Short communication

Determination of Cu, Fe, Mn and Zn by flame atomic absorption spectrometry in multivitamin/multimineral dosage forms or tablets after an acidic extraction

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Abstract

This work presents the development of a methodology for the determination of Cu, Fe, Mn and Zn in samples of multivitamin/multimineral tablets, by flame atomic absorption spectrometry (FAAS), after extraction of the analytes with diluted hydrochloric acid solution. Several parameters that could influence the extraction process such as acid extraction solution concentration and nature, mixing mode (ultrasonic or magnetic stirring), extraction time and sample composition were evaluated. The obtained results showed that Fe, Mn and Zn were easily extracted with 1 mol/L HCl solution after 5 min of mixing with either ultrasonic or magnetic stirring for all studied samples. On the other hand, Cu extraction appeared to be more complex since it could only be extracted at the same conditions for silicate-free samples. For samples containing silicates the time of contact between solid sample and extraction solution presented remarkable influence, being necessary up to 12 h to achieve quantitative recovery with 1 mol/L HCl solution. The developed methodology was applied in the determination of Cu, Fe, Mn and Zn in seven commercially available multivitamin/multimineral tablets. The results obtained with the developed method were compared with those obtained after total digestion of samples using a closed-vessel microwave oven device.
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1. Introduction

The utilization of multivitamin or multimineral preparations is widespread nowadays. It has been estimated that approximately 40% of the United States population consumes vitamin and/or mineral preparations [1]. Multivitamin preparations can contain several elements and many vitamins and/or pro-vitamins in concentrations varying from few to thousands of $\mu g\,g^{-1}$. Copper, Fe, Mn and Zn are essential elements present in most of multivitamin/multimineral formulations due to their physiological importance and biological roles [2,3]. The development of reliable methods for the determination of elements in these supplements is an important issue because of their widespread consumption. Several analytical techniques and different strategies for sample preparation have been used for such purpose [2–10].

Sample preparation still represents the most sensitive and time-consuming step in most analytical procedures. Only total digestion enables the determination of total metallic content in different types of samples. In spite of its versatility total digestion exhibits some drawbacks depending on the experimental procedure utilized. Dry ashing procedures are very simple to perform but some elements can be lost by volatilization. In turn, wet acid digestion is faster than dry procedures but requires large amounts of reagents and constant supervision [11]. Analyses of multivitamin/multimineral samples have usually been performed after total digestion of samples. Canfranc et al. [9] determined Fe and Mo in pharmaceutical preparations by flame atomic absorption spectrometry (FAAS), after dry ashing of samples at 600 °C. No volatilization of the analytes under study was observed at

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this temperature. Hight et al. [4] utilized boiling acids and acid mixtures containing HNO_3, $HClO_4$, H_2SO_4 and H_2O_2 for total dissolution of dietary supplements before measurement of 36 elements in 42 samples. A multicommutation flow system was developed for the spectrophotometric determination of Fe, Zn, Ca and Mg in multivitamin samples. Total acid digestion of samples was carried out with a mixture of concentrated HNO_3 and $HClO_4$ [6,7].

Closed-vessel microwave-assisted digestion of solid samples with concentrated acids or acid mixtures has also been employed in several studies for the determination of metallic elements in complex matrices [12–16]. The main advantages of closed-vessel microwave-assisted digestion are the high relative speed, low possibility of contamination and the minimum loss of volatile elements. However, the high cost of instrumentation seems to be an important limitation. This technique has also been successfully applied in sample preparation for the determination of Cr and other elements in multivitamin/multimineral supplements [8]. Also, microwave radiation was used as energy source for the decomposition of 95 dietary supplement products and NIST reference materials with concentrated nitric acid aiming the determination of As, Cd, Hg and Pb [5].

Application of extraction procedures has gained a considerable space in the field of sample preparation [11,17]. Some advantages such as low cost, high speed, possibility to process a large number of samples simultaneously and low requirements in terms of personal supervision are observed when this kind of procedure is applied. Although these advantages, only a few works were found reporting the use of extraction approaches for elemental determination in multivitamin tablets [10].

Present work was focused on the study of the extraction of Cu, Fe, Mn and Zn from multivitamin/multimineral preparations using diluted acid solutions followed by their determination by FAAS. Different approaches such as ultrasonic and magnetic stirring mixing were tested to carry out the extraction. Extraction efficiencies were calculated considering data obtained by microwave-assisted digestion with concentrated HNO_3 as the total content of metals in the samples.

2. Experimental

2.1. Apparatus

A Perkin-Elmer Analyst 100 atomic absorption spectrometer (Norwalk, CT, USA) equipped with single hollow cathode lamps for measurements of Cu, Fe, Mn and Zn were used. The equipment was operated at standard conditions recommended by the manufacturer for each element determination.

A DGT-100 Plus microwave oven from Provecto (Jundiaí, Brazil) was used for total digestion of samples through a four-step program.

Ultrasound-assisted extraction was performed in an ultrasonic bath with constant frequency of 40 MHz from Lab-Line Instruments (Melrose Park, IL, USA), model 9332.

A magnetic stirrer Quimis (Rio de Janeiro, Brazil), model Q-221 was also employed for sample extraction. A stirring velocity of approximately 300 rpm was applied in all cases.

2.2. Reagents and solutions

Analytical grade concentrated acids (HCl and HNO_3 from Merck, Rio de Janeiro, Brazil) were used without further purification. All solutions used in the experimental work were prepared by using purified water obtained in a Milli-Q Water System (Millipore, Bedford, MA, USA).

Individual solutions containing the elements of interest were prepared by adequate dilution of 1000 mg/L stock standard solutions of each element (Merck, Darmstadt, Germany).

2.3. Sample preparation procedures

2.3.1. Solid sample pretreatment

Solid multivitamin/multimineral preparations were purchased from the local market. Prior to analysis, a set with 20 tablets was manually grinded with an agate mortar and pestle, homogenized and sieved through a 1 mm pore diameter plastic sieve.

2.3.2. Total digestion of samples

Total digestion of samples was carried out by mixing approximately 0.12 g of the sample with 5 mL of concentrated nitric acid directly in the vessels of the microwave oven. The vessels were closed, adjusted in the oven cavity and submitted to the following four-step heating program: (1) 2 min irradiation at 300 W power; (2) 5 min irradiation at 720 W power; (3) 5 min irradiation at 200 W power and (4) 2 min standing. After cooling, which took approximately 30 min, the vessels were opened and their contents were quantitatively transferred into 100 mL volumetric flasks. The volumes were made up to the marks with purified water and the solutions obtained were filtrated when necessary. The concentrations of the metals of interest were determined in the solution after suitable dilutions to fit working linear ranges.

2.3.3. Ultrasonic and magnetic stirring extractions

Portions of 0.12 g of multivitamin/multimineral preparations were accurately weighed, mixed with 20 mL of 1 mol/L HCl solution and agitated for 5 min using ultrasonic bath or magnetic stirring. After this, the suspension was filtrated and metals concentrations were determined by FAAS. When necessary, the obtained solutions were diluted to fit working linear ranges.

2.3.4. Overnight standing extraction

Portions of 0.12 g of the samples were mixed with 20 mL of 1 mol/L HCl solution and stirred for 5 min. The resulting suspensions were left to stand for 12 h and then filtrated. The concentrations of metals of interest were determined in the extracts after suitable dilutions.

3. Results and discussion

The main goal of this work was to develop a methodology for the extraction of Cu, Fe, Mn and Zn from multivitamin/multimineral tablets employing diluted acid solutions, as an alternative to the total digestion of samples that has many drawbacks [3,4]. For this task, a systematic study was performed

in order to evaluate the influence of parameters such as: (a) extraction mode (ultrasonic-assisted or magnetic stirring); (b) extraction time; (c) acid concentration and nature and (d) ultrasonic power.

Prior to the evaluation of extraction conditions, the total contents of Cu, Fe, Mn and Zn in a sample of multivitamin/multimineral tablet were determined using a closed-vessel microwave-assisted method with concentrated HNO_3 [4,5,11].
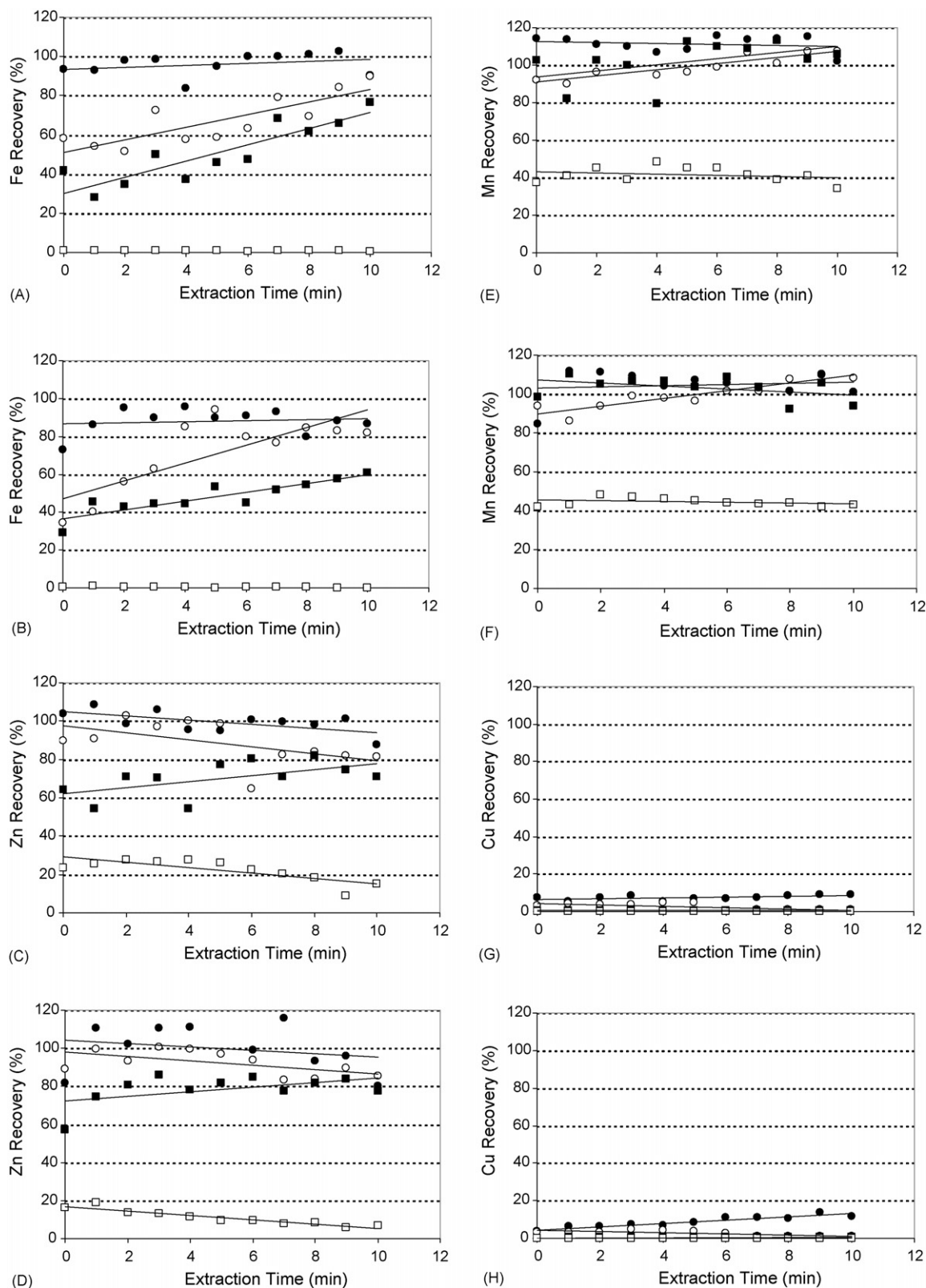

Fig. 1. Effects of extraction time, HCl concentration [(□) 0.01 mol/L, (■) 0.05 mol/L, (○) 0.1 mol/L and (●) 1 mol/L] and mixing mode (A, C, E and G = ultrasonic and B, D, F and H = magnetic stirring) in the extraction of Cu, Fe, Mn and Zn from the reference sample.

Table 1
Found and labeled concentrations (mg g^{-1}) of the metals in the sample taken as reference used in the study

Element[a]	Concentration found (mg g^{-1})[b]	Labeled value (mg g^{-1})
Cu ($n=4$)	1.24 ± 0.04 (3.2%)	1.33
Mn ($n=6$)	1.32 ± 0.04 (3.0%)	1.36
Fe ($n=6$)	12.2 ± 0.5 (4.1%)	12.3
Zn ($n=6$)	9.87 ± 0.03 (3.4%)	10.2

Presented results are the means ± standard deviations.

[a] The number between parentheses indicates the number of independent determinations.

[b] Relative standard deviations are between parentheses.

The obtained values (Table 1) were taken as reference to derive extraction efficiencies in all further studies.

The first experiment that was performed to establish the best extraction condition was based on the simultaneous study of the roles of extraction mode (ultrasonic-assisted and magnetic stirring), extraction time and acid concentration and nature (HCl and HNO$_3$). The results obtained with HCl are shown in Fig. 1(A–H). It is important to stress that this experiment consisted of the extraction of approximately 0.12 g of a powdered reference sample with 20 mL of 0.01, 0.05, 0.10 and 1.0 mol/L HCl solutions for times between 10 s and 10 min. The extraction mode showed no remarkable influence on the extraction process, since the profiles of the curves for each metal were very similar when ultrasonic-assisted and magnetic stirring extractions were compared. Therefore, it is possible to conclude that the cavitation process (characteristic of the ultrasonic extraction) does not play an important role on the extraction of any of the metals under study. Also, it can be deduced that the ultrasonic bath, in this case, could only be considered as a device for mixing of the suspension, being responsible to increase the contact between solid sample and acid solution, similar to magnetic stirring.

On the other hand, HCl concentration seems to be more important for the extraction process of Fe and Zn, since highest recoveries were obtained with the increase of HCl concentrations. In these cases, quantitative recovery (higher than 90%) was only verified when 1 mol/L HCl was employed. The behavior of Mn was a little different, since quantitative recoveries were verified even to acid concentrations equal or higher than 0.05 mol/L. Also, higher amounts of Mn than Cu, Fe or Zn were extracted from the solid when the lowest concentration of HCl (0.01 mol/L) was used, indicating that this element is weakly bonded to the solid matrix when compared to the others. However, Cu presented a quite different behavior, not being extracted at appreciable amounts (no more than 18%) in any of the evaluated conditions.

Another test was carried out replacing HCl by HNO$_3$, which is a stronger oxidizing agent. In this experiment, total acid concentration (HNO$_3$ or HNO$_3$ + HCl) was always maintained at 1 mol/L. No change in the behavior of any of the studied elements was observed in relation to HCl, evidencing that the ion H$^+$ could be responsible for the extraction of metals in a process similar to ionic exchange. Also, the results indicate that, in this kind of sample (or in this sample specifically), Cu is strongly bonded to the solid phase – different from Fe, Mn and Zn – or
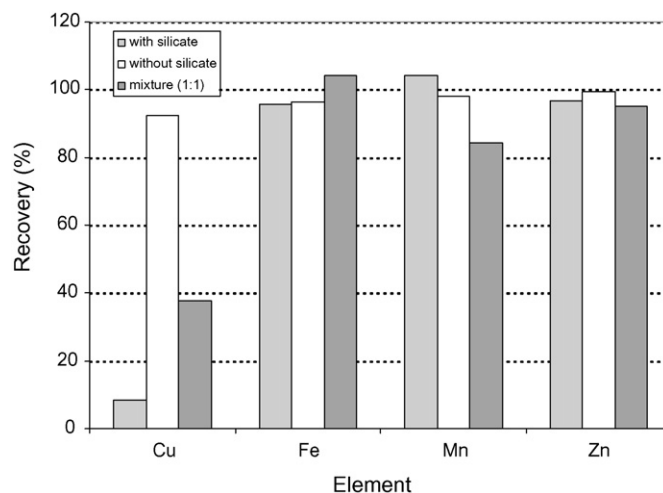

Fig. 2. Effect of silicate on the extraction of Cu, Fe, Mn and Zn from samples.

that the kinetic involved in the Cu releasing from the solid phase is slower than for the others. In terms of extraction time, excluding Cu that is not appreciably extracted in the tested conditions, all elements are readily extracted at the first 5 min when 1 mol/L HCl and either ultrasonic or magnetic stirring are used.

Taking into account that the poor Cu extraction could be related to sample composition, the influence of silicate was investigated. This component was chosen since it appears in large amount in the sample taken as reference, as an inert concomitant, while some other commercial samples searched in the market do not present it in their composition. For this task, the metals under study were extracted from a sample containing silicate (reference sample), from a similar sample not containing silicate (also analyzed in terms of the total metals content) and from a mixture of both samples in a 1:1 ratio. The results obtained in this study are shown in Fig. 2. Such results clearly show that the presence of silicate reduces Cu extraction from the samples, since in the sample containing silicate Cu recovery was approximately 10 times lower than that observed for the sample free of silicate. This phenomenon was not observed for the other metals under study.

The effect of the applied power of the ultrasonic was also examined in the range of 20–120%. This parameter showed no relevant influence on the recoveries of Fe, Mn and Zn, while presented a little effect on Cu extraction, increasing the recovery from 9% up to approximately 18%, which is not enough to quantitative analysis of this element. This observation reinforces the previously raised hypothesis that cavitation does not have significant influence on the extraction of this kind of sample as previously stated [17].

On the base of the obtained results, a condition (5 min mixing using ultrasonic or magnetic stirring with 1 mol/L HCl as extractor) was established for the determination of Fe, Mn and Zn and further studies were focused on Cu extraction.

3.1. Evaluation of copper extraction

The problem of Cu extraction from multivitamin tablets was evident in the previous experiments. In order to achieve Cu

Table 2
Analytical features of the developed procedure

Parameter	Element			
	Cu	Fe	Mn	Zn
Typical calibration line[a]	$A = (0.078 \pm 0.002)$ $Cu + (0.001 \pm 0.001)$	$A = (0.050 \pm 0.002)$ $Fe + (0.002 \pm 0.001)$	$A = (0.188 \pm 0.007)$ $Mn + (0.005 \pm 0.003)$	$A = (0.309 \pm 0.003)$ $Zn + (0.012 \pm 0.003)$
Correlation coefficient	0.9999	0.9998	0.9997	0.9997
Limit of detection ($\mu g\, g^{-1}$)	8.56	16.7	12.4	11.3
Limit of quantification ($\mu g\, g^{-1}$)	28.5	55.6	41.2	37.7

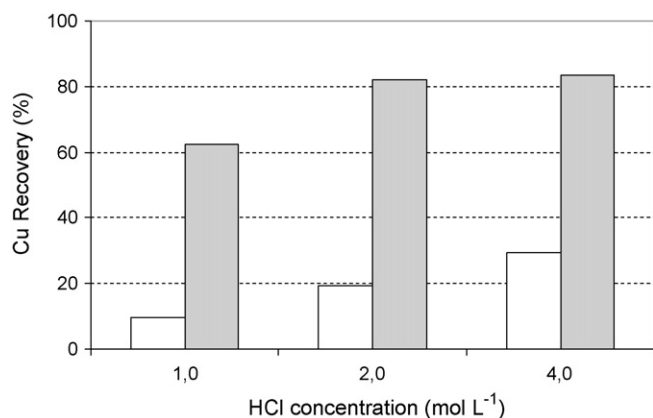[a] Concentrations of metals are in $mg\, L^{-1}$.

Fig. 3. Effect of HCl concentrations on Cu recovery from reference sample. Samples were extracted by magnetic stirring for 5 min and filtrated after 1 h standing time (gray bars) and just after extraction (white bars).

quantitative extraction from the sample containing silicate, the influence of HCl concentrations higher than 1 mol/L was evaluated. This study was carried out employing magnetic stirring as mixing mode and applying the previously established conditions (5 min extraction time, 0.12 g of sample and 20 mL of solutions containing 1, 2 and 4 mol/L HCl). The effect of standing time of the suspension between mixing and filtration was also evaluated, filtration being tested just after mixing and 1 h after mixing. As can be seen in Fig. 3, the increase of HCl con-
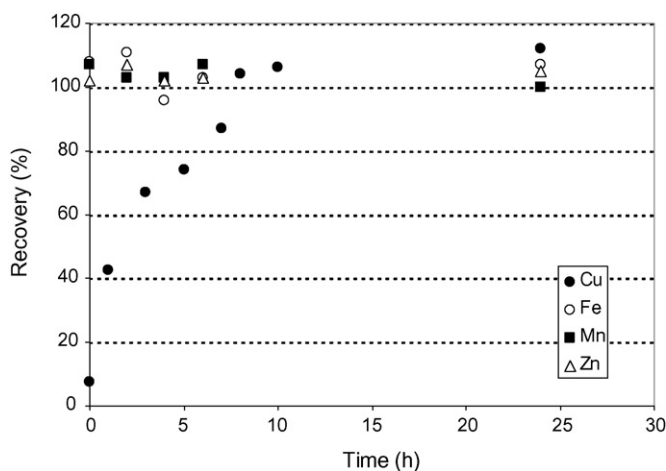

Fig. 4. Recoveries of Cu, Fe, Mn and Zn in standing solutions of 1 mol/L HCl (after 5 min magnetic stirring of the suspension) along a 24 h study. Zero time corresponds to only 5 min magnetic stirring of the suspension.

centration did not show an important influence on Cu extraction, although its recovery was increased from 9.6 to 29.4%, which is not sufficient for Cu determination in the samples. However, when the suspension was left to stand for 1 h before filtration, Cu recoveries presented remarkable increase, reaching values of 62.4 and 83.7% for 1 and 4 mol/L HCl solutions, respectively. Such results denoted that the time of contact between sample

Table 3
Results obtained in the analysis of commercial multivitamin/multimineral tablets

Sample	Procedure			
	MS	US	12 h	TD
Cu				
A	0.72 ± 0.06	0.77 ± 0.04	0.81 ± 0.01	0.83 ± 0.02
B	1.97 ± 0.03	1.94 ± 0.05	2.06 ± 0.02	2.03 ± 0.01
C	0.65 ± 0.02	0.87 ± 0.03	0.74 ± 0.01	0.86 ± 0.06
D	0.20 ± 0.07	0.26 ± 0.08	0.91 ± 0.06	0.95 ± 0.13
E	0.16 ± 0.04	0.21 ± 0.02	1.25 ± 0.01	1.24 ± 0.03
F	0.89 ± 0.02	0.83 ± 0.07	0.89 ± 0.08	0.89 ± 0.01
G	0.69 ± 0.06	0.70 ± 0.05	0.76 ± 0.06	0.71 ± 0.07
Fe				
A	5.82 ± 0.18	6.51 ± 0.73	5.43 ± 0.26	5.72 ± 0.59
B	0.28 ± 0.02	0.27 ± 0.04	0.34 ± 0.02	0.41 ± 0.01
C	8.13 ± 0.29	9.21 ± 0.14	8.80 ± 0.03	9.51 ± 0.05
D	2.69 ± 0.42	2.93 ± 0.17	2.91 ± 0.32	2.92 ± 0.40
E	11.4 ± 0.4	10.9 ± 0.5	12.1 ± 0.9	11.7 ± 0.1
F	32.7 ± 1.4	32.7 ± 3.2	32.5 ± 1.8	31.6 ± 2.4
G	6.00 ± 0.63	6.48 ± 1.18	7.56 ± 2.54	6.26 ± 0.96
Mn				
A	0.39 ± 0.02	0.46 ± 0.05	0.41 ± 0.02	0.49 ± 0.06
B	0.29 ± 0.03	0.33 ± 0.01	0.29 ± 0.01	0.31 ± 0.01
C	0.20 ± 0.01	0.27 ± 0.02	0.22 ± 0.02	0.33 ± 0.01
D	1.54 ± 0.11	1.68 ± 0.12	1.65 ± 0.02	1.61 ± 0.06
E	1.29 ± 0.01	1.29 ± 0.06	1.28 ± 0.04	1.28 ± 0.01
F	0.56 ± 0.01	0.54 ± 0.03	0.56 ± 0.01	0.52 ± 0.02
G	0.45 ± 0.05	0.42 ± 0.03	0.47 ± 0.04	0.41 ± 0.03
Zn				
A	0.77 ± 0.06	0.75 ± 0.06	0.71 ± 0.05	0.76 ± 0.05
B	13.4 ± 0.3	15.7 ± 0.6	12.9 ± 1.2	15.8 ± 0.8
C	0.35 ± 0.01	0.37 ± 0.03	0.35 ± 0.03	0.44 ± 0.02
D	9.05 ± 1.14	9.63 ± 0.59	8.88 ± 0.04	9.66 ± 1.46
E	9.53 ± 0.11	9.30 ± 0.29	9.14 ± 0.33	9.03 ± 0.18
F	<LOQ	<LOQ	<LOQ	<LOQ
G	0.45 ± 0.02	0.52 ± 0.10	0.87 ± 0.10	0.81 ± 0.10

Results are expressed in $mg\, g^{-1}$ (mean $\pm$ standard deviation for three independent determinations). Samples D and E contain silicates in their composition. MS = magnetic stirring extraction, US = ultrasound extraction and 12 h = overnight standing extraction.

Table 4
Comparison between all studied approaches studied for the determination of each metal in samples of multivitamin/multimineral tablets

Comparison	Equation			
	Cu	Fe	Mn	Zn
US vs. TD	$y = 0.553x + 0.6319$, $r = 0.698$	$y = 0.967x + 0.196$, $r = 0.999$	$y = 0.948x + 0.0315$, $r = 0.998$	$y = 0.991x + 0.092$, $r = 0.999$
MS vs. TD	$y = 0.534x + 0.669$, $r = 0.711$	$y = 0.957x + 0.570$, $r = 0.998$	$y = 0.982x + 0.045$, $r = 0.992$	$y = 1.100x - 0.069$, $r = 0.992$
12 h vs. TD	$y = 0.951x + 0.065$, $r = 0.994$	$y = 0.969x + 0.088$, $r = 0.998$	$y = 0.943x + 0.050$, $r = 0.994$	$y = 1.155 - 0.2425$, $r = 0.992$

US = ultrasound-assisted extraction, MS = magnetic stirring extraction, 12 h = overnight standing extraction and TD = total digestion with microwave oven.

and extracting solution could play a more important role than acid concentration in Cu extraction.

In order to study in detail Cu release from the sample containing silicate an "elution experiment" was performed. In such experiment, the extraction of Cu was carried out by the established conditions. Then, the obtained suspension was filtrated and 20 successive fractions of 5 mL of the filtrate were collected. Additional volumes of 1 mol/L HCl solution were added to the filter paper in order to maintain a constant solution level in the filter and, consequently, to maintain the filtration flow rate. The amount of Cu in each fraction was determined and cumulative recoveries were calculated by summing those amounts. By using ultrasonic mixing, Cu recovery (89.6%) was higher than magnetic stirring (44.7%) one. This probably occurred because of the long time required to accomplish the filtration of the suspensions yielded from ultrasonic mixing, which was 196 min and only 83 min after magnetic stirring. After performing these studies, it was possible to conclude that the most important variable for Cu extraction was the time of contact between sample and acid solution. This way, an experiment was carried out to establish how long this contact must be maintained. For this purpose, 0.12 g of sample were mixed with 20 mL of 1 mol/L HCl solution and stirred for 5 min. Then, the suspensions were left to stand from 0 to 24 h before filtration. After this, each suspension was filtrated and Cu, Fe, Mn and Zn recoveries were calculated after measurement of their concentrations in the filtrate. The results are shown in Fig. 4. As expected, Fe, Mn and Zn were readily extracted and quantitative recoveries were obtained when filtration and measurement were performed just after mixing. However, total release of Cu from sample was noted only after 8 h of contact. Nevertheless, in order to ensure total release of Cu even for samples containing higher concentrations of this element, a time of contact of 12 h (overnight) was established for the methodology.

4. Analytical features

After performing all studies, it was verified that the Cu determination in multivitamin tablets could be carried out by maintaining the powdered sample in contact with 20 mL of 1 mol/L HCl solution by 12 h. On the other hand, the quantitative determination of Fe, Mn and Zn could be achieved by stirring or sonicating the powdered sample with the same solution for only 5 min. The analytical features of the methodology, obtained at these conditions, are shown in Table 2.

5. Application

In order to demonstrate the applicability of the developed methodology in the quality control of multivitamin/multimineral tablets, it was applied for the determination of Cu, Fe, Mn and Zn in different samples purchased in the local market. The results for this experiment are shown in Table 3.

As can be seen from the results, the utilization of a 12 h extraction (after 5 min stirring of the suspension for homogenization) was enough to promote total release of the analytes from all samples. However, when 5 min of magnetic stirring or sonication were employed, Cu was only totally recovered from silicate-free samples, while the other analytes were quantitatively recovered from all samples evaluated.

In order to compare the results obtained by applying different extraction strategies with total digestion, a correlation test was performed (Table 4). For Fe, Mn and Zn, the slopes of the derived curves and their correlations were always close to unity, indicating that there is no statistical difference in the results obtained between tested methods. However, in the case of Cu, this situation was only verified, as expected, when a overnight standing extraction (12 h) was compared to total digestion. This occurs due to the strong influence of the presence of silicates on the ultrasonic and magnetic stirring extractions.

6. Conclusions

Through obtained results in this study it is possible to conclude that extraction with diluted acid (1 mol/L HCl) is a good alternative to total (or partial) digestion of samples for the determination of Cu, Fe, Mn and Zn in multivitamin/multimineral preparations.

For any kind of sample, quantitative extraction of Fe, Mn and Zn is achieved by sonicating or stirring the suspension (solid sample + extraction solution) for only 5 min, indicating that these elements are weakly bonded to the solid matrix. Nevertheless, for Cu, the time of contact between sample and extracting solution and sample composition showed to be the most important parameters in the selection of the extraction strategy. In this case, for samples containing silicates Cu is extracted if the contact between sample and extraction solution is maintained for times as high as 12 h, indicating that there is a slow kinetics regulating the Cu releasing process. On the other hand, for samples not containing silicates, the same strategy used for the other analytes can be applied.

The mixing mode (ultrasonic or magnetic stirring) has not showed relevant effect on the extraction process, indicating that the major role of ultrasonic energy in the preparation of such samples only relies in the improvement of the contact between the extraction solution and the solid sample.

Acknowledgments

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