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Trace levels of Cr in empty medicine capsules determined in less than 12 min sample^{-1} (LOD = 0.4 µg g^{-1}).

Direct determination of chromium in empty medicine capsules by tungsten coil atomic emission spectrometry

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Abstract

Tungsten coil atomic emission spectrometry (WCAES) is used to determine trace levels of Cr in medicine capsules. No sample preparation other than 10-min vortex mixing with HNO_3 and H_2O_2 is required. Matrix decomposition is carried out directly on the atomizer to minimize matrix effects and improve precision and accuracy. The entire analysis takes less than 12 min sample^{-1} including sample preparation. The instrumental setup is based on a tungsten filament extracted from 150 W, 15 V microscope light bulbs, solid state power supply, fused silica lens, crossed Czerny-Turner spectrograph and a thermoelectrically-cooled charge-coupled device detector. The limits of detection (LOD) and quantification (LOQ) for Cr are 3 and 9 µg L^{-1}, which correspond to procedure LOD and LOQ of 0.4 and 1 µg g^{-1}, respectively. These values allow for quantification at a level 28-fold lower than the maximum daily Cr intake from medicine and medicine formulations recommended by the United States Pharmacopeial Convention (USP). The procedure's linear dynamic range is between 3 - 100 µg L^{-1}, with a R^2 = 0.9992. It was applied to different empty medicine capsule samples and WCAES results were not significantly different from values found by inductively coupled plasma optical emission spectrometry (ICP OES) by applying a single-factor ANOVA test at the 95 % confidence level ($p > 0.05$). The precision, calculated as % RSD, is between 5.2 - 7.4 %. This is a simple, fast, efficient and potentially portable analytical procedure that may be used in quality control and regulation enforcement applications.

Introduction

The global market for pharmaceutical products has been rapidly growing in the last few decades. This trend is expected to continue especially due to an aging population and its increasing access to more accurate diagnosis methods and more efficient health treatments.[1-3] An important, but often overlooked component of the pharmaceutical industry is associated with medicine capsules. In 2012, 300 billion units of these containers were produced in China alone, and in 2014, the global market for empty medicine capsules represented $1.3 billion. For 2019, the expected revenues generated by these products should reach the $1.8 billion mark, a 7 % increase in just five years.[4]

Medicine capsules are pharmaceutical delivery containers with different shapes, compositions and with volumes varying between 0.12-1.27 mL.[5] The materials used to make these products can have different consistencies, but should only have inactive ingredients in their composition, which is not always the case. An important source of contamination for patients ingesting medicine capsules is related to elemental impurities. Metal catalysts and other materials used to produce these capsules may remain at trace levels in the final product and then accumulate in the patient's organism, eventually causing potentially serious health conditions.[6,7] In this context, the United States Pharmacopeial Convention (USP) has recently established more restrictive regulations to the maximum intake concentrations of elemental impurities from medicine and medicine formulations. Although not specifically targeting medicine capsules, USP's chapters 232 and 233 regulate 15 elements with default concentration limits varying from 0.15 μg day^{-1} for inorganic As to 100 μg day^{-1} for Cu.[8,9]

Chromium is one of the elements included in USP's new regulations mainly because of its toxic characteristics and carcinogenic effects when present as Cr (VI).[10] In 2012, the Food and Drug Administration of China (SFDA) suspended commercialization of all medicine capsules produced in that country after finding excessively high concentrations of Cr in 13 types

of capsules from Zhejiang and 28 other provinces. Further investigations by the SFDA revealed that the Cr high levels were all related to the use of contaminated industrial gelatin to produce the medicine capsules.[11] Following these episodes, the SFDA has closed plants throughout the country and established more restrict regulations to the production of drugs and other pharmaceutical products.[12]

Considering all these aspects, the need for simple, fast and efficient analytical procedures to determine low concentrations of Cr in complex matrices such as medicine capsules become evident. The procedures recommended by the USP for determining trace element impurities in drug compounds and excipients are based on inductively coupled plasma with either optical emission spectrometry or mass spectrometry detection (ICP OES or ICP-MS, respectively).[9] These are two of the most sensitive, precise and accurate methods in atomic spectrometry, with limits of detection (LOD) at the μg L^{-1} and ng L^{-1} levels. On the other hand, costs associated with acquiring, maintaining and running these instruments may be limiting factors to their application, especially if one is interested in only one or just a few analytes. For Cr determinations in medicine capsules, a less expensive, potentially portable and equally efficient alternative is tungsten coil atomic emission spectrometry (WCAES).[13] First described in 2005,[14,15] WCAES uses a simple tungsten filament extracted from microscope light bulbs as atomization and excitation source to determine trace element levels in liquid samples by atomic emission spectrometry. Using simple optical apparatus and a handheld spectrometer, or a crossed Czerny-Turner spectrograph combined with a charge-coupled device (CCD) detector, WCAES has been successfully employed in elemental determinations at the μg L^{-1} level for such complex matrices as soil,[16,17] plant and biological material,[18-20] beverages,[21] biodiesel,[22] and lubricant oil.[23] In addition to WCAES, recent publications have also demonstrated the applicability of other potentially portable electrothermal AES-based systems for different applications.[24-26]

Although many works in the literature evaluate drug composition in pharmaceuticals, no study describes the determination of trace element impurities in empty medicine capsules to our knowledge. The present work describes a simple procedure to determine Cr in these samples which is based on WCAES and on matrix decomposition directly on the tungsten atomizer, with almost no sample preparation required.[21] As it will demonstrated, WCAES results are comparable to values obtained with ICP OES, for a simple, efficient and less expensive procedure.

Experimental

Apparatus

The WCAES instrumental setup used in this work is represented in Fig. 1. Tungsten filaments extracted from 150 W, 15 V microscope light bulbs (Osram Xenophot 64633 HXL, Pullach, Germany) are used as atomizer and excitation source for atomic emission measurements. The coil is kept in a borosilicate glass cell with fused silica windows (Ace Glass, product no. D131703, Vineland, New Jersey, USA) and powered by a solid state constant current power supply (200 W, Vicor, VI-LU1-EU-BM, Andover, MA, USA). A protective gas (10 % H_2 in Ar) flowing at all times during the analysis (1 L min^{-1}) prevents the atomizer from oxidizing and contributes to improving the Cr analytical signal.[27] The radiation produced during the atomization step is then collected and projected onto the entrance slit (25 µm width) of a crossed Czerny-Turner spectrograph (MonSpec 18, Scientific Measurement Systems Inc., Grand Junction, CO, USA) using a 25 mm diameter, 75 mm focal length fused silica lens. The 1:1 atomizer image is placed slightly off axis from the spectrograph entrance slit (Fig. 1c and Fig. 1S) to minimize the intense atomizer blackbody emission.[28] Analytical signals are finally collected by a thermoelectrically-cooled CCD detector (Spec-10, Princeton Instruments, Roper

Scientific, Trenton, NJ, USA) operating at -40 ^{o}C. More details on the atomization cell and the spectrograph can be found in the literature.[16,29]

Twenty-five-microliter aliquots of the analytical solutions are directly introduced onto the atomizer using an automatic micropipette (Eppendorf 10-100 µL, Brinkman, Westbury, NY, USA). The heating cycle shown in Table 1 is then applied to vaporize the solvent (step 1), pyrolyze the sample (step 2), and atomize and excite the analyte (step 4). A digital multimeter (RadioShack, Fort Worth, TX, USA) is used to monitor the potential across the atomizer and estimate its surface temperature during each step of the heating cycle.[29-31] A digital-to-analog converter (Measurement Advantage MiniLab 1008, Measurement Computing, Norton, MA, USA) and a lab-written Visual Basic 6.0 program (Microsoft, Seattle, WA, USA) are also used to control the time and the constant current delivered by the solid state power supply (Vicor). An integration time of 30 ms, with collection of 35 spectra during atomization was adopted for all determinations to maximize the Cr signal-to-noise ratio. Additional details on the heating cycle and the conditioning program used for new tungsten filaments can be found in the literature.[29,31]

A Prodigy High Dispersion ICP OES (Teledyne Leeman Labs, Hudson, NH, USA) was used to check the procedure's accuracy. All Cr determinations by ICP OES were carried out in plasma axial view under the following operational conditions: 1.2 kW RF power, 18 L min^{-1} plasma gas flow rate, 30 psi nebulizer pressure, and 0.6 mL min^{-1} sample introduction pump rate. The Cr 267.716 nm emission line and a 15 s integration time were used in all ICP OES determinations. A vortex mixer (Vortex-Genie, Fisher, Bohemia, NY, USA) was used for sample preparation.

Reagents, standards and samples

All solutions were prepared with distilled-deionized water (18 M Ω cm, Milli-Q®, Millipore, Bedford, MA, USA) and trace grade nitric acid (Fisher, Pittsburgh, PA, USA). The external calibration method was used in all determinations, and the calibration solutions were prepared by diluting a 1000 mg L^{-1} Cr stock solution (SPEX CertPrep, Metuchen, NJ, USA). Hydrogen peroxide 30% v v^{-1} (Acros, Morris Plains, NJ, USA) and trace grade nitric acid (Fisher) were used to dissolve the samples. Empty medicine capsules originated in China were evaluated in this study.

Sample Preparation

Approximately 0.4 g of the empty medicine capsule sample was accurately determined using an electronic balance (Mettler AE 100, Hightstown, NJ, USA). The sample aliquots were then mixed with 1.0 mL concentrated HNO_3 (Fisher) and 3.0 mL H_2O_2 (Acros) for 5 min using a vortex mixer (Fisher). Finally, the solutions were diluted to 50.0 mL with distilled-deionized water before Cr determination either by WCAES or ICP OES.

Results and discussion

On-the-coil matrix decomposition

One of the main advantages of using methods based on electrothermal atomization is the possibility of performing sample preparation directly on the atomizer. Graphite tubes and tungsten filaments have been used to decompose sample matrix and improve precision and accuracy in determinations by ICP-MS,[32,33] ICP OES[34] and graphite furnace atomic absorption spectrometry (GFAAS).[35,36] On-the-coil sample decomposition followed by WCAES has also been successfully applied to fish, beverage and biodiesel samples.[18,21,22] Table 1 shows the heating cycle used to vaporize the solvent, decompose the medicine capsule samples, and

atomize and excite Cr. Atomizer surface temperatures are presented to facilitate the transfer of procedures between different systems.[31] The first step is divided in three sub-steps with increasingly lower applied currents (not shown) that would result in dry coil surface temperatures of 910, 890 and 970 K, respectively. In this case, each sub-step lasts for 25, 20 and 15 s, respectively. As the solvent is vaporized, no temperature change should be observed, so the boiling point of water (*i.e.* 373 K) is shown as the estimated coil surface temperature for step 1. Additional details on the inverted ramp heating cycle and the optimization of the drying step can be found in the literature.[29,31,37] In the second step, the sample matrix is decomposed and some smoke is observed. Pyrolysis temperatures either higher or lower than 1300 K have resulted in poor sensitivity probably due to analyte loss or matrix effects, respectively. At the pre-atomization step (step 3), the atomizer returns to room temperature, which contributes for more symmetrical emission profiles. Finally, a high current is applied to the coil to allow for atomization and excitation of Cr. Considering a 10-min sample preparation step combined to the on-the-coil matrix decomposition described, the entire procedure takes last than 12 min per sample.

Analytical figures of merit and medicine capsule analysis

The Cr 425.4 nm emission line was used in all WCAES determinations. The linear dynamic range was between 3 - 100 µg L^{-1}, with R^2 = 0.9992. The limit of detection (LOD), calculated according to IUPAC's recommendations as 3 times the standard deviation of the blank (S_{bl}, n = 20) divided by the calibration curve slope (m), was 3 µg L^{-1}. This corresponds to a procedure LOD of 0.4 µg g^{-1}, with a limit of quantification (LOQ = $10S_{bl}$ / m) of 1 µg g^{-1}. Thus, assuming a person ingesting only one medicine capsule per day, and the average capsule mass determined as 0.0889 g, the procedure described allows for quantification at a level 28-fold lower than USP's maximum recommended Cr intake of 2.5 µg day^{-1}.[8]

The accuracy of the procedure was evaluated by comparing WCAES results with values obtained by ICP OES for 3 medicine capsule samples showing different apparent compositions (Fig. 2S). As it can be seen in Table 2, no significant differences are observed between WCAES and ICP OES results by applying a single-factor ANOVA test at the 95 % confidence level ($p > 0.05$). Using data from Table 2, the procedure's precision (% RSD) can be calculated as 6.5, 7.4 and 5.2 % for samples A, B and C, respectively. These values can be considered adequate for an all-manual, non-isothermal open-system.[27,38]

The results in Table 2 show a significant contamination of Cr in sample C. Once again assuming an average capsule mass of 0.0889 g, a patient taking just one pill with the same composition as sample C would be ingesting a daily Cr concentration almost 5-fold higher than the recommended USP maximum value.[8] Although lower, sample B also exceeds USP's recommendations, with a 2.97 μg day^{-1} intake considering the same scenario. On the other hand, a patient taking medicine in sample A capsules would need to ingest at least 11 pills per day to exceed the USP guidelines.

Conclusions

WCAES is a simple and effective method to determine μg L^{-1} levels of Cr. Its main advantages are the low sample consumption, instrument simplicity, no residue generation, and low power requirements (*e.g.*, even a 12 V car battery can be used as power supply in WCAES determinations). By combining the simple sample preparation and on-the-coil matrix decomposition described in this work, it is possible to determine trace levels of Cr in medicine capsules in less than 12 min per sample. Considering WCAES potential portability, the entire procedure may be applied in the field, for faster response times in emergency situations.

The results in this study demonstrate the urgency for monitoring trace elements in pharmaceutical products and the importance of USP's new regulations. In this context, WCAES may be a simple and efficient alternative for fast and accurate determinations.

Acknowledgements

The authors would like to thank Wake Forest University for the support to this work, and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (Grant No 99999.002566/2014-01) for the fellowship provided to D. A. G.. We would also like to thank Bruker Elemental for the support to J. G. and for providing the medicine capsule samples used in this study.

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Tables

Table 1. Heating cycle used for sample drying, pyrolysis and atomization in WCAES determinations of Cr.

Step	Temperature (K)	Time (s)	Signal acquisition
1	373	60	No
2	1300	20	No
3	298	10	No
4	3560	1	Yes

Table 2. Chromium concentrations (μg g^{-1}) in medicine capsules determined by WCAES and ICP OES. Values are the mean ± 1 standard deviation (n = 3).

Sample	**WCAES**	**ICP OES**	**p***
A	2.76 ± 0.18	2.51 ± 0.07	0.083
B	33.38 ± 2.46	36.66 ± 0.60	0.088
C	132.78 ± 6.86	138.21 ± 0.64	0.24

* p-value for a single-factor ANOVA test with $\alpha = 0.05$.

Figure Captions

Fig 1. Schematic diagram of the WCAES instrumental setup (a). The insets show alternative views of the atomization cell (b) and the coil image projection on the entrance slit of the spectrograph (c).

Figure

Fig 1. Schematic diagram of the WCAES instrumental setup (a). The insets show alternative views of the atomization cell (b) and the coil image projection on the entrance slit of the spectrograph (c).