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The development of analytical procedures using ICP-OES and ICP-MS for the analysis of trace metals in pharmaceutical formulations

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SUMMARY

New regulations regarding elemental impurities in pharmaceuticals will be implemented in January 2018 and the guidelines include the use of inductively coupled plasma optical emission spectroscopy (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS). In this work, a method using each instrument was developed for the analysis of arsenic (As), cadmium (Cd), mercury (Hg), lead (Pb), cobalt (Co), nickel (Ni) and vanadium (V) and validated to meet the international conference of harmonisation (ICH Q3D) guidelines. Liquid and solid samples were prepared using microwave assisted acid digestion method that was developed using reverse aqua regia. The results obtained from the validation showed good linearity (R2>0.995) with low limits of detections (LODs) and limits of quantifications (LOQs). The percentage recoveries for both the standard reference material (SRM) and the spiked samples were between 95-105% with relative standard deviation (RSD) of less than 5. Cold symptoms relief products were purchased and analysed. Levels of Pb and Cd in certain products were found to exceed the permitted daily exposure limit (PDE) when the maximum dose was taken.

INTRODUCTION

Elemental impurities in pharmaceutical products are of great concern, since they do not have a therapeutic benefit and some contaminants have inherent toxicity. In addition, these elements may have adverse effects on the pharmaceutical active ingredient stability and shelf life by catalysing the degradation of drug substances.

The United States Pharmacopeia (USP) method, USP 231 proved to be unreliable, so new regulations regarding elemental impurities in pharmaceutical products using techniques like inductively coupled plasma optical emission spectroscopy (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS) were introduced in the USP Chapters 232 and 233 as well as the International Conference of Harmonisation (ICH Q3D) guidelines which will be introduced in all pharmaceutical products in January 2018. In the new guidelines, the allowed elemental impurities limits differ for different routes of administration; oral, parenteral or inhalation and are expressed as permitted daily exposure (PDE) doses in µg (of element)/day.

MATERIALS AND METHODS

Trace metal grade nitric acid (67-69% HNO3) and hydrochloric acid (34-37% HCl) were used for all

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experiments (Fisher Scientific, UK). Elements standards for ICP-OES and ICP-MS 1000 µg/mL each (SCP Science, EU) were used for calibration. Ultrapure water with a resistivity of 18 MΩ cm was obtained using TripleRed water purification system (TripleRed laboratory technology, UK). Standard reference material, SRM 3280 Multivitamin /Multielement tablets (National Institute of Standards and Technology, USA) was used to validate the method. Cold symptoms relief remedies were purchased from local retail outlets. For samples preparation, Mixer Mill MM200 (Retsch®) was used to grind the tablets and for microwave assisted acid digestion SP-D Microwave (CEM®) was used with 35 mL Pyrex® vessels. Elemental analysis was performed using: 1) ICP-OES (Thermo® iCAP 6500 Duo), 2) ICP-MS (Thermo® X series) both with standard nebuliser, spray chamber and fittings. The instrument's optimisation was performed by comparing signals and signal to blank ratios to get settings with the best sensitivity for each of the elements.

RESULTS AND DISCUSSION

The optimised and validated methods showed good linearity (R2>0.995) over a wide range with low limits of detection (LODs) and limits of quantification (LOQs) as shown in Table 1. The percentage recoveries for both the standard reference material (SRM) and the spiked samples were between 95-105% with relative standard deviation (RSD) of less than 5. When commercially available cold relief products were analysed, six products had Pb levels exceeding the permitted daily exposure limit (PDE) when the maximum dose is taken and four products contain Cd in concentrations that exceed the ICH Q3D PDE, which is 5 µg/day for both elements. Other elements were also quantified in some of products including Hg, Co and Ni, but were within the PDEs. See Table 2.

Table 1. *LODs and LOQs (ng/ml) obtained using ICP-OES / ICP-MS.*

Element	ICP-OES		ICP-MS (Standrd Mode)		ICP-MS Collision/Reaction cell (CCT Mode)	
	LOD	LOQ	LOD	LOQ	LOD	LOQ
As	1.95	5.86	0.73	2.1	0.05	0.15
Cd	0.29	0.87	0.04	0.09	0.01	0.03
Hg	0.8	2.3	0.59	1.83	0.57	1.7
Pb	1.56	4.73	0.07	0.2	0.02	0.05
Co	0.77	1.58	0.08	0.22	0.09	0.29
Ni	0.74	1.72	0.2	0.59	0.07	0.23
V	2.75	7.64	6.33	19.06	0.15	0.48

Table 2. *Elemental impurities in cold relief remedies (mean ± σ, n=3)*

Element	Product 1	Product 2	Product 2	Product 4	Product 5	Product 6	Product 7
As	<LOD	<LOD	<LOD	**<LOD**	**<LOD**	<LOD	<LOD
Cd	0.55 ± 0.09	6.19 ±2.3	<LOD	2.22 ±0.48	7.23 ±4.2	9.69 ±2.2	7.56 ±0.59
Hg	<LOD	<LOD	16.87 ±3.1	<LOD	9.01 ±2.7	<LOD	<LOD
Pb	4.14 ± 0.52	22.68 ±4.3	35.89 ±3.8	7.79 ±1.9	20.24 ±5.1	25.84 ±1.0	37.29 ±2.6
Co	<LOD	17.86 ±2.4	11.44 ±4.7	42.63 ±3.9	6.02 ± 2.1	9.13 ± 4.8	42.63 ±3.9
Ni	<LOD	13.67 ±2.0	21.86 ±2.5	2.70 ±1.0	10.01 ±2.0	14.45 ±1.1	35.69 ±6.4
V	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

CONCLUSIONS

From the validated results obtained using ICP-OES and ICP-MS it can be concluded that both techniques are suitable for the determination of elemental impurities in pharmaceutical products.

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