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Investigation of chemical impurities in formulations, phytotherapics and polyvitaminic medicines by k_0-instrumental neutron activation analysis

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Abstract

In this work, comparative k_0-Instrumental Neutron-Activation Analysis was performed by CDTN/CNEN/Brazil and SCK.CEN/Belgium in order to investigate the elemental concentration in samples of the same industrialised and manipulated medicine, a phytotherapic and a polyvitaminic, commonly commercialised in Brazil. The preliminary results from both Institutes are in very good agreement. Any serious contamination with possible risks to human health were found in the medicines compared with the expected values. In the case of polyvitaminic, some impurities, unexpected elements, such as La, Ti and Sm, were found in very low concentration. This first assessment confirmed the effectiveness of the k_0-method in analysing such matrices.
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1. Introduction

Due to the enormous growth during the last years of the market of phytotherapic and manipulated medicines in Brazil, the assessment of the quality of such products is, at present, a very important question of public health. There are now more than five thousand drugstores which sell this kind of products [1].

The very rapid growth of the consumption of such medicines represent a serious problem due to the difficulties in implementing an efficient official control. Some products, mainly some medicinal herbs or teas, can be found in the popular markets with any quality control. The biological and inorganic contamination found in these medicines can cause health-related risks. It is also important to control the quality of the manipulated medicines, prepared upon request by some special drugstores. In this case, the dose of each compound can, sometimes, not be totally assured and the contamination by impurities, not included in the original formula, can be present in the final product. A long-term exposure to low-level metal concentrations, for instance, may cause injuries to human beings, mainly those elements that are not included in the current list of elements considered essential to humans [2].

In this work, a preliminary assessment of chemical elements in these kinds of medicines was carried out by analysing different samples: one polyvitaminic (ascorbic acid) and one polymineral, three different samples of phytotherapics: *Passiflora incarnata, Salix alba and Passiflora oxyacantha: sample 1, Cassia senna, Collinsonia canadensis, Polygonium punctatum*, sodium picosulfate: sample 2 and Chamomile tea: sample 3, and two samples of fluoxetine hydrochloride [$C_{17}H_{18}F_3NO.HCl$]; industrialised and formulated [3,4]. The same matrices were analysed at both Institutes, the Nuclear Technology

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Development Centre/Brazilian Commission for Nuclear Energy (CDTN/CNEN), Brazil and the Belgian Nuclear Research Centre (SCK.CEN), Belgium. The possibility of analysing several elements simultaneously, in very low concentration, make neutron-activation analysis with k_0 standardisation an appropriate method for this investigation [5–7]. This was the technique applied at both Institutes [8–10].

2. Experimental

All the medicines were purchased in the local market (Belo Horizonte, Minas Gerais, Brazil). Both institutes followed the same procedure to prepare the samples. They were either crushed or ground by hand using agate mortar with pestle, whenever necessary, to avoid any contamination.

No additional sample preparation, nor transfer to non-irradiated vials was performed. Two aliquots of each medicine were weighed in polyethylene vials and irradiated together with several Al–0.1%Au [11] neutron-flux monitors. Table 1 shows the characteristics of the applied technique such as the parameters f (thermal to epithermal fluxes ratio) and α (parameter which measures the epithermal flux deviation from the ideal $(1/E)$ distribution), irradiation time and gamma-spectrometry system at each Institute. A more-detailed description about the determination of f and α parameters at CDTN and SCK can be found in Refs. [12,13], respectively. The validation of the method using CRM that is matching the matrix was not possible, since such CRM is not available. In order to validate the irradiation/calculation protocol a CRM NIST 1633b and a SMELS-material were introduced [14,15].

In most cases, unless the amount of material did not allow it, two replicates were taken. SCK.CEN and CDTN used HDPE-irradiation vials yielding approximately 500 and 200 mg samples, respectively, which is the standard geometry in each institute.

3. Results and discussion

Only the elements that present suitable nuclear characteristics to be determined by neutron-activation analysis were researched and Tables 2 and 3 report only the detected elements.

Table 2 shows all the results obtained by both Institutes, CDTN/CDTN and SCK.CEN, related to polyvitaminic 1, phytotherapics 1–3 and the samples of fluoxetine. Table 3 shows the results related to polyvitamic 2. In general, the results achieved by both Institutes are in very good agreement. The inconsistencies suggest heterogeneous distribution of some elements. The elements Br, Fe, La, K, Mn, Sb, Sc, Zn and specially Ca, found in the sample of the industrialised fluoxetine, may be related to the residues from the synthetic materials used in the formulation, which can explain their absence in the manipulated sample. There are not toxicological levels foreseen for those elements described in official compendiums or other guidance documents. Anyway, some of them—Au, Br, La, Rb, Sb, Sm and Ti—are not considered essential elements for human beings. The elements Ca, Mg, Na and Zn determined in the industrialised capsules are in the materials used in the formulation, such as magnesium stearate, a lubricant for tablets and capsules. The element Zn is an impurity commonly found in such substances [16].

The quantity of Cl detected by CDTN/CNEN in fluoxetine hydrochloride, both industrialised and formulated, is in good agreement with the expected value for this element in capsules. 10% uncertainty is an acceptable result for medicines. However, the higher content determined by SCK.CEN, suggest possible contamination during the product formulation.

The polyvitaminic 2, Table 3, is the only medicine presenting elemental concentration values printed in the label. This table points out that the experimental results obtained at both institutes are in good agreement with the printed technical information in the medicine label. However some elements such as Br, Co, La, Na, Sc, Sm

Table 1
Application of the k_0 standardisation method at CDTN/CNEN and SCK.CEN

Experimental information	CDTN/CNEN	SCK.CEN
Reactor channel	TRIGA MARK I IPR-R1 IC40	BR1 -Y4
Thermal flux (neutrons $cm^{-2} s^{-1}$)	6.4×10^{11} at 100 kW	3×10^{11} at 700 kW
Reactor parameters		
f	20.4 ± 0.2	35.6 ± 0.6
α	0.197 ± 0.02	0.06 ± 0.01
Irradiation time (h)	8	7
Detector nominal efficiency	15%	40%
Software used for:		
Acquisition spectra	GeniePC (CANBERRA)	Accuspec Genie
Spectra analysis	Hyperlab [8]	Hyperlab [8]
Concentration calculation	KAYZERO/SOLCOI® [9]	KAYZERO/SOLCOI® [9]
Sample mass (mg)	200	500
Number of aliquots used	2	2

Table 2
Elemental concentrations (mg kg^{-1}) obtained for several medicines

	Elements	Institute	Polyvitaminic 1 (industrialised)	Phytotherapic 1	Phytotherapic 2 (medicinal tea)	Phytotherapic 3	Fluoxetine (industrialised)	Fluoxetine (manipulated)
Au	CDTN/CNEN	ND	ND	<0.01	ND	ND	ND	
	SCK.CEN	ND	ND	0.011±0.001	ND	ND	ND	
Br	CDTN/CNEN	ND	ND	60±2	16±1	<1	<1	
	SCK.CEN	ND	ND	70±7	18±2	0.20±0.03	0.30±0.05	
Ca	CDTN/CNEN	ND	ND	<10000	ND	29,800±1800	ND	
	SCK.CEN	ND	ND	7400±800	ND	31,800±3100	ND	
Cl	CDTN/CNEN	4100±400	115±8	8500±310	6410±240	18,000±700	17,000±600	
	SCK.CEN	3700±390	33±2	7300±700	5300±500	16,000±700	23,700±1100	
Co	CDTN/CNEN	ND	<0.1	0.31±0.05	0.16±0.02	<0.1	<0.1	
	SCK.CEN	ND	0.037±0.003	0.30±0.04	0.15±0.02	0.022±0.007	0.006±0.005	
Cr	CDTN/CNEN	ND	ND	<5	ND	ND	ND	
	SCK.CEN	ND	ND	3.6±0.4	ND	ND	ND	
Fe	CDTN/CNEN	ND	<150	<150	ND	<150	ND	
	SCK.CEN	ND	8±2	131±16	ND	23±5	ND	
K	CDTN/CNEN	ND	ND	28,000±1000	4900±190	<80	<80	
	SCK.CEN	ND	ND	28,000±2800	4900±500	46±3	60±8	
La	CDTN/CNEN	ND	ND	1.1±0.1	ND	0.18±0.02	ND	
	SCK.CEN	ND	ND	1.0±0.1	ND	0.2000±0.012	ND	
Mg	CDTN/CNEN	ND	494±25	3650±240	1850±110	1500±140	ND	
	SCK.CEN	ND	389±24	3250±360	1390±150	1370±140	ND	
Mn	CDTN/CNEN	ND	ND	84±3	6.7±0.4	<5	ND	
	SCK.CEN	ND	ND	76±8	5.4±0.6	3.2±0.2	ND	
Na	CDTN/CNEN		66,000±7000	3270±150	320±29	2100±90	520±20	230±80
	SCK.CEN		64,000±7000	2190±220	380±50	3400±340	650±40	130±6
Rb	CDTN/CNEN	ND	ND	70±6	4±1	ND	ND	
	SCK.CEN	ND	ND	65±10	4±1	ND	ND	
Sb	CDTN/CNEN	ND	ND	ND	ND	0.15±0.03	0.24±0.03	
	SCK.CEN	ND	ND	ND	ND	0.20±0.03	0.20±0.05	
Sc	CDTN/CNEN	ND	<0.01	0.04±0.01	0.015±0.006	0.02±0.01	<0.01	
	SCK.CEN	ND	0.0006±0.0002	0.023±0.003	0.004±0.001	0.023±0.001	0.0010±0.0001	
S	CDTN/CNEN	ND	ND	0.05±0.01	ND	ND	ND	
	SCK.CEN	ND	ND	0.06±0.01	ND	ND	ND	
Ti	CDTN/CNEN	ND	ND	ND	1800±150	<800	ND	
	SCK.CEN	ND	ND	ND	1700±170	760±39	ND	
Zn	CDTN/CNEN	3550±120	<50	41±3	<50	<50	<50	
	SCK.CEN	3260±330	0.47±0.08	30±3	6±1	6.3±0.5	5.7±0.4	

and Ti not foreseen were determined in extremely low concentration. These impurities originated from the process of production and could be expected in such polymineral containing several different elements. The presence of Ti can be explained by the technology of film coating during the tablet production [1].

The low concentration of some elements makes the discussion about toxicity levels very difficult. The toxicological effects cannot be previewed because these elements are not mentioned in the Nutritional Dietary Reference Intake (NDRI) table [17]. According to the literature, the deviation between the technical information of medicine labels and the determined elemental concentration is usually not higher than 10% [18–21]. The deviation higher than 20%, found for Cr in this sample is also probably due to the contamination during the process of producing these medicines.

3. Conclusions

The results obtained shows that k_0 standardisation method is suitable to analyse different medicines in different shapes and matrixes determining several elements in a large range of concentrations.

Although for NAA several reference materials that are used in each laboratory to validate the results exist, there are no reference materials (medicines) in order to verify the accuracy of the method. Anyway, the results obtained by both institutes are in agreement with the medicine label.

The lower detection limits for some elements achieved by SCK.CEN is mainly due to the higher nominal efficiency of the gamma-detection system compared to the system used by CDTN/CNEN. Besides, more-thermalised channel where the samples were irradiated in the SCK.CEN

Table 3
Elemental concentration results versus label concentration, Polyvitaminic 2 (industrialised)

Element	Institute	mg (element) pill^{-1}	
		This work	Label conc.
Br	CDTN/CNEN	0.0040±0 0003	NI
	SCK.CEN	0.0040±0.0006	
Ca	CDTN/CNEN	169±7	162
	SCK.CEN	159±2	
Cl	CDTN/CNEN	35±2	36
	SCK.CEN	38±4	
Co	CDTN/CNEN	0.0020±0.0001	NI
	SCK.CEN	0.0017±0.0001	
Cr	CDTN/CNEN	48±1	25
	SCK.CEN	48±1	
Cu	CDTN/CNEN	1.8±0.3	2
	SCK.CEN	1.9±0.2	
Fe	CDTN/CNEN	19±1	18
	SCK.CEN	17±2	
I	CDTN/CNEN	143±7	150
	SCK.CEN	173±18	
K	CDTN/CNEN	42±2	40
	SCK.CEN	43±4	
La	CDTN/CNEN	0.00060±0.00003	NI
	SCK.CEN	0.00071±0.00007	
Mg	CDTN/CNEN	95±3	100
	SCK.CEN	99±10	
Mn	CDTN/CNEN	2.0±0.2	2.5
	SCK.CEN	2.4±0.2	
Na	CDTN/CNEN	0.53±0.03	NI
	SCK.CEN	0.52±0.03	
Sc	CDTN/CNEN	0.00006±0.00001	NI
	SCK.CEN	0.00005±0.00001	
Se	CDTN/CNEN	25±1	25
	SCK.CEN	21±2	
Sm	CDTN/CNEN	0.0001±0.00003	NI
	SCK.CEN	0.00016±0.00006	
Ti	CDTN/CNEN	6.8±0.3	NI
	SCK.CEN	4.5±0.5	
V	CDTN/CNEN	11±1	10
	SCK.CEN	11±1	
Zn	CDTN/CNEN	16±1	15
	SCK.CEN	14±1	

NI, Not Informed; uncertainties correspond to 95% confidence interval.

reactor, contributes for better analysis of the elements with higher thermal cross-section.

Concerning the medicines, the elements determined that are not included in the list of the essential elements for human being—Au, Br, La, Rb, Sb, Sm and Ti—represent risk to human's health. The results revealed that the ingestion of such elements for a long term may lead to endogenous contamination. Even the essential elements like Fe, K and Na should have their maximum limits permitted in medicines because they may play the role of toxic elements.

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