Use of a Portable X-Ray Fluorescence Analyzer for Determination of Iron in Vitamins and Supplements

Cassandra Casillas, Swee Chew, Alex Lam, Juan Castillo, and Peter T. Palmer[a, 1]

[a]*Department of Chemistry & Biochemistry, San Francisco State University, San Francisco, CA 94132*

Abstract

This study describes the development of an X-Ray Fluorescence (XRF) method to quantify iron in vitamins and supplements. Four different products and a NIST Standard Reference Material (SRM) were prepared by homogenizing 20 tablets in a mixer mill and diluting known masses of each sample into known masses of cellulose. Calibration standards were similarly prepared by diluting known masses of iron oxide into known masses of cellulose. Analyses were performed using a handheld XRF analyzer using one-minute analysis times. The method gave linear calibration curves with R^2 values greater than 0.9995, and good accuracy as demonstrated by relative errors of 9% in the analysis of the NIST SRM. Experimentally determined concentrations of the samples were compared to the nominal concentration of the samples based on the mass of iron per tablet and the average tablet mass. XRF results gave relative differences of +4% and -4% for two iron supplements. XRF results gave a larger relative difference of -19% for the women's vitamin product. Although the label on the men's vitamin product stated it was iron-free, XRF and Microwave Plasma Atomic Emission Spectrometry (MP-AES) analyses showed it contained iron levels of 157 and 133 µg/g (ppm), respectively. This XRF method offers a simpler, faster, and less expensive alternative to conventional atomic spectrometry-based methods for this type of application.

Abbreviations:

FAAS	Flame Atomic Absorption Spectrometry
ICP-AES	Inductively Coupled Plasma – Atomic Emission Spectrometry
ICP-MS	Inductively Coupled Plasma – Mass Spectrometry
LOD	Limit of Detection
MP-AES	Microwave Plasma – Atomic Emission Spectrometry
NIH	National Institute of Health
NIST	National Institute of Standards and Technology
ppm	part-per-million (µg/g)
RSD	relative standard deviation (standard deviation divided by mean)
SRM	Standard Reference Material
UV/Vis	Ultraviolet/visible (in context of spectrometry)
w/w	mass (weight) of analyte divided by mass (weight) of sample
XRF	X-Ray Fluorescence

Keywords: XRF, screening, iron, vitamins, supplements

[1]Corresponding Author: Pete Palmer @ e-mail palmer@sfsu.edu,

1. Introduction

Iron (Fe) is an essential nutrient to regulate and sustain human body functions [3, 5]. Many individuals take iron-containing vitamins on a daily basis. People with low iron levels and anemia are routinely prescribed iron supplements. Vitamin and supplement products are widely available, sold over the counter, and have sales reaching into the billions of dollars per year in the U.S. alone [26]. However, the supplement industry is somewhat loosely regulated and these products are typically not subjected to frequent regulatory oversight. FDA requires manufacturers to provide information on the content of vitamins on the product label, requires testing for all "*reasonably anticipated contaminants*", and can pursue regulatory action if levels/doses are shown to be toxic [9].

While there are no published guidelines for the expected tolerance of ingredients in a dietary supplement, anecdotal information and experience indicates that these products contain iron levels that are usually within ±20% of the amount indicated on the product label. While these products typically do not pose a health risk, young children and infants can consume several pills at once and are at risk of an accidental iron overdose. Indeed, "*iron overdose has been one of the leading causes of poisoning deaths in children younger than 6 years*" [15]. Recommended daily amounts of iron are given in Table 1 [14]. The upper tolerable intakes as set by the National Institute of Health (NIH) range from sub-mg levels for infants to 27 mg for pregnant women.

Determination of iron and other metals can be accomplished via UV/Vis Spectrophotometry [7, 8, 10, 12], Flame Atomic Absorption Spectrometry (FAAS) [1], Inductively Coupled Plasma - Atomic Emission Spectrometry (ICP-AES) [29], and Inductively Coupled Plasma - Mass Spectrometry (ICP-MS) [30]. These methods require significant sample preparation to digest, filter, and dilute the sample prior to analysis. In contrast to these more common elemental analysis methods, X-Ray Fluorescence (XRF) offers the advantages of minimal sample preparation, simplicity, low cost, and speed [11, 20, 21].

There are several published methods on the use of XRF for determination of iron in supplements [4, 6, 16, 25]. In one study, a lab-grade XRF instrument and the emission transmission method were used to quantify iron at levels ranging from 70 µg/g to 37% (w/w or g Fe divided by g sample * 100%) in Ayurvedic herbal supplement products [17]. In a second study, a lab-grade XRF instrument and the fundamental parameters-based quantification method were used to determine iron levels in 10 herbal supplement products ranging from 68 to 6100 µg/g, with the analysis of reference materials demonstrating relative errors less than 10% [2]. In a third study, a portable XRF analyzer was used to determine iron levels in nine supplement products, and showed relative errors less than 6% from the analysis of two SRMs [28].

Many XRF applications are focused on screening (i.e., assessing the elemental composition of a sample) [16, 20-23, 27]. This screening may play a role in a common misconception that XRF can at best provide only semi-quantitative results. As shown in this and other studies, *XRF can provide accurate and reliable quantitative results* if one prepares homogeneous samples, uses standards prepared in a matrix that closely matches that of the samples matrices, and utilizes appropriate calibration procedures,

[24, 25]. This manuscript describes the development of a portable XRF-based methods to quantify iron in vitamins and supplements.

Key features of this method include the preparation of homogenous samples for analysis and dilution into cellulose to reduce matrix effects, preparation and use of a set of standards to calibrate instrument response, and analysis times on the order of one minute per sample. Validation included assessment of the method's accuracy, precision, linearity, and LOD. This method was applied to four different products, including two iron supplement products and two vitamin products.

Table 1 Recommended daily amount of iron for humans based on sex and age [14].

Life Stage	Recommended Amount in mg
Birth to 6 months	0.27
Infants 7-12 months	11
Children 1-3 years	7
Children 4-8 years	10
Children 9-13 years	8
Teen boys 14-18 years	11
Teen girls 14-18 years	15
Adult men 19-50 years	8
Adult women 19-50 years	18
Adults 51 years and older	8
Pregnant teens	27
Pregnant women	27
Breastfeeding teens	10
Breastfeeding women	9

2. Materials and Methods

2.1 Standards

Standards were prepared by mixing known amounts of 99.9% purity powdered Fe_2O_3 (Sigma-Aldrich) into microcrystalline high purity powdered cellulose (Premier Lab Supply) followed by serial dilutions. Table 2 provides an example describing the preparation of standards, masses of Fe_2O_3 (or 5000 ppm standard) and cellulose used, and equivalent concentrations reported in

units of µg/g (ppm or mass of iron divided by total mass * 10^6). The two different powders were mixed for 5 minutes at a rate of 30 Hz in a Retsch model MM400 mixer mill using a 50-mL stainless steel grinding vessel and five 10-mm diameter stainless steel grinding balls. The grinding vessel and balls were cleaned and dried between each preparation. A method blank prepared by placing cellulose in the mixer mill immediately after processing the 5000 µg/g standard showed non-detectable levels of iron via XRF analysis, demonstrating that this procedure did not result in cross contamination. The initial nominal 5000 µg/g standard was used to prepare a set of calibration standards in the range of ~100 to 1000 µg/g by diluting known masses of the nominal 5000 µg/g standard into cellulose, and following the same homogenization process described above. It should be noted that the limit of linearity of XRF response is ~2000 µg/g (ppm). At concentrations higher than this, XRF response "rolls off" due to self-absorption of fluorescence.

Table 2. Example showing the gravimetric preparation of a set of iron standards in a cellulose matrix. Note the computed concentration is equivalent to mg of Fe divided by the total g (mass of standard plus cellulose). Ideally, each mass should be > 0.1000 g to reduce the relatively uncertainty of the mass measurement and computed concentration.

nominal conc. (µg/g or ppm)	mass of Fe_2O_3 (g)	mass of 5000 µg/g standard (g)	mass of cellulose (g)	*computed* conc. (µg/g or ppm)
5000	0.0359	N/A	4.9356	5051
1000	N/A	1.0039	4.0015	1013
500	N/A	0.5082	4.4949	513
200	N/A	0.2013	4.7901	204
100	N/A	0.1016	4.8960	103

2.2 Samples

Four different products were purchased from a local store, representing two iron supplements (Target brand supplement containing 65 mg Fe/tablet and a Now brand supplement containing 25 mg Fe/tablet), and two vitamin products (Target brand women's multivitamin and Target brand men's iron-free multivitamin). Iron levels in the tablets ranged from 0 to 17% based on mass of Fe per pill stated on the product label and the average tablet masses determined by weighing 10 individual tablets from each product. 20 tablets of each product were placed in the mixer mill and homogenized using the same procedure described for the standards. A NIST multivitamin SRM 3280 [18] was prepared and processed in a manner similar to the samples.

The samples required subsequent dilution to place their concentrations into the linear portion of the calibration curve and reduce matrix effects due to the different densities, compositions, and matrices of the original products and standards. Table 3 provides an

example describing the preparation of a set of samples. Homogenized portions of each product were diluted by mixing known masses of each into known masses of cellulose in the mixer mill. For the 65 mg iron supplement product, two consecutive (serial) dilutions were used to dilute the relatively high levels of iron in this product into the range of the standards. As per the table below, preparation of this sample did not use a sufficiently large dilution factor to generate a nominal concentration after dilution that was below that of the highest (1000 µg/g) standard.

Table 3. Example showing the preparation of a set of samples. The dilution factor is equivalent to the total g (mass of sample plus cellulose) divided by mass of sample. The nominal concentration is based on the mass of iron per tablet reported on the product label divided by the average tablet mass divided by the dilution factor.

Sample	mass of sample (g)	mass of cellulose (g)	dilution factor	nominal conc. after dilution (µg/g or ppm)
SRM	0.2087	4.7876	23.94	518
27 mg supplement	0.0659	4.9327	75.85	517
65 mg supplement - first dilution	0.4173	4.5713	11.95	14145
65 mg supplement - second dilution	0.8012	4.1895	6.229	2271
Women's vitamin	0.0618	4.9475	36.48	251
Men's vitamin	2.4994	2.5122	2.0051	0

2.3 XRF Analyzer

The standards and samples were placed into single open-ended XRF sample cups, sealed with 3.5 µm Mylar (polyethylene terephthalate) film, and analyzed using an Olympus/Innov-X Delta Premium model handheld XRF analyzer operated in closed-beam mode in a test stand. XRF spectra were acquired in soil beam 2 mode using one-minute live times. XRF spectra were downloaded from the portable XRF analyzer into Excel to facilitate data analysis and processing.

A common misconception in the use of portable XRF analyzers is trusting their results without verification or validation. The XRF analyzer's soil mode is *not* designed for determination of iron in a vitamin matrix. Users should always consider the use of matrix-matched standards and appropriate calibration techniques to ensure accurate results.

In this work, three different methods were evaluated to calibrate XRF response:

1. Fe K_α intensity (maximum peak emission intensity at 6.40 ± 0.05 keV versus standard concentration) versus the known concentration of the standard
2. Compton-normalized Fe K_α intensity (Fe K_α peak intensity divided by the

Compton peak intensity at 20-21 keV) versus the known concentration of the standard
3. XRF analyzer's reported concentration versus the known concentration of the standard (henceforth referred to here as "recalibration", in which the vendor's factory-based calibration is corrected for the analyte and matrix of interest)

All three modes provided similar linearity and accuracy (as assessed by relative error in the analysis of the SRM). Method 2 is preferred over method 1, as the use of Compton Normalization partially corrects for the different densities and matrices of the samples and standards. Note that both methods 1 and 2 required downloading the XRF spectra into Excel to process the data and generate calibration curves. Method 3 is the most sophisticated, as it relies on vendor software that utilizes peak areas instead of peak heights (intensities) and attempts to correct for spectral overlaps of other elements with that of the element of interest to compute element concentrations. To implement this "recalibration", a linear regression was used to fit the analyzer reported concentration to the known concentration of the standard, and the computed slope and intercept were programmed into the handheld analyzer to provide computed concentrations based on this calibration.

2.4 MP-AES Analysis

A Varian model 4200 Microwave Plasma – Atomic Emission Spectrometry (MP-AES) instrument was used to confirm the presence and levels of iron in the men's vitamin product. A single pill weighing 1.2885 g was digested in 25 mL of water and 1 mL of concentrated nitric acid. This solution was quantitatively transferred to a 50 mL volumetric flask and analyzed via MP-AES. The MP-AES instrument was set to monitor iron emission at 404.581 nm using 1-s integration times and calibrated with standards ranging from 0 to 200 µg/mL (ppm) Fe in 2% concentration nitric acid. The resulting calibration curve (not shown here) gave an R^2 value of 0.9999 and used to determine the concentration of Fe in the extract solution. Using this concentration and factoring in the extract volume and sample mass, the Fe content in the original tablet was computed.

3. Results and Discussion

3.1 XRF Spectra

Figure 1 shows expanded XRF spectra of the 27 mg iron supplement and men's vitamin products. The supplement shows only two peaks representing Fe K_α and K_β fluorescence at 6.40 and 7.06 keV, respectively. The men's vitamin spectrum shows the presence of several elements including Ca (K_α at 3.69 and K_β at 4.01 keV), Mn (K_α at 5.90 keV and K_β at 6.49 keV), Ni (K_α at 7.48 keV), Cu (K_α at 8.05 keV), Zn (K_α at 8.54 and K_β at 9.57 keV) and Se (K_α at 11.22 and K_β at 12.50 keV).

3.2 Method Validation

Figure 2 shows the "recalibration" of the XRF soil mode response (method 3 as described above). This curve shows a linear response with an R^2 value of 0.9998, which supports the viability of the mixer mill method in preparing a homogenous set of standards. The slope of this calibration curve is greater than 1, meaning that when used the XRF analyzer is used in soil mode, it gives a determinate error and a positive bias for this element and matrix.

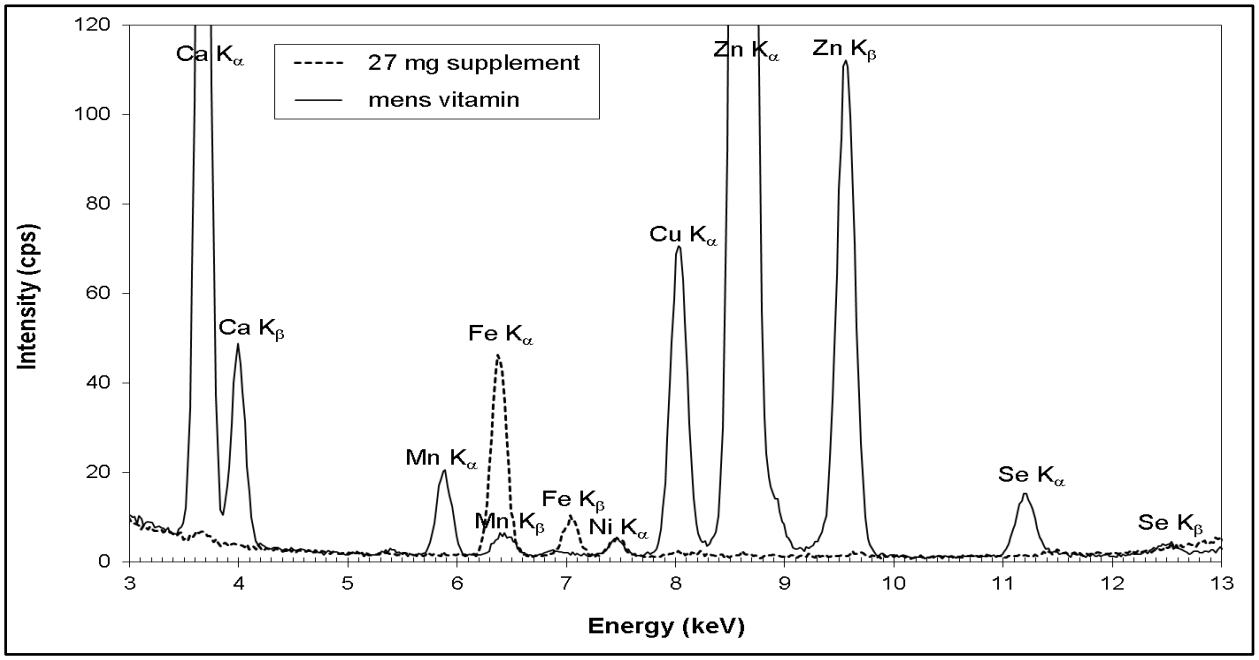

Figure 1. Expanded XRF spectra of 27 mg iron supplement and men's vitamin products.

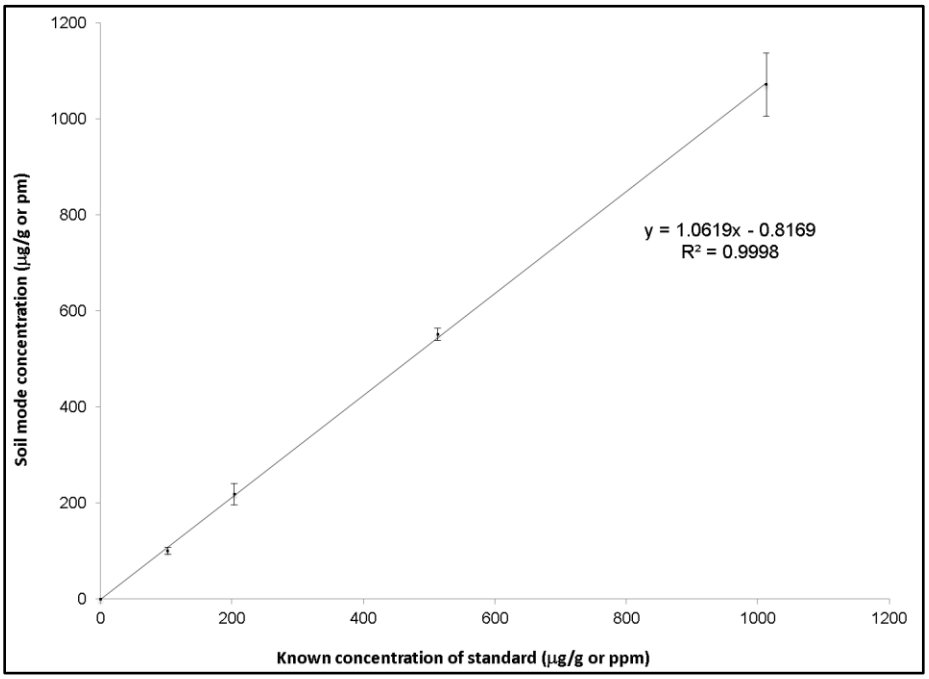

Figure 2. Calibration curve plotting analyzer reported concentration versus known concentration. Error bars denote the standard deviation from three replicate measurements.

The LOD of this method was determined from 10 replicate measurements of the 103 µg/g standard, computing its signal-to-noise ratio (where signal represents the average Fe K_α peak height above the baseline, and the noise represents the standard deviation), and computing the concentration of a standard giving a signal-to-noise ratio of 3. This gave an LOD of 20 µg/g (ppm), which is slightly higher than the vendor-reported LOD of 10 µg/g (ppm), which was computed using 2-minute live times with the XRF analyzer operated in soil mode.

Precision was assessed by performing replicate analyses of each standard and sample. The relative standard deviations (RSDs) varied from 0.5-10%, with higher RSDs for standard/sample concentrations closer to the LOD. These RSDs are within the range of the typical <5% RSDs commonly provided by portable XRF [19].

Accuracy was assessed by analyzing NIST SRM 3280 which contains 1.235 ± 0.91% (w/w) Fe in a vitamin pill type matrix. Note that the instructions on the certificate of analysis for this SRM state that "*at least 15 tablets must be ground to obtain a homogeneous sample prior to removal of a test portion for analysis"*. As described above, the SRM and samples required dilution to reduce determinate errors that arise from the different compositions and matrices of the standards and samples. A dilution factor of ~20 or higher was found to give good accuracy with relative errors of -12%, -4% and 9% from three separate preparations and analyses of the SRM.

3.3 XRF Results

Table 4 provides results from analyses of the SRM and samples. The nominal concentration of iron in the samples were computed using the manufacturer-reported iron levels per tablet and average tablet masses. It should be understood that these nominal concentrations are *not certified* (with the exception of the SRM). The relative difference between the experimentally computed and nominal concentrations of iron in the samples ranged from -19% to 4%. These differences are within the expected range for quantitative analysis via XRF of homogenized solid materials. The heterogeneity of these products is supported by the fact that the *certified* level of Fe in the NIST SRM has an RSD of 7.4% (12.35 ± 0.91 mg/g) and the following statement in the certificate of analysis: "*the variation of measured element mass fractions from tablet-to-tablet ranges from approximately 15-25%*" [18]. The men's vitamin product label indicates that it is "iron-free" with the label stating 0 mg of Fe per tablet. A closer look at the XRF spectrum of the men's vitamin product in Figure 1 shows a small peak at 6.50 keV, which can be attributed to the presence of Mn and/or trace levels of Fe in in this product. The results of the XRF analysis indicated a Fe concentration of 107 µg/g in this product. Subsequent analysis of this same sample via digestion, dilution, and Microwave Plasma - Atomic Emission spectrometry (MP-AES) analysis gave a Fe concentration of 133 µg/g. Based on this evidence, one can conclude that the men's vitamin product is *not* iron free and contains low levels of Fe (< 0.1 mg/tablet).

4. Conclusions

This work describes the development, validation, and application of a method based on the use of a portable XRF analyzer to determine iron in vitamins and supplements.

It offers several advantages versus conventional atomic spectrometry methods

as indicated in Table 5, particularly simplicity, speed, and cost. Although the method requires sample homogenization and dilution into a cellulose matrix, this involves less time and effort compared to sample preparation associated with conventional atomic spectrometry techniques (i.e., homogenization, digestion, filtration, and dilution). Sample dilution provides the additional advantages of folding the relatively high concentrations of iron in these products into the linear portion of the calibration curve and providing sample matrices which more closely match that of the standards (i.e., >90% cellulose).

Table 4. Results of XRF analyses, including experimentally computed concentrations of *diluted* samples, concentration of *original* samples (folding in the dilution factors from Table 3), nominal concentration of samples (based on mass of iron per tablet on product label and average tablet mass), and % relative difference between the experimentally computed and nominal concentrations.

Sample	*diluted* sample conc. (µg/g)	*original* sample conc. (%Fe)	nominal sample conc. (%Fe)	% relative difference
SRM	563	1.35	1.24	9%
27 mg supplement	530	4.02	3.87	4%
65 mg supplement	2162	16.1	16.8	-4%
Women's vitamin	91	0.739	0.916	-19%
Men's vitamin	53	0.0107	0	N/A

Potential limitations of the method are its selectivity which can be compromised by spectral overlaps (it should be noted that the same is true for both MP-AES and ICP-AES), detection limits which are not as low as ICP-AES or ICP-MS (but more than adequate for this application), and the lack of familiarity of many analysts in preparing homogeneous standards in a solid matrix.

This same method could be modified to determine other nutritional elements in vitamin and supplement products (i.e., calcium, manganese, zinc, and selenium) and would be suitable for use by manufacturers, regulatory agencies, and/or private labs to provide better quality control of these products. For future work, the use of a lab-based XRF instrument with more sophisticated calibration options including the use of Fundamental Parameter-based quantification coupled with the analysis of certified reference materials may provide accurate determination iron of these products without dilution [2].

5. Disclaimer

The authors declare that there is no conflict of interest. The views expressed here are those of the authors and should not be construed to represent the views or policies of the FDA. Any reference to a specific commercial product, manufacturer, or otherwise is for the information and convenience of the public and does not constitute an endorsement, recommendation, of favoring by the FDA.

Table 5: Comparison of selected figures of merit for XRF and MP-AES methods to determine iron in vitamins and supplements.

Figure of merit	Portable XRF	MP-AES
Standard preparation	Standards can be prepared in advance and are typically stable for weeks	Aqueous standards must be prepared just prior to analysis
Sample preparation	Relatively simple - tablets are ground and mixed into cellulose	Requires more time and effort - tablets are ground, weighed, digested, filtered, and diluted to known volume
Limit of Detection	10 µg/g (ppm) for Fe in sample prepared for analysis	2 µg/g (ppm) for Fe in *original sample* (based on 0.1 g sample mass, 0.1 L dilution volume, and 2 µg/L (ppb) MP-AES LOD for Fe)
Precision	RSDs <5%	RSDs <2%
Instrument Cost	US $25,000 - $50,000	US $55,000 - $65,000 (does not include nitrogen or argon costs, note ICP-AES instruments US $120,000)

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