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Trace element impurity determination in aspirin tablets by INAA

E. K. Miyoshi,[1,2] M. Saiki[1]*

[1] *Instituto de Química, Universidade de São Paulo, Av. Professor Lineu Prestes, 748 , CEP 05508-900, São Paulo, SP, Brazil*
[2] *Instituto de Pesquisas Energéticas e Nucleares, IPEN-CNEN/SP, Av. Prof. Lineu Prestes, 2242, CEP 05508-000, São Paulo, SP, Brazil*

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Instrumental neutron activation analysis (INAA) was applied to assess trace element concentrations in six samples of aspirin tablets acquired in São Paulo city, Brazil. Concentrations of the elements Br, Ca, Co, Cr, Fe, K, La, Na, Sc and Zn were determined. Comparisons were made between the results obtained with published data for aspirins from foreign countries. Certified reference materials, INCT-MPH-2 Mixed Polish Herbs were analyzed for quality control of the analytical results.

Introduction

Aspirin or acetylsalicylic acid (ASA) is one of the most widely consumed drugs in the world as an analgesic, antipyretic, anti-inflammatory and due to its anti-platelet effect. It is one of the safest and least expensive pain relievers available in pharmacies, drugstores and food stores under different dosages, forms and brands. With the increasing use of remedies containing ASA several types of this product are present in drugstores. The determination of trace elements in aspirin tablets should be some concern since they may contain, in addition to aspirin, coloring and flavoring agents, binders, pH stabilizing buffers or effervescent inducing compounds which may contain contaminants which in turn may cause adverse effects to human health.

This study presents results obtained in the analyses of six samples of aspirin tablets acquired in São Paulo city, Brazil in order to evaluate other elements that may cause undesirable side effects.

Experimental

Aspirin samples and its preparation for the analyses

Six samples of aspirin commercially available in São Paulo city were analyzed by instrumental neutron activation analysis (INAA). Eight tablets of each aspirin sample were weighted to obtain the mean values of mass per tablet. For the analyses, the tablets were homogenized by grinding in an agate mortar and to obtain a powder form. Aliquots (500 mg) of each sample were dried at 85 °C for approximately 10 hours to obtain weight loss percentage during this drying process. Table 1 presents the characteristics of the aspirin samples analyzed.

Preparation of the standards

The synthetic standards were prepared by pipetting 50 μL of the elemental standard solutions onto sheets of Whatman No. 40 filter paper. These solutions containing one or more elements were prepared using certified standard solutions provided by Spex Certiprep Chemical, USA. All the pipetters and volumetric flasks were calibrated before the use. These filter sheets were dried at room temperature inside a desiccator with fresh silica and, then placed into clean polyethylene involucres which were then heat sealed. In these standards the quantities of each element, in μg (in parentheses) were the following: Br (5.2), Ca (1000), Co (0.150), Cr (2.0), Fe (280), K (1,000.0), Na (500.0), Sc (0.080) and Zn (35.0).

Neutron activation analysis procedure

Aliquots of about 200 mg of each aspirin sample weighed in polyethylene involucres were irradiated in the IEA-R1 nuclear research reactor along with the synthetic element standards for 16 hours under a thermal neutron flux of about $4 \cdot 10^{12}$ n·cm^{-2}·s^{-1}. Samples and standards were measured by a hyperpure Ge detector Model GX2020 coupled to Model 1510 Integrated Signal Processor, being both from Canberra. The resolution (FWHM) of the system was 0.90 keV for 122 keV gamma-ray peak of ^{57}Co and 1.78 keV for 1332 keV gamma-ray of ^{60}Co. Each sample and standards were measured at least twice for different decay times. Counting times from 6,000 to 50,000 seconds were used, depending on the half-lives or activities of the radionuclides considered. The radionuclides measured were identified according to their half-lives and gamma-ray energies. The concentrations of elements were calculated by a comparative method. The radionuclides used in aspirin analyses were: ^{82}Br, ^{47}Ca, ^{60}Co, ^{51}Cr, ^{59}Fe, ^{42}K, ^{24}Na, ^{46}Sc, and ^{65}Zn.

* E-mail: mitiko@ipen.br

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Table 1. Characteristics of the aspirin samples analyzed

Sample code	Mass of each tablet – dry basis, g	Mass of ASA per tablet, mg	Weight loss percentage in drying, %	Main characteristic obtained from the label
A	3.24 ± 0.02	400	0.88	Effervescent aspirin + C (with lemon flavor)
B	0.677 ± 0.009	500	2.04	Buffered aspirin
C	0.122 ± 0.002	100	1.59	Aspirin for children
D	0.619 ± 0.003	500	0.79	Generic ASA
E	0.5934 ± 0.0005	500	0.82	ASA for adults
F	0.849 ± 0.006	650	1.46	Aspirin with caffeine

Table 2. Element concentrations obtained in the analysis of INCT-MPH-2 Mixed Polish Herbs certified reference material

Element	This work				Values of certificate[1]
	Mean ± SD	RSD, %	Er, %	Zscore	
Br, $mg \cdot kg^{-1}$	8.04 ± 0.65	8.1	4.2	0.5	7.71 ± 0.61
Ca, %	1.09 ± 0.07	6.3	0.9	0.1	1.08 ± 0.07
Co, $\mu g \cdot kg^{-1}$	235 ± 22	9.2	11.5	1.0	210 ± 25
Cr, $mg \cdot kg^{-1}$	1.83 ± 0.16	8.7	8.3	1.1	1.69 ± 0.13
Fe, $mg \cdot kg^{-1}$	535 ± 22	4.2			(460)*
K, %	1.96 ± 0.06	3.1	2.6	0.4	1.91 ± 0.12
La, $\mu g \cdot kg^{-1}$	559 ± 47	8.4	2.1	–0.3	571 ± 45
Na, $mg \cdot kg^{-1}$	402 ± 11	2.6			(350)
Sc, $\mu g \cdot kg^{-1}$	124.7 ± 5.9	4.8	1.4	0.2	123 ± 9
Zn, $mg \cdot kg^{-1}$	35.2 ± 0.7	2.0	5.1	0.8	33.5 ± 2.1

Mean ± SD = Arithmetic mean and standard deviation;
RSD = Relative standard deviation;
Er = Relative error;
* Numbers in parentheses indicate informative values.

The quality of the analytical results was evaluated by analyzing the certified reference material INCT-MPH-2 Mixed Polish Herbs[1] provided by the Institute of Nuclear Chemistry and Technology, Poland. The element concentrations of reference material were evaluated on a dry weight basis, as recommended in the certificate. A moisture weight loss of 7.1% was found to correct the final results.

Results and discussion

To evaluate the precision and the accuracy of the results, INCT-MPH-2 Mixed Polish Herbs reference material was analyzed. Data obtained in this analysis presented in Table 2 indicate good precision and good agreement with the certified values. The relative standard deviations of the results were lower than 9.2% and relative errors varied from 0.9 to 11.5%. The standardized difference or Zscore values[2] obtained for most of the elements analyzed were $|Zscore|<2$, indicating that our results are satisfactory and are within the ranges of certified data at the 95% confidence level.

The concentrations Br, Ca, Co, Cr, Fe, K, La, Na, Sc and Zn determined in six samples of aspirin are presented in Table 3. For some samples, not all these elements were detected due to their low concentrations or to interferences from high activity of ^{24}Na. Detection limit values were evaluated according to Currie criteria[3] in some sample of aspirin and were included in this Table 3. Toxic elements such as As, Cd, Cu, Hg and Sb were not detected in these six aspirin samples analyzed. The amount of element present in each tablet was calculated using the element concentration presented in Table 3 and the mass of each tablet. The highest quantities of elements obtained were for Na (418.1 mg), Sc (14.9 μg) and Zn (3.95 μg) in the Effervescent aspirin sample, Br (0.47 μg) and Cr (0.435 μg) in Buffered aspirin and Ca (4.9 μg) in Generic ASA. Each tablet of Effervescent aspirin presented relatively high amount of Na if we compare it to the Adequate Intake value[4] of 1500 mg per day for young adults for this element.

The element concentration ranges obtained for Brazilian aspirin samples compared to the published data for Egyptian and American aspirin brands indicated the element concentrations in this drug vary with their origins, as can be seen in Table 4. Br results were lower than the published data. However for other elements, their levels in the samples depended on their origins or brands.

Table 3. Concentrations of elements in aspirin samples on dry basis

Element	Samples[a]					
	A	B	C	D	E	F
Br, $\mu g \cdot kg^{-1}$	<33	709 ± 19	200 ± 8	82 ± 3	172 ± 8	105 ± 2
Ca, $mg \cdot kg^{-1}$	44.0 ± 3.4	190 ± 10	511 ± 48	8028 ± 298	<14	69 ± 4
Co, $\mu g \cdot kg^{-1}$	2.4 ± 0.5	12.5 ± 0.7	<2.3	<2.3	<2.3	7.5 ± 1.0
Cr, $\mu g \cdot kg^{-1}$	22.7 ± 2.2	657.7 ± 6.2	34.6 ± 3.1	<24	33.6 ± 0.5	41.9 ± 4.4
Fe, $mg \cdot kg^{-1}$	<2.1	39 ± 0.3	<1.4	<3.3	<2.6	<2.1
K, $mg \cdot kg^{-1}$				10.7 ± 0.4		6.1 ± 0.7
La, $\mu g \cdot kg^{-1}$				22.7 ± 0.5	<1.0	<1.0
Na, $mg \cdot kg^{-1}$	130100 ± 257	12350 ± 26	802.3 ± 0.8	12.19 ± 0.05	1132.6 ± 4.4	32.26 ± 0.06
Sc, $\mu g \cdot kg^{-1}$	4.63 ± 0.04	0.46 ± 0.02	<0.25	3.17 ± 0.07	<0.35	<0.5
Zn, $mg \cdot kg^{-1}$	1.23 ± 0.02	1.66 ± 0.03	1.96 ± 0.03	4.88 ± 0.03	1.49 ± 0.03	2.45 ± 0.04

A = Effervescent aspirin +C (with lemon flavor);
B = Buffered aspirin;
C = aspirin for children;
D = Generic ASA;
E= ASA for adults and
F = Aspirin with caffeine.

Table 4. Element concentration ranges obtained and published data

Element	This study	Egyptian aspirin samples[5]	American aspirin sample[6]
Br, $\mu g \cdot kg^{-1}$	"0"[a]–709	"0"–9000	"0"–190
Co, $\mu g \cdot kg^{-1}$	"0"–12.5	"0"–105000	35.1–290
Cr, $\mu g \cdot kg^{-1}$	"0"–657.7	"0"–253000	23.1–272
Fe, $mg \cdot kg^{-1}$	"0"–39	"0"–94	4.25–143
K, $mg \cdot kg^{-1}$	"0"–10.7		"0"–18.9
Na, $mg \cdot kg^{-1}$	32–130100		7.30–1320
Sc, $\mu g \cdot kg^{-1}$	"0"–4.63		<1
Zn, $mg \cdot kg^{-1}$	1.23–4.9	1–24	<1

"0" – indicates that the element was not detected in some samples.

In conclusion, the findings of this study suggest a careful evaluation of whether or not to prescribe some aspirin brands presenting high level of Na to hypertensive individuals. The study also showed that INAA is a valuable tool to analyze pharmaceutical products due to its simplicity, precision and accuracy of the results and mainly due to the possibility of simultaneous determination of several elements present in a large range of concentrations.

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