was not significant, and our goal is to perform microextraction in the shortest time possible, the optimum time for the mechanical shaker was decided to be 60 seconds.

Effect of eluent volume on microextraction for Fe^{3+}

In our preliminary studies, it was necessary to use an appropriate solvent for the recovery of analytes adsorbed by the adsorbent. The most suitable solvent for this process is HNO_3. After optimizing all conditions in our study, the effect of eluent volume on microextraction was investigated. For this, 30 mL of 500 µg/L Fe^{3+} solution was added to 1 mL of pH 5 buffer and shaken for 10 seconds.

Then, 0.03 g of Co-MNP was added, and the mixture was shaken for 60 seconds in a rotator. After the liquid part was decanted using a magnet to hold the MNP, different volumes of HNO_3 (1 mL, 1.5 mL, 2 mL, 2.5 mL, and 3 mL) were added as the eluent. When less than 1 mL of solvent was used, insufficient analyte was obtained during measurement, so the measurements started with 1,5 mL of eluent. The results of the study are shown in Figure 7. As seen in the figure, the best absorption value was observed when 1,5 mL of HNO_3 was used.

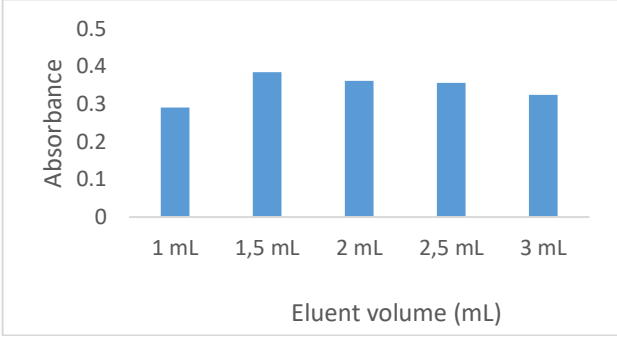

Figure 7. Effect of eluent volume on Fe^{3+} retention (N=4)

Effect of temperature on microextraction for Fe^{3+}

In the Fe^{3+} extraction process, five different temperatures were tested to determine the optimum temperature. For this purpose, 30 mL of 500 µg/L Fe^{3+} solution was added with 1 mL of pH 5 buffer and shaken for 10 seconds. Then, 0.03 g of Co-MNP was added, and the mixture was shaken for 60 seconds in a mechanical shaker. Afterward, the sample was left at different temperatures (25°C, 40°C, 50°C, 60°C, and 75°C) for 15 minutes.

The MNP part was then held with a magnet, and the upper liquid was discarded. Finally, 1,5 mL of concentrated nitric acid was added, and the solution was diluted 50% before measuring the absorbance value using FAAS. The best adsorption was observed at 25°C. The results are shown in Figure 8.

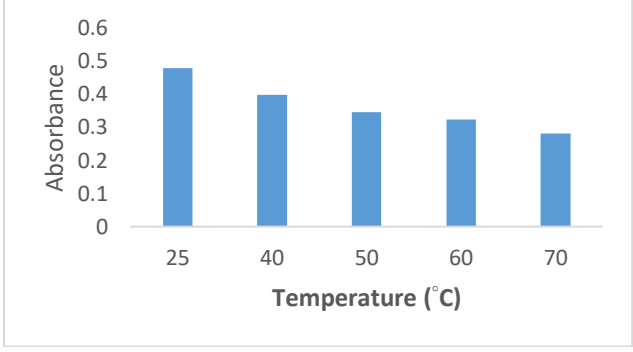

Figure 8. Effect of temperature on Fe^{3+} retention (N=4)

Effect of contact time on microextraction for Fe^{3+}

After determining the optimum temperature for Fe^{3+} extraction, experiments were conducted at five different temperatures. For this purpose, 30 mL of 500 µg/L Fe^{3+} solution was added with 1 mL of pH 5 buffer and shaken for 10 seconds. Then, 0.03 g of Co-MNP was added, and the mixture was shaken for 60 seconds in a mechanical shaker.

The sample was then kept at 25°C for 15, 30, 45, 60, and 120 minutes. Afterward, the MNP part was held with a magnet, and the upper liquid was discarded. Then, 1 mL of concentrated nitric acid was added, and absorbance values were measured using FAAS. The best adsorption was observed after 15 minutes at 25°C. The results are shown in Figure 9.

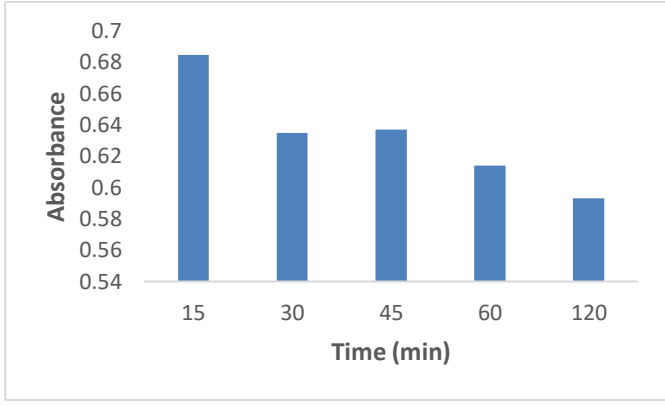

Figure 9. Effect of contact time on Fe3+ retention (N=4)

Maximum Concentration of Fe^{3+} Ion

In this section of the study, a concentration experiment was conducted with MNP. To determine the maximum concentration for the extraction process, solutions of Fe^{3+} were prepared with concentrations of 150, 300, 400, 500, 600, and 700 µg/L. Afterward, 1 mL of pH 5 buffer was added, followed by shaking for 10 seconds. Then, 0.03 g of Co-MNP was added, and the mixture was shaken for 60 seconds in a mechanical shaker. The sample was then kept at 25°C for 15 minutes.

The MNP part was held with a magnet, and the upper liquid was discarded. Then, 0.5 mL of concentrated nitric acid was added, and absorbance values were measured using FAAS. As shown in the figure, it was determined that the maximum concentration for Fe^{3+} solution under these conditions was 500 µg/L. The results are shown in Figure 10.

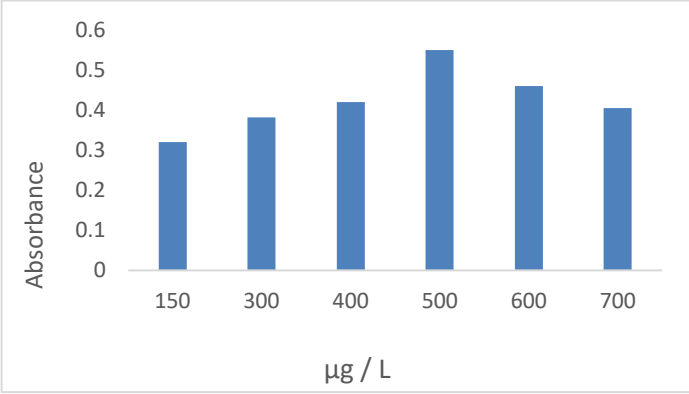

Figure 10. Maximum concentration of Fe^{3+} ion (N=4)

Interference Effects in Fe^{3+} Microextraction

To examine the interference effects, after the retention of Fe^{3+} ions by MNP using liquid-phase microextraction, solutions of metals such as Silver (Ag), Gold (Au), Copper (Cu), Cobalt (Co), Nickel (Ni), and Chromium (Cr) were added at ratios of 1:1, 1:10, and 1:100, while keeping the Fe^{3+} concentration constant. The interference effects of these elements on absorbance were determined by measuring with FAAS. Thus, the effects of certain metals that could be present in the sample environment on the recovery of analytes pre-concentrated with the developed microextraction technique were investigated in AAS analyses. The results obtained are shown in Figure 11.

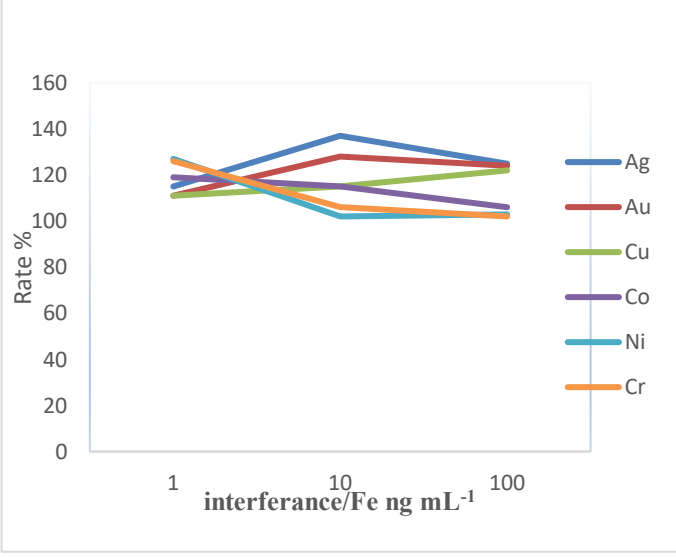

Figure 11. Interference effects of certain elements on Fe^{3+} retention

As seen in Figure 11, when Ag, Cu, Au, Co, Ni, and Cr ions are present in the environment during Fe^{3+} analysis with MNP, the absorbance values decrease. Therefore, when these ions are present in the environment, analyses should be conducted using wavelengths that do not interfere with these elements or these elements should be removed by chemical methods.

In our experimental study, 30 mg of MNP was added to a solution containing 1 mL of pH=5.0 buffer, and after being shaken in a rotator for 60 seconds, the measurements were performed using SQT-FAAS. The optimal values obtained are shown in Table 1.

Table 1. Optimum Experimental Parameters for Co-MNP Microextraction of Fe^{3+} Ions

Parameters	Values
pH and buffer amount	5.0 - 1 mL
MNP amount	30.0 mg
Shaking method and time	Mechanical shaker (60 seconds)
Eluent type and amount	1500 µL (HNO_3)
FAAS sample flow rate	7.6 mL/min
FAAS acetylene flow rate	52.0 L/h
SQT height	1.0 mm
Wavelength for Fe	248.3 nm
FAAS current	12 mA
FAAS slit width	0.2 nm

This table outlines the optimum experimental conditions for the microextraction of Fe^{3+} ions using Co-MNP, specifically tailored for FAAS analysis.

The calculations for LOD and LOQ

A crucial parameter in the study is the determination of LOD (Limit of Detection) and LOQ (Limit of Quantitation) values. LOD is the minimum detection limit at which the presence of an analyte can be quantitatively identified under specific conditions, while LOQ refers to the minimum concentration of the analyte that can be reliably and quantitatively measured under specific conditions. For determining the LOD and LOQ values, the lowest standard was measured 12 times on the instrument, and the standard deviation of the results was calculated. The calculations were carried out using the following formulas:

- LOD = (3s)/m
- LOQ = (10s)/m

In these formulas, **s** represents the standard deviation, and **m** represents the slope of the concentration versus response curve.

Table 2. LOD and LOQ values for Co-MNP-based microextraction of Fe^{3+} ions

	LOD, mg/L	LOQ, mg/L	R^2	y= mx + n	Lineer range (mg/L)
FAAS	108.0	359.64	0.9944	y= 0.0002 + 0.0036	50 - 500
SQT-FAAS	64.1	213.45	0.9839	y= 0.0015x - 0.004	25 - 300
CoMNP-SPME-FAAS	12.3	40.96	0.9907	y= 0.0077x -0002	0.5 - 50
CoMNP-SPME-SQT	1.12	3.73	0.9921	y=0.0096x + 0.0005	0.3 - 10

In the experiments conducted with FAAS, the LOD value was found to be 108.0 mg/L, while in the method developed with OAMNP-SPME-SQT, the LOD value was determined to be 1.12 mg/L. This indicates that the LOD has improved by a factor of 96.43.

Application of the method to real samples

Our study then continued with iron-containing drugs. The work was focused on the pills given to patients by doctors for iron deficiency. It is known that 100 mg of iron is present in the pills of two different brands. Five pills in total, from two different pharmacies, were taken and properly dissolved, then analyzed using the method we developed. The results are presented in Table 3.

Table 3. Analysis results of iron drugs sold in pharmacies

Sample	Found amount (mg)	Amount stated in prospectus (mg)
A1	100.05 ± 2.14	100
A2	101.32 ± 1.69	100
A3	99.96 ± 0.28	100
B1	102.34 ± 0.76	100
B2	101.92 ± 1.73	100

A and B: 2 different brands of iron tablets
As seen from the table, the amount of iron in the pills corresponds to the results of the analysis we performed. Thus, it has been determined that with our analytical method, Fe analysis in drugs and other matrices can be performed accurately and reliably.

CONCLUSION

In our study, accurate and sensitive determination of iron at trace levels in iron-containing drugs samples was performed by the combination of Co-MNP-DSPE and SQT-FAAS systems. Co-MNP sorbent was purchased commercially.

Univariate optimization studies were conducted to increase the signal to noise ratio for the analyte. When the analytical performance of the developed Co-MNP-DSPE-SQT-FAAS system was compared to conventional FAAS system, 96,43 times enhancement in detection power was attained for the analyte. Real sample application was also performed using iron-containing drugs samples. All quantitative results for the samples were in accordance with the iron amount stated in prospectuses. In conclusion, the developed Co-MNP-DSPE-SQT-FAAS method was easily and successfully performed to determine ironin iron-containing drugs samples. These results also show that the method can be applied to different samples.

Ethics Committee Approval: This is not a study that requires ethics committee approval.
Author Contributions: Concept - A.T,I.A; Design - A.T,I.A,F.A; Supervision - I.A,F.A; Resources - A.T; Materials - A.T; Data Collection and/or Processing - A.T,I.A; Analysis and/or Interpretation - I.A,F.A; Literature Search - A.T; Writing Manuscript - A.T,I.A,F.A; Critical Review - A.T,I.A,F.A.
Declaration of Interests: The authors have no conflicts of interest to declare.
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