Trends in Analytical Chemistry xxx (2017) 1–13

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

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

Impact and practicability of recently introduced requirements on elemental impurities

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Elements
Pharmaceuticals
Sample preparation
Inductively coupled plasma optical emission (ICP-OES)
Inductively coupled plasma mass spectrometry (ICP-MS)

ABSTRACT

Spectrochemical elemental analysis of pharmaceuticals and raw materials used for their production will be in the nearest future an obligatory part of quality and safety control for compliance with new standards announced by the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Q3D). The present paper surveys R&D articles and scientific papers devoted to determination of the elemental impurities by inductively coupled plasma optical emission spectrometry and mass spectrometry (ICP-OES and ICP-MS) in different pharmaceuticals products that have been published since 2000. In reference to recent changes described in the United States Pharmacopoeia (USP) general chapters <232> and <233>, different aspects of such measurements are presented, including appropriate sample preparation procedures, possible interferences and means of their avoidance, suitable calibration strategies and validation parameters that have to be assessed to prove reliability of the analytical results on the elemental impurities in pharmaceutical products.

1. Introduction

Quality control and assurance (QC/QA) is an essential part of production of drug substances and pharmaceutical formulations and a major area of concern [1–5]. Determination of the elemental impurities in active pharmaceutical ingredients (APIs), excipients and final medications at different stages of their formulation and production is justified and necessary according to the concentration limits defined by the respective supervising authorities and official compendia, such as pharmacopoeias [1–3,6,7]. Necessity of dependable results of such elemental analysis in shorter time lines is related to the production process of pharmaceutical substances as well as fast and unequivocal characterization and specification of these products [8].

Metal-, non-metal- or metalloid-containing species can be included in APIs themselves or contamination of drug substances and their intermediates with different elemental species, *e.g.*, As, Cd, Hg, Ni, Pb, may be non-intentionally introduced through contaminated raw materials, *i.e.*, water and solvents, reagents for APIs synthesis, and different excipients, *i.e.*, stabilizers, fillers, binders, colors, flavors and coatings, associated with production of pharmaceuticals [3,5,7,9–18]. Another non-intentional source of contamination of pharmaceutical ingredients and final dosage forms with the elemental impurities, *i.e.*, Cr, Cu, Mo, Ni, V, can be through contact of these products with surface of the reaction vessels or other equipments and materials used during the fabrication process, *e.g.*, mixing tanks, filters, filling lines, and subsequent packing and storage [3,5,13,14,19]. Quite often, elements such as Ir, Os, Pd, Pt, Rh and Ru can directly be introduced to pharmaceuticals through catalysts that are used at various steps of APIs synthesis [1,3,5–7,9–14,16,18,20]. In this case, remnants of catalysts in final pharmaceutical products may give rise to presence of certain elemental impurities at trace or ultra-trace levels.

In general, presence of the elemental impurities in pharmaceutical products is of a great concern for their manufacturers and consumers due to inherent toxicity of given elemental contaminants and health threat they may pose [3,5,15,18,21–24]. The elemental impurities can catalyze decomposition of APIs and hence shorten their shelf-life or present themselves different side- and

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http://dx.doi.org/10.1016/j.trac.2017.09.011
0165-9936/

undesirable effects that result in poisoning the human body [3,7,9,10,15,21,23–25], *e.g.*, in case of As, Cd, Hg and Pb, in addition to Cr, Cu, Fe, Mn and Zn.

For that reason, the content of the inorganic (elemental) impurities in final dosage forms and raw materials used for manufacturing the drugs, *e.g.*, water, excipients, APIs, and all resultant intermediates need to be under control and monitored using one of the pharmaceutical standard tests. This can ensure compliance of the elemental impurities level with specifications and regulations related to desired product quality, safety and effectiveness [3–5,8–10,14–16,24]. Residual presence of elements in APIs or drugs can be treated in this way as a general quality marker of final pharmaceutical products according to compendial limits and appropriate recommendations [10,22].

1.1. The USP general chapter <231>

Considering various pharmacopoeias, the United States Pharmacopoeia (USP), as an example, has recommended for many years the general chapter <231> Heavy Metals for evaluation of the elemental impurities in different pharmaceutical products. This USP general chapter and compendial test included in it will, however, become obsolete and be omitted from the USP monographs starting January 1, 2018 [26]. This is because the mentioned compendial test for determination of the elemental impurities in the pharmaceutical substances and products is based on precipitation of colloidal sulfides of elements. The sample preparation recommended in the USP general chapter <231> is either inconvenient. The 1st method is limited to the substances that can be dissolved in and diluted with water only. In the 2nd method, the substances to be tested have to be charred with concentrated H_2SO_4 at first, then, the carbonized residues are ashed at 500–600°C. The resulting mineral ashes have to be digested, evaporated to dryness, and finally re-dissolved with water. The 3rd method, an open-vessel wet-digestion method, is used in those cases when neither two first methods can be applied, however, it is also time-consuming and labor-intensive [27].

Although simple and inexpensive, the compendial test and the sample preparation methods proposed in this general chapter for monitoring and controlling the elemental impurities in medicinal preparations has been recognized by many experts to be inaccurate and incomprehensive to provide quantitative and element-specific information. The main deficiency of the mentioned compendial test is that it allows to assess the content of 10 elements only, *i.e.*, Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu and Mo [24,26–28]. Formation of sulfides of target elements in the prepared sample solutions is affected by the sample matrix, hence, the results are seldom reliable and reproducible [3,5,8,9,21,24,27,28]. The color change of sulfides of target elements is subtle and ranges from white to yellow, orange brown and black, making visual comparison difficult and subjective. The samples usually require to be ashed and/or heated in open-vessel systems that can result in loss of elements. As experimentally proved, this process is matrix-dependent and provides poor recoveries of target elements, *i.e.*, <10% for Hg, Ru, Sb, Se and Sn; 30–50% for As, Cd, In, Mo, Pb, Pd and Pt [8]. Unsuitability of dry ashing as the sample preparation procedure has also been confirmed by Barin *et al.* [2], who reports complete loss of Hg in addition to ~60% and ~10% loss of As and Pb, respectively.

1.2. The new USP general chapters <232> and <233>

Recognizing all drawbacks of the compendial test described in the USP general chapter <231>, particularly lack of specificity and sensitivity, it is clear that it will no longer be suitable [29–33]. Instead of this, the elemental impurity tests will have to conform the compendial limits outlined in the new harmonized USP general chapter <232> Elemental Impurities – Limits [34] that defines the maximum limits of 24 elements in the pharmaceutical products in compliance with the Q3D guideline on the elemental impurities of the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [35]. All new analytical procedures defining how to test for the elemental impurities and validate the results of these compendial tests are set out in the USP general chapter <233> Elemental Impurities – Procedures [36]. Rationale behind introduction of both mentioned general chapters by USP is to provide a modern equivalent to the general chapter <231>, replacing the "heavy metals test" with more sensitive, precise and accurate analytical methods, allowing specific measurements of individual elements in a quantitative manner, and enabling unequivocal examination of potential toxicity of the pharmaceutical products related to presence of certain elemental species [28]. That is why the USP general chapter <233> makes reference to two of the most sensitive, common and very useful (because providing multi-elemental analysis) spectrometric techniques, *i.e.*, inductively coupled plasma optical emission spectrometry (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS). Alternative spectrometric techniques, *i.e.*, flame or graphite atomic absorption spectrometries (FAAS or GFAAS), can also be used, however, they have to meet the performance requirements defined in both USP general chapters <232> and <233> [36]. ICP-MS with appropriate sample preparation particularly seems to be nowadays the technique of choice for determination of the elemental impurities on a routine basis. It provides good sensitivity, high sample throughput and quantification of target elements both at the ng g^{-1} and sub ng g^{-1} levels [8,22,24,27,37–39].

Taking into account the highest quality of medicines and their safety, it is mandatory for pharmaceutical manufacturers and pharmaceutical organizations and their testing laboratories to demonstrate that their products are compliant with the specified levels of the elemental impurities, *i.e.*, permissible daily exposure (PDE) limits for 24 elements, included in official documentation (see Table 1). These PDE limits of elements in finished drug products are set considering the toxicological data and the route of administration [28,40]. Therefore, to evaluate risk of likelihood of contamination of the drug products with different elemental impurities and determine their compliance with the specified PDE limits, ICP-OES and/or ICP-MS along with appropriate sample preparation procedures must be applied [28]. Certainly, to accurately measure the low concentrations of the elemental impurities in the pharmaceutical ingredients and products, sample preparation prior to ICP-OES and ICP-MS analysis used by the pharmaceutical companies needs to be changed as well to meet the new safety limits [28,38].

Guidance on the elemental impurities set out in the USP general chapter <232> is in a strict compliance with guidelines of ICH Q3D, finalized in December 2014 [35]. It includes 24 elements that are grouped into four main categories, *i.e.*, class 1, class 2A, class 2B and class 3. This classification is based on relative toxicity of target elements, their likelihood of occurrence and route of administration [28,40]. The permissible levels of 24 elements in finished drug products are set considering the toxicological data and the route of administration, rather than method capability (as is in the USP general chapter <231>). They are given in μg in the form of maximum PDEs (see Table 1). Since the finished pharmaceuticals are to be diluted or digested prior to spectrochemical elemental analysis, the PDE limits (in μg day^{-1}) have to be converted to the respective concentration limits (in μg L^{-1}) as measured in the prepared sample solutions. Therefore, the USP general chapter <232> additionally defines the target concentrations in the

Please cite this article in press as: P. Pohl, et al., Impact and practicability of recently introduced requirements on elemental impurities, Trends in Analytical Chemistry (2017), http://dx.doi.org/10.1016/j.trac.2017.09.011