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Application Note
Pharma

Ultrapure Water for Determination of Elemental Impurities in Pharmaceuticals

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Abstract

This paper discusses the importance of reagent water quality for trace element analyses in the pharmaceutical industry. The suitability of fresh ultrapure water produced using Milli-Q® water purification systems for ICP-OES and ICP-MS trace element analyses is also demonstrated.

Key words or phrases

trace elements, elemental impurities, metals, ICP-MS, ICP-OES, contamination, BEC, LOD, water quality, interferences, pharmacopeia, validation, data management

Introduction and Water Quality Requirements

The purpose of trace element analyses for pharmaceuticals

In the pharmaceutical industry, it is absolutely crucial to monitor and control trace elements at all stages of development and production. This is explained by three major reasons:

- Metals and metalloids are used as reagents and catalysts in the synthetic processing of raw materials, intermediates and active pharmaceuticals ingredients, as well as in the formulation and manufacturing of products. It is therefore important to ensure that medicinal products do not contain toxic metal contaminants at concentrations that could be detrimental for human health.
- For certain customers and authorities, it is important that products, such as multi-vitamins or metal-based drugs, contain elements they are purported to contain and at levels reported on the packaging.
- Metals can be introduced into pharmaceutical products unintentionally through contaminated reagents or when products are in contact with metal surfaces during development or production processes. Moreover, metals can find their way into a product from packaging. Thus, the material of containers used to store products must be evaluated for the trace element leachables and extractables.

Analytical techniques

Flame atomic absorption spectrometry (FAAS) and graphite furnace atomic absorption spectrometry (GFAAS) are techniques that have, until recently, been the first choice of analytical chemists for trace element analyses. Today, these techniques are frequently being replaced by modern, more sophisticated instrumentation, such as inductively coupled plasma–mass spectrometry (ICP-MS) and inductively coupled plasma–optical emission spectroscopy (ICP-OES).[1] The use of this instrumentation is encouraged by the United States Pharmacopeial Convention (USP) as they allow rapid, specific and reliable multi-element analyses of a variety of sample types.[2] This modern instrumentation is characterized by high sensitivity and established, strict requirements for the quality of experimental reagents. Indeed, reagents of very high quality must be selected to achieve the best performance of ICP-MS or ICP-OES instrumentation.

Water requirements

In ICP-MS or ICP-OES trace element analyses, ultrapure water is used extensively. It is often present in mixtures at high percentages compared to other mixture components because it is used for direct dilution during sample and standard preparation, as a reagent blank, and for instrument and sample container cleaning (**Figure 1**). Any contamination, and in this particular case, trace element contamination, introduced during sample preparation will carry throughout analysis affecting the final results. Therefore, water selected for trace element analyses must be of very high and consistent quality and should not contaminate samples or the analytical instrument with elements.[3]

In the pharmaceutical industry, the choice of water quality is dictated by its intended use.[4] However, water selected as an analytical reagent must not only comply with specific pharmacopeial standards, but must also meet the requirements of modern analytical instrumentation to ensure the success of any trace element analysis.

Milli-Q® ultrapure water purification systems are designed to be compliant* with water quality standards determined in various pharmacopeias. The aim of this study was to evaluate the suitability of fresh ultrapure water produced using Milli-Q® ultrapure water purification systems for ICP-MS and ICP-OES trace element analyses.

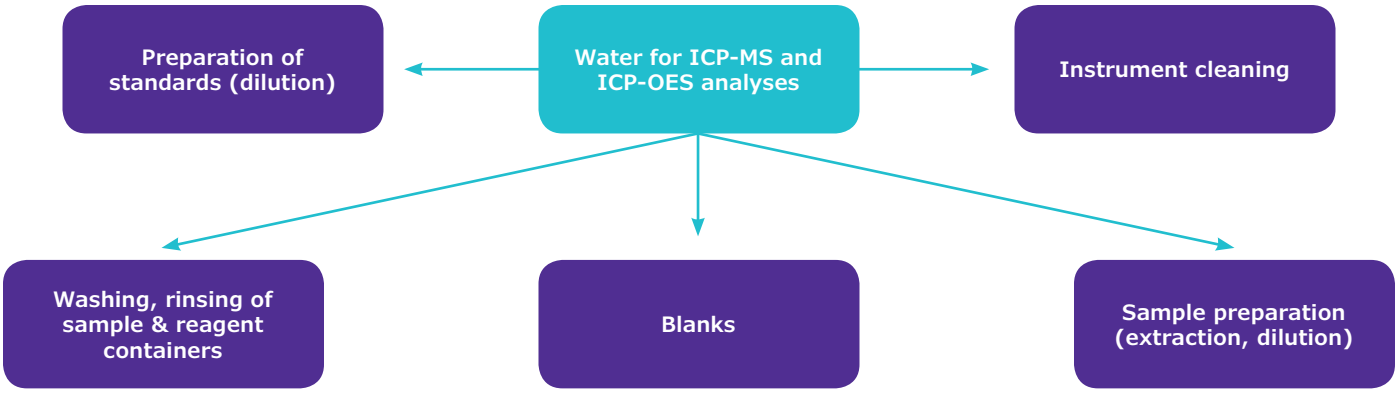

Figure 1. Different types of uses for ultrapure water in ICP-MS and ICP-OES analysis.

* Compliance reports are available on demand.

Results and Discussion

In spite of increased interest from the pharmaceutical industry to analyze trace elements in products and packaging, there is no agreement on which elements should be monitored. The element that is subject to control is completely dependent on the stage of a product's development or manufacturing process. Therefore, a number of elements were selected based on USP Chapter 233[2], the ICH Q3D Guideline for Elemental Impurities[5] proposed by the EMA for the Evaluation of Medicinal Products, as well as various scientific publications.[3,6] In **Table 1**, background equivalent concentration (BEC) and limit of detection limits (LOD) are demonstrated for each element in ng/L (ppt) level.

Element	BEC (ppt)	LOD (ppt)	Element	BEC (ppt)	LOD (ppt)	Element	BEC (ppt)	LOD (ppt)
^{7}Li	0.00	0.00	^{85}Rb	0.07	0.14	^{157}Gd	0.18	0.13
^{9}Be	0.24	0.28	^{88}Sr	0.36	0.15	^{159}Tb	0.03	0.03
^{11}B	7.71	1.84	^{89}Y	0.11	0.11	^{163}Dy	0.11	0.08
^{23}Na	17.49	2.72	^{90}Zr	0.47	0.09	^{165}Ho	0.03	0.02
^{24}Mg	13.17	0.52	^{93}Nb	0.23	0.15	^{166}Er	0.10	0.06
^{27}Al	0.47	0.06	^{95}Mo	0.62	0.36	^{169}Tm	0.04	0.03
^{39}K	38.72	1.00	^{101}Ru	0.69	0.19	^{172}Yb	0.14	0.10
^{40}Ca	63.60	2.17	^{103}Rh	0.16	0.26	^{175}Lu	0.03	0.03
^{45}Sc	7.50	1.89	^{105}Pd	0.07	0.06	^{178}Hf	0.12	0.09
^{49}Ti	2.08	2.49	^{107}Ag	0.59	0.11	^{181}Ta	0.15	0.13
^{51}V	0.72	0.39	^{111}Cd	0.06	0.20	^{182}W	0.59	0.40
^{52}Cr	2.10	0.37	^{115}In	0.07	0.06	^{187}Re	0.06	0.03
^{55}Mn	2.64	0.14	^{118}Sn	0.47	0.85	^{189}Os	0.28	0.23
^{56}Fe	0.60	0.19	^{121}Sb	0.06	0.11	^{193}Ir	0.08	0.12
^{58}Ni	0.76	0.18	^{125}Te	3.77	2.61	^{195}Pt	0.29	0.19
^{59}Co	0.30	0.11	^{133}Cs	0.05	0,00	^{197}Au	0.40	0.32
^{63}Cu	0.19	0.11	^{137}Ba	3.90	0.50	^{202}Hg	0.49	0.25
^{66}Zn	14.07	1.17	^{139}La	0.13	0.06	^{205}Tl	0.50	0.21
^{69}Ga	0.02	0.10	^{141}Pr	0.05	0.04	^{208}Pb	1.37	0.33
^{72}Ge	8.05	4.96	^{146}Nd	0.22	0.17	^{209}Bi	0.07	0.08
^{75}As	3.10	0.72	^{147}Sm	0.25	0.18	^{232}Th	0.10	0.08
^{78}Se	1.05	0.91	^{153}Eu	0.05	0.05	^{238}U	0.11	0.05

Table 1. Element levels in ng/L (ppt) in freshly produced ultrapure water from a Milli-Q® system measured under normal laboratory conditions (not in a clean room).

In the pharmaceutical industry, trace element analyses are performed in the range from mg/L (ppm) to sub-µg/L (sub-ppb), and it is desirable that BEC values of target elements do not exceed the ppt (ng/mL) or sub-ppt range. Moreover, as sensitivity, accuracy, precision and recovery must be appropriately demonstrated during the method validation process, achieving a low and stable detection limit is of high importance. From **Table 1**, it can be observed that certain elements have slightly higher values than sub-ppt, which is explained by contamination coming from the laboratory environment, since the analyses were performed under normal laboratory conditions.[7] If there is a need to achieve significantly lower levels of elements, it is reasonable to use additional polishing steps, such as Q-POD® Element unit which makes it possible to obtain BECs at sub-ppt levels.[8,9]

Experimental

Ultrapure water samples from a Milli-Q® Advantage A10 water purification system, equipped with Q-Gard® and Quantum® TEX cartridges, Millipak® final filter, and fed by an Elix® Essential 5 water purification system, were analyzed for the levels of Li, Be, B, Na, Mg, Al, K, Ca, Ti, V, Cr, Mn, Ni, Co, Cu, As, Se, Sr, Mo, Pd, Ag, Cd, Sn, Sb, Cs, Ba, Tl, Pb, Th and U using an Agilent® 7700s ICP-MS instrument, and for levels of Sc, Fe, Zn, Ga, Ge, Rb, Y, Zr, Nb, Ru, Rh, In, Te, La, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, W, Re, Os, Ir, Pt, Au and Bi using an Agilent® 7500s ICP-MS instrument. Ultrapure water samples from a Milli-Q® Direct water purification system, equipped with Q-Pak® TIX cartridge and Millipak® final filter, were analyzed for Hg levels using an Agilent® 7500s ICP-MS instrument. All experiments were performed under regular laboratory conditions (not in a clean room).

Agilent® 7700s instrumental details and parameters: PFA-50 nebulizer, PFA spray chamber, sapphire inert torch, quartz 2.5 mm i.d. torch injector, platinum sample and skimmer cone, RF power 600/1600 W, sampling position 12 / 8 mm, carrier gas flow 0.90 L/min, makeup gas flow 0.32 / 0.51 L/min, auto detector mode, calibration through 1, 5, 10, 50 ng/L.

Agilent® 7500s instrumental details and parameters: quartz nebulizer, quartz spray chamber, quartz i.d. torch injector, nickel sample and skimmer cone, RF power 1300 / 1550 W, sampling position 8 mm, carrier gas flow 0.96 L/min, makeup gas flow 0.23 L/min, auto detector mode, calibration through 1, 20, 50, 100 ng/L.

The calibration standards used in experiments with the Agilent® 7700s were a mixture of Agilent® and SPEX CertiPrep®, and with the Agilent® 7500s, ROMIL PrimAg®-xtra was used. Containers were all PFA pre-cleaned with ultrapure water. All ultrapure water samples (resistivity of 18.2 MΩ·cm and TOC below 5 ppb) from Milli-Q® water purification systems were analyzed immediately after water collection.

Conclusion

The needs of reagent water for trace analyses in the pharmaceutical industry were discussed, and it was demonstrated that ultrapure water produced by a Milli-Q® water purification system contains low ppt levels of trace elements. Therefore, laboratories in the pharmaceutical industry that perform trace element analysis can rely on Milli-Q® systems to meet their stringent requirements for the highest purity water for these experiments. Choosing ultrapure water produced from a Milli-Q® system for trace element analyses will help to ensure the generation of high quality data.

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