Elemental Impurities in Pharmaceutical Excipients

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ABSTRACT: Control of elemental impurities in pharmaceutical materials is currently undergoing a transition from control based on concentrations in components of drug products to control based on permitted daily exposures in drug products. Within the pharmaceutical community, there is uncertainty regarding the impact of these changes on manufactures of drug products. This uncertainty is fueled in part by a lack of publically available information on elemental impurity levels in common pharmaceutical excipients. This paper summarizes a recent survey of elemental impurity levels in common pharmaceutical excipients as well as some drug substances. A widely applicable analytical procedure was developed and was shown to be suitable for analysis of elements that are subject to United States Pharmacopoeia Chapter <232> and International Conference on Harmonization's Q3D Guideline on Elemental Impurities. The procedure utilizes microwave-assisted digestion of pharmaceutical materials and inductively coupled plasma mass spectrometry for quantitative analysis of these elements. The procedure was applied to 190 samples from 31 different excipients and 15 samples from eight drug substances provided through the International Pharmaceutical Excipient Council of the Americas. The results of the survey indicate that, for the materials included in the study, relatively low levels of elemental impurities are present. © 2015 The Authors. *Journal of Pharmaceutical Sciences* published by Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:4197–4206, 2015

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INTRODUCTION

Procedures for controlling elemental impurities in pharmaceutical products are undergoing significant revision. Elemental impurity levels in pharmaceutical materials are currently controlled through concentration specifications for metal catalysts and reagents in drug substances and/or concentration-based compendial acceptance criteria for select elements or classes of elements in drug substances and excipients. For some materials, pharmaceutical manufacturers currently demonstrate that they meet the compendial limits on drug substances and excipients by applying pharmacopeial heavy metals tests based on sulfide precipitation such as the procedure described in the United States Pharmacopeia (USP) General Chapter <231> Heavy Metals.[1] These acceptance criteria are being replaced by element specific permitted daily exposures (PDEs) from finished drug products that are based on current toxicological assessments of the elements. The PDE concept was firmly established in the International Conference on Harmonization (ICH) Q3C guideline on residual solvents. These major changes in the control of elemental impurities in pharmaceutical products are the culmination of many years of discussion and planning.

In 1995, the USP published a stimuli article in Pharmacopeial Forum describing several problems with the sulfide precipitation method including poor, variable recoveries, lack of selectivity, loss of volatile elements, and questionable validity.[2] The article recommended the use of spiked control samples during validation and substitution of atomic absorption and other instrumental methods for USP <231>. In 1998, the European Medicines Agency (EMA) began to develop a guideline on residual catalysts in pharmaceuticals with the goal of establishing limits based on toxicological safety assessments of common catalytic elements.[3] In 2008, the EMA Guideline on Specification Limits for Residues of Metal Catalysts or Metal Reagents was officially implemented for new drug products. The EMA guideline introduced mass-based PDEs to establish permissible exposures in drug products rather than concentration limits in drug substances. The PDEs in the EMA guideline were based on assessments of toxicological data on individual metals.

Between 2000 and 2008, the USP initiated a series of workshops and stakeholder forums for the purpose of revising General Chapter <231> Heavy Metals. During this time, several papers evaluated the suitability of modern instrumental methods of analysis for elemental impurities in pharmaceutical articles and products.[4–6] In 2008, the USP commissioned the United States Institute of Medicine to organize a workshop to evaluate current elemental toxicology and capabilities of modern methods of elemental analysis. Later in 2008, the USP

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proposed to replace <231> with two chapters: <232>, which would establish safety based limits on elemental impurities in pharmaceutical products, and <233> which would establish appropriate criteria for methods for elemental analysis.[7] After several years of revision with input from a broad group of stakeholders, these chapters were finalized, and became official in February of 2013.

In 2009, the ICH initiated the Q3D expert working group on elemental impurities in pharmaceutical products with the intention of harmonizing technical requirements for elemental impurities in pharmaceutical products across three regions: Europe, Japan, and the US.[8] As with the EMA guideline and the USP chapters, the Q3D expert working group endeavored to set maximum PDEs for elemental impurities in pharmaceutical products based on an assessment of existing toxicological data for the oral, parenteral and inhalation routes of administration. Q3D reached Step 2 of the ICH process in June, 2013 and the guideline was published for public review and comment. Q3D reached step 4 in November of 2014, and the USP Expert Panel on Elemental Impurities aligned General Chapters <232> and <233> with Q3D to the extent possible.

A PDE is the total daily mass of an impurity which is considered safe on the basis of direct toxicity. This is now a well-established approach which limits the amount of an impurity that is ingested by the patient rather than setting concentration limits on pharmaceutical materials. However, when applied to elemental impurities in drug products, the PDE approach poses some challenges for users and suppliers of drug substances and excipients because measurable acceptance criteria are no longer imposed on individual components of the drug product. Rather, the drug product manufacturer must determine what concentrations of elemental impurities are permissible for a drug product on the basis of the mass of a maximum daily dose of the drug product and the element-specific PDEs. Elemental impurity levels in drug products may also be controlled by setting appropriate concentration limits on all components of a drug product, based on the mass of each component of the drug product.

Manufacturers and suppliers of drug substances and excipients are understandably concerned about the impact of the new standards and guidelines on the requirements for elemental impurities in their products. At present, when applicable, ingredient manufacturers demonstrate that their products comply with compendial concentration limits for elemental impurities. There is concern that pharmaceutical manufacturers may now request extensive quantitative assessment of all elemental impurities in the components of drug products to demonstrate that the drug products comply with the new standards and meet the recommendations of new guidances. Currently there is a dearth of publically available data on elemental impurity levels in most pharmaceutical ingredients, which imposes additional uncertainty on the impact of these new standards and guidances.

The purpose of this paper is to present a survey of elemental impurity concentrations in a variety of excipients commonly used in pharmaceutical products as well as some drug substances. The samples for this survey were provided by the members of International Pharmaceutical Excipient Council-Americas (IPEC-Americas), and were analyzed at the United States Food and Drug Administration (US FDA) Division of Pharmaceutical Analysis. The analysis of these materials utilized a robust method of closed vessel digestion which is suitable for a wide variety of excipients and drug substances with appropriate modification, and the digested samples were analyzed by inductively coupled plasma mass spectrometry (ICP-MS). The experimental section of this paper describes the details of the analytical procedure. This is followed by the analytical results and a description of the capabilities of the procedures. The paper concludes with a brief discussion of some analytical challenges, and some potential solutions to those challenges.

EXPERIMENTAL

Reagents and Materials

Concentrated nitric acid (70%), concentrated hydrochloric acid (37%), hydrogen peroxide (30%), and hydrofluoric acid (49%) were purchased from Fisher Scientific (Fair Lawn, New Jersey). All of these regents were trace metal grade. Diluted nitric acid and hydrochloric acid were used for analytical solutions and sample dilutions. 18 MΩ-cm deionized water was produced through a Milli-Q water purification system (Millipore, Bedford, Massachusetts). Multi-element standards and individual standards were purchased from High-Purity Standards (Charleston, South Carolina). Instrument tuning solution and pulse/analog (P/A) tuning solution were purchased from Agilent Technologies (Newport, Delaware). Metal-free polpropylene centrifuge tubes 15 mL and 50 mL were purchased from VWR (Radnor, Pennsylvania).

One hundred and ninety pharmaceutical excipient samples and 15 drug substance samples were supplied by excipient manufacturers through IPEC-Americas. The samples included 31 different excipients that are commonly used in pharmaceutical manufacturing and eight different drug substances, and many were provided from multiple manufacturers and in several lots from the same manufacturer. The samples were coded by IPEC-Americas' counsel before being shipped to the US FDA Division of Pharmaceutical Analysis such that the analysts were informed of the name of each material, but were blind to their precise lot number and origin, which were only known to counsel. Different manufacturers were denoted with letters, and different lots were denoted with numbers to convey information on material variability without disclosing the specific products under test.

Instrumentation

All quantitative analyses were performed with an Agilent 7700x quadruple ICP-MS system and a model ASX-500 Autosampler (Agilent Technologies). Standard, sample, and quality control solutions were delivered to the nebulizer via a peristaltic pump at 0.1 mL per minute, and the nebulizer converted the sample solution to a spray mist using gas (Ar). For most samples in this study, a glass nebulizer was used, but when hydrogen fluoride was included in the digestion cocktail a perfluoroalkoxyalkane nebulizer was used. The peristaltic pump also continuously delivered a multi-element solution containing lithium-6, scandium, yttrium, indium, terbium, holmium, lutetium, and bismuth to the nebulizer. These elements, delivered at a fixed composition relative to the sample flow rate, were used as internal standards to compensate for matrix effects and instrumental instabilities during analysis. Internal standards were selected for each elemental analyte such that their first ionization energies were similar and interferences were minimized.

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