

Investigation of chemical impurities in formulations, phytotherapies 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 phytotherapeutic 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 phytotherapeutic 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 phytotherapies: *Passiflora incarnata*, *Salix alba* and *Passiflora oxyacantha*: sample 1, *Cassia senna*, *Collinsonia canadensis*, *Polygonum punctatum*, sodium picosulfate: sample 2 and Chamomile tea: sample 3, and two samples of fluoxetine hydrochloride [C₁₇H₁₈F₃NO.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, phytotherapies 1–3 and the samples of fluoxetine. Table 3 shows the results related to polyvitaminic 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

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