Journal of Pharmaceutical and Biomedical Analysis 122 (2016) 52–58

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Feasibility of wavelength dispersive X-ray fluorescence spectrometry for the determination of metal impurities in pharmaceutical products and dietary supplements in view of regulatory guidelines

Alexandra Figueiredo[a,b,c], Tânia Fernandes[a,b], Isabel Margarida Costa[a,b], Luísa Gonçalves[a,b], José Brito[a,b,*]

[a] Instituto Superior de Ciências da Saúde Egas Moniz (ISCSEM), Campus Universitário—Quinta da Granja, 2829-511, Monte de Caparica, Portugal
[b] Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Campus Universitário—Quinta da Granja, 2829-511, Monte de Caparica, Portugal
[c] PhD student at Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Rua de Jorge Viterbo Ferreira, n°228, 4050-313 Porto, Portugal

ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form
19 December 2015
Accepted 12 January 2016
Available online 21 January 2016

Keywords:
Metal impurities
X-ray Fluorescence
Validation
Pharmaceutical products
Dietary supplements

ABSTRACT

The aim of this study was to investigate the feasibility of Wavelength Dispersive X-ray Fluorescence (WDXRF) spectrometry for the measurement of As, Cd, Cr, Cu, Hg, Ir, Mn, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru and V impurities in pharmaceuticals and dietary supplements, in view of the requirements by EMA and USP for the measurement of elemental impurities in drug products and according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH guidelines).

For that purpose, a 4 kW WDXRF spectrometer (S4 Pioneer, Bruker AXS) was used after system calibration. The linearity of the method was demonstrated by correlation coefficients in excess of 0.9 and by appropriate test of lack of fit, except for Cd, Hg, Pd, V and As, which were excluded from analysis. The calculated limits of detection and quantification were in the ranges 0.6–5.4 μg/g and 1.7–16.4 μg/g meeting defined acceptance criteria, except for Pb. The accuracy of the method, determined by the percent recovery (*R*) of known amounts of each element added to a selected drug, at 3 different concentration levels, was in the acceptance range 70–150% except for Os and Pt, in which case *R* was marginally outside that range. The repeatability of the method, assessed as the % residual standard deviation (%RSD) of 3 replicate measurements at 3 concentration levels, produced %RSD values lower than 20%, as required.

These results show that the WDXRF method complies with the validation requirements defined by the European Pharmacopeia for Cu, Cr, Ir, Mn, Mo, Ni, Os, and Pt, and by the United States Pharmacopeia for Ir, Ni, Os and Pt. Therefore, it may be an alternative to the compendial analytical procedures recommended for such elements. The novelty of the present work is the application of WDXRF to final medicines and not only to active pharmaceutical ingredients and/or excipients.

© 2016 Elsevier B.V. All rights reserved.

1. Introduction

Medicines may incorporate metal impurities through catalysts or reagents used in the synthesis of active substances and excipients, or as a result of manufacturing, piping and packaging processes; without any therapeutic benefit but with potential toxic effects these impurities put the product quality, efficacy and the consumerís safety in jeopardy and their levels in drug products should be controlled within acceptable limits [1,2]. Similarly, heavy metals can accumulate to a certain extent in medicinal plants growing in nature and limits for such elements in foodstuffs and medicinal products have been set by health authorities [3].

Although the Guideline for Elemental Impurities (Q3D) by the International Conference for Harmonization (ICH) presents a process recommended for adoption to the regulatory parties to ICH to assess and control elemental impurities in the drug product [4], the standards defined by different authorities in the European Union and the United States do not seem to be fully harmonized in what concerns the listing of elements and compliance limits for each element (Table 1), and implementation dates. For example,

* Corresponding author at: Instituto Superior de Ciências da Saúde Egas Moniz (ISCSEM), Campus Universitário—Quinta da Granja, Monte de Caparica, 2829-511, Portugal.
E-mail addresses: alexandra.f@netcabo.pt (A. Figueiredo), tania.apf@gmail.com (T. Fernandes), imargaridac@gmail.com (I.M. Costa), lmlgoncalves@gmail.com (L. Gonçalves), jaabrito@netcabo.pt (J. Brito).

http://dx.doi.org/10.1016/j.jpba.2016.01.028
0731-7085/© 2016 Elsevier B.V. All rights reserved.

Table 1
Current EMA and USP limits for metals impurities in pharmaceuticals (oral route) [1,5].

EMA		USP 38	
Classification of elements	Concentration(μg/g)	Element	Concentration (μg/g)
Class 1A	10	As[b]	0.15
Pt, Pd		Pb	0.5
Class 1B	10[a]	Hg[b]	1.5
Ir, Rh, Ru, Os		Cd	2.5
		Ir	10
Class 1C	25	Mo	10
Mo, Ni, Cr, V		Os	10
		Pd	10
Class 2	250	Pt	10
Cu, Mn		Rh	10
		Ru	10
Class 3	1300	V	10
Fe, Zn		Ni	50
		Cu	100
		Cr	*

*not a safety concern.
[a] Combination of the 4 elements should not exceed the specified limit.
[b] inorganic.

chapter 5.20 of the European Pharmacopeia (EP) [2], implementing the European Medicines Agency (EMA) Guideline [1], defines limits for 14 elements (Cr, Cu, Fe, Ir, Mn, Mo, Ni, Os, Pd, Pt, Rh, Ru, V, Zn), which apply to new drug products submitted for approval in Europe in June 2016 and to existing products in December 2017. Instead, the United States Pharmacopeia (USP) [5] regulates limits for 15 elements (As, Cd, Cr, Cu, Hg, Ir, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru, V) and announced plans to establish January 2018 as the new date of applicability of these limits. As for metals in herbal drugs and food supplements, permissible levels (in mg/kg) were also proposed following the World Health Organization (WHO) guidelines for Cd (0.3) and Pb (10) in medicinal raw plant materials, whereas limits were set in 2007 by the European Commission for Pb (3), Cd (1) and Hg (0.1) for plant-based food supplements only [6,7].

In the past, most of the testing for metal impurities in drug products included general semi-quantitative analysis commonly based on sulfides precipitation and colorimetric tests. Such tests, however, are not suitable to quantitatively determine the actual levels of a specific metal residue in a pharmaceutical substance, and their use has been ended by the EP and USP [1,8,9]. As alternative, although the ICH-Q3D document does not include any information on preferred sample preparation or instrumental methods, both USP <233> and EP 2.4.20 chapters list a range of suitable techniques, including Inductive Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) and ICP Optical Emission Spectroscopy (ICP-OES), Atomic Absorption Spectrometry (AAS) and X-ray Fluorescence Spectrometry (XRFS), as long as the requirements for validation described therein are met [4,8,9]. In this scenario, compliance with not fully harmonized ICH-Q3D, EMA, EP, and USP requirements is a considerable challenge to the analytical performance of many solid state systems and to the economical capacity of laboratories and industry.

In fact, most systems available in the market are designed to analyze liquid samples while the majority of pharmaceuticals are in the solid state. This requires time-consuming sample preparation prior to analysis, including simple dissolution or microwave assisted digestion with elevated associated costs [10,11]. Moreover, when using ICP Mass Spectroscopy (ICP-MS) techniques, some elements such as Pd, Pt and Ir need concentrated acid mixtures of nitric acid and hydrochloric acid to guarantee a suitable solubilization, which may cause interferences due to residual carbon content in final sample and consequent suppression or enhancement of analytical signal for some elements [12]. Concerning the determination of the specified heavy metals in medicinal plants, this is commonly performed using AAS, MS and voltametric methods [3,13–15]. The use of such techniques, however, is hindered with the economic issues reported above, in addition to problems arising from the chemical methods put in place and which usually require numerous reagents, the destruction of the matrix by acids mixtures in non-consensual number, with risk of cross-contamination or element losses due to incomplete solubilization or volatilization [16,17].

In order to overcome these problems, alternative methods for the direct and multi-elemental analysis in drug products, vegetal matrices and food samples are required. Work with High Resolution Continuum Source Graphite Furnace Atomic Absorption Spectrometry (HR CS GFAAS) has shown that this method is suitable for the direct measurement of Rh, Pd, Ir and Pt in active pharmaceutical ingredients (API) samples [18]. An analytical procedure based on Wavelength Dispersive X-ray Fluorescence spectrometry (WDXRF) was validated and applied for the determination of Zn, Fe, Ni in API, showing that the API matrix significantly influences the determination of metals by WDXRF spectrometry and must be taken into account when selecting the best compound candidate to prepare the synthetic calibration standards for quantitation purposes [19]. Thus, more work is necessary before WDXRF can be established as a good alternative method because the observed matrix effects need to be accounted for, if the broader set of metals listed by EMA and the USP is potentially present in the APIs. Moreover, and from a consumer's perspective, what is important is the safety and therapeutic efficacy of the final drug products, which may incorporate residues of metal elements throughout the above mentioned routes.

Therefore, it is important to investigate the feasibility of the different analytical methodologies when applied to samples of drug products available for sale and public consumption, and not only to individual APIs used by the industry in the manufacturing of those products. For that purpose, an analytical procedure using WDXRF for the determination of Cu in medicines has been validated by our group, following the EMA and the International Conference for Harmonization (ICH) guidelines [20,21]. The work has also shown that the WDXRF method has the degree of linearity, sensitivity, precision and accuracy necessary for the determination of Zn, Fe and Cr in pelletized samples of medicines, following the guidelines of EMA e ICH specifications and requiring little sample preparation if compared to ICP and AAS. The work reported here continues our previous investigation of the feasibility of WDXRF spectrometry for the determination of metal impurities in drug products.

In view of the above mentioned divergences between ICH-Q3D, EMA, EP and USP [1,2,4,5], a practical approach was followed by

Download English Version:

https://daneshyari.com/en/article/1220425

Download Persian Version:

https://daneshyari.com/article/1220425

Daneshyari.com