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Article

Measurement of ^{227}Ac by Isotopic Ratio with ^{225}Ac Using ICP-MS

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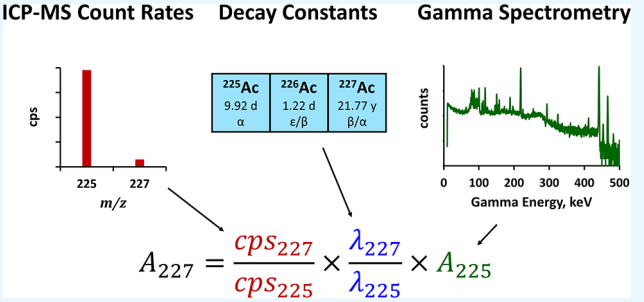
ABSTRACT: A method is reported for the measurement of ^{227}Ac using inductively coupled plasma mass spectrometry (ICP-MS) and isotope ratio analysis. The method has application for the quality testing of ^{225}Ac produced as an active pharmaceutical ingredient (API). The ^{225}Ac/^{227}Ac isotope ratio is measured directly from ICP-MS count rate data and converted to an ^{225}Ac/^{227}Ac activity ratio by using basic nuclear decay equations. The activity ratio, which is itself a measure of radioisotopic purity, is coupled with an orthogonal measurement of ^{225}Ac activity to obtain an absolute ^{227}Ac activity. Thus, the method may be used to report the ^{227}Ac content of an ^{225}Ac API in absolute or relative terms. The methodology was evaluated against appropriate validation criteria (e.g., linearity, accuracy, precision, specificity) by analyzing a series of solutions containing known quantities of ^{225}Ac and ^{227}Ac. Accuracy was evaluated using a spike recovery study. The spike recoveries were 100−108% for samples with 0.100 to 2.00 ng L^{-1} of ^{227}Ac and 74−91% for 0.025 ng L^{-1} of ^{227}Ac. Intermediate precision was measured as 4.1% using replicate measurements (n = 12, two instruments) of ^{227}Ac spiked samples (0.5 ng L^{-1}). The instrumental detection limits for ^{227}Ac were shown to be as low as 23 Bq L^{-1} (0.0086 ng L^{-1}), which is lower than comparable methods for the quantification of ^{227}Ac in ^{225}Ac APIs. Actinium-225 samples are analyzed under this method without any need for ^{225}Ac decay or ^{227}Ac daughter in-growth. Sample preparation involves simple dilution of the ^{225}Ac API in 3% HCl/1% HNO_3. The analysis takes as little as 2 h using equipment common to radioanalytical laboratories. Thus, the measurement of ^{227}Ac by this method can be performed as part of routine ^{225}Ac API quality testing and reported on release documents. This is a significant advantage over radiometric methods reported for the quantification of ^{227}Ac in ^{225}Ac APIs, which require days to weeks before reportable results can be obtained. The measurement of ^{227}Ac by ICP-MS and isotope ratio analysis is rapid, accurate, and sensitive. The implementation of this method for ^{225}Ac API quality testing will help ^{225}Ac producers and end-users ensure product quality and demonstrate regulatory compliance.



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INTRODUCTION

Targeted α therapy (TAT) is an emerging approach to cancer treatment that involves the selective delivery of α-emitting radionuclides to cancerous tissues. The therapeutic effect stems from the emission of α particles in close proximity to the cancerous cells. α particles are heavy (4 amu) and highly charged (+2). They exhibit high linear energy transfer (LET) and short-range (20−100 μm) in biological tissues, making them highly effective cell-killing agents. When delivered to cancerous tissues by means of a targeting vector, α-emitting radionuclides can cause significant cellular damage to the targeted, diseased tissues while sparing adjacent healthy tissues.

Actinium-225 ($t_{1/2}$ = 9.9172 d) is the most widely used α-emitting radionuclide for TAT[1] owing to its favorable nuclear properties.[2] The long half-life of ^{225}Ac allows for centralized production and distribution, which simplifies logistics for both isotope producers and end-users. The ^{225}Ac decay chain produces a cascade of four α particles and two β particles. The multiplicity of charged particles increases the cytotoxicity and, thus, the therapeutic efficacy of ^{225}Ac-based radiopharmaceuticals. This efficacy has been demonstrated through preclinical and clinical studies against various forms of cancer.[3−6]

The clinical development of ^{225}Ac-based radiopharmaceuticals has been hindered by limited global supply of ^{225}Ac.[7] The primary production route used to obtain ^{225}Ac for clinical trial use is by isolation from ^{229}Th decay in the form of ^{229}Th-generators.[8−12] However, the ^{233}U stockpiles from which ^{229}Th-generators are manufactured are finite global resources, which limits the total ^{225}Ac output available through this production route. Several nuclear reaction routes are being

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developed to meet growing clinical demand for ^{225}Ac including: ^{232}Th spallation via ^{232}Th(p,x)^{225}Ac or ^{232}Th-(p,x)^{225}Ra → ^{225}Ac,[13−15] cyclotron production via ^{226}Ra(p,2n) or ^{226}Ra(d,3n),[16−18] photonuclear production via ^{226}Ra-(γ,n)^{225}Ra → ^{225}Ac,[19−22] or reactor production via ^{226}Ra-(n,2n)^{225}Ra → ^{225}Ac.[23,24]

A common concern for these new production routes is the potential coproduction of ^{227}Ac ($t_{1/2}$ = 21.772 y). Actinium-227 is a long-lived radionuclide that is subject to stringent regulatory limits.[25] In the United States, reporting limits for accidental ingestion and contamination are 15 and 74 Bq, respectively.[25,26] Financial assurance is required for any license holder with an ^{227}Ac possession limit greater than 370 kBq.[27] Demonstrating compliance with these regulatory limits is complicated by the difficulty in measuring ^{227}Ac quickly with high sensitivity. Actinium-227 has no readily detectable photon emissions and only low-intensity α-emissions.[28] It is typical to quantify ^{227}Ac using its decay daughters ^{227}Th ($t_{1/2}$ = 18.718 d) and ^{223}Ra ($t_{1/2}$ = 11.43 d); however, these radionuclides grow in slowly. Given the considerations above, many radiopharmaceutical manufacturers and clinical sites are reluctant to handle ^{225}Ac with even small amounts of ^{227}Ac. It is imperative for those developing new ^{225}Ac production routes to minimize or eliminate ^{227}Ac impurities. For production routes that directly produce ^{225}Ac, coproduced ^{227}Ac cannot be chemically separated from ^{225}Ac, and is thus intrinsic to the ^{225}Ac product. For production routes that directly produce ^{225}Ra, coproduced ^{227}Ac can be removed from ^{225}Ra prior to formulation of the ^{225}Ra/^{225}Ac generator allowing for in-growth of isotopically pure ^{225}Ac.[13]

The advent of new and diverse ^{225}Ac production routes creates a need for common quality requirements and analytical methods.[8] There is currently no standard method for the quantification of ^{227}Ac in ^{225}Ac pharmaceutical products. The usual techniques for quantification of isotopically pure ^{227}Ac sources are γ spectrometry[29] and α spectrometry.[30−32] However, these techniques are inadequate when applied to ^{225}Ac API quality control where ^{227}Ac is present as a trace impurity in a matrix containing a relatively large amount of ^{225}Ac. The background radiation caused by ^{225}Ac and its daughter products overwhelms the photopeaks produced by ^{227}Th and ^{223}Ra.[33] The only way to measure trace ^{227}Ac in ^{225}Ac using conventional radiometric techniques is to wait several weeks for ^{225}Ac to decay away and for the ^{227}Ac daughters to grow in. This time delay creates a problem, however, as the ^{227}Ac content of the ^{225}Ac product will be determined only after the useful life of the ^{225}Ac, rather than as part of product release testing. New approaches are needed to quantify ^{227}Ac in ^{225}Ac pharmaceutical products with high sensitivity and short analysis times.

Two new radiometric methods have been reported for ^{227}Ac quantification: decay energy spectrometry (DES)[34] and α-decay spectrometry of recoil progeny (α-srp).[33] The DES method has a reported detection limit (stated in terms of the ^{227}Ac/^{225}Ac activity ratio) of 0.14%. The method involves a five-day hold period after ^{225}Ac purification, followed by a 24 h acquisition time.[34] Thus, the total reported time for the DES method to produce a quantitative result is 6 days. In this period, ^{225}Ac will decay by 34%, which is a significant loss of useful activity. The α-srp method does not have a reported detection limit; however, ^{227}Ac/^{225}Ac activity ratios as low as 2.00 × 10^{-4}% have been measured using the methodology.[33] The problem with the α-srp method is the significant time requirement. The α-srp method proceeds through three successive phases: accumulation, implantation, and measurement. The reported durations for these phases are 32−68 days (accumulation), 21−38 days (implantation), and 10−19 days (measurement).[33] The total duration is well outside of the useful life of ^{225}Ac; thus, the α-srp method is only applicable as a retrospective analysis. The fundamental issue with quantifying long-lived radionuclides by radiometric techniques is that the relatively low nuclear emission rates lead to poor counting statistics. Long count times are required to give results with acceptable precision.

Inductively coupled plasma mass spectrometry (ICP-MS) is an alternative approach for quantifying long-lived radionuclides that relies on counting ions rather than nuclear emissions.[35] Several studies have reported ^{227}Ac quantification using ICP-MS[36,37] including one study from Robertson et al. centered on ^{225}Ac production.[13] The Robertson study focuses on improving the ^{232}Th-spallation production route to yield ^{225}Ac with a reduced ^{227}Ac content. ICP-MS was used to quantify ^{227}Ac in ^{225}Ac directly produced from ^{232}Th-spallation and from ^{225}Ac obtained from the decay of purified ^{225}Ra. The reported detection limit—stated in terms of ^{227}Ac concentration—is less than 0.1 ng L^{-1} (268 Bq L^{-1}), while samples with ^{227}Ac/^{225}Ac activity ratios less than 7.1 × 10^{-5}% are reported. Though the Robertson study reports low detection limits, there is little detail given about the analytical methodology itself. It is not clear how the ICP-MS method quantifies ^{227}Ac, or how it performs when evaluated against standard validation criteria (e.g., accuracy, precision, and linearity).

The purpose of this work is to report a new ICP-MS method for the quantification of ^{227}Ac in ^{225}Ac APIs and then evaluate the method against validation criteria appropriate for pharmaceutical products. Isotope ratio analysis was used to quantify ^{225}Ac/^{227}Ac activity ratios directly from ICP-MS count data rather than from external calibration standards. The measured activity ratios were combined with orthogonal ^{225}Ac activity measurements to arrive at absolute ^{227}Ac activities. The data demonstrate that the isotope ratio method is appropriate as an industry standard method for ^{227}Ac quantification in ^{225}Ac APIs.

EXPERIMENTAL SECTION

Radionuclides. Actinium-227 was purchased from Eckert & Ziegler Analytics as a Standard Reference Source (SRS 133349). The ^{227}Ac SRS was received as 2.08160 g of 1 M HNO_3 solution, carrier-free. The calibrated ^{227}Ac activity was 3.719 × 10^3 kBq with a combined uncertainty, μ_c, of 2.5%. The reported α- and γ-emitting impurities in the ^{227}Ac were each <0.1% by activity.

Actinium-225 was purchased from the National Isotope Development Center (NIDC). The ^{225}Ac was produced at Oak Ridge National Laboratory (ORNL) as a product of ^{229}Th decay. The reported radionuclidic purity for the ^{225}Ac was >99.9%. An aliquot of the ORNL ^{225}Ac was diluted in 3% HCl/1% HNO_3 to prepare an ^{225}Ac stock solution. The ^{225}Ac stock solution was characterized on a high-purity germanium (HPGe) γ spectrometer using γ emissions from ^{221}Fr (218 keV) and ^{213}Bi (440 keV). Spectra were collected with ^{225}Ac in secular equilibrium with these daughter radionuclides. The activity concentration of the ^{225}Ac stock solution was 185 ± 5 MBq L^{-1} (86.1 ± 2.2 ng L^{-1}). The uncertainty of the ^{225}Ac

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stock solution concentration incorporates the uncertainty of the HPGe measurement (2.00%) with the uncertainties of the solution preparation steps.

γ Spectrometry. A P-type coaxial HPGe γ Spectrometer from Mirion (Model GC 1018, 10% efficiency) was used for quantification of ^{225}Ac and daughter radionuclides. The detector energy, peak width, and efficiency calibrations were performed using a mixed nuclide source (Eckert & Ziegler Analytics 7500 Type).

The geometry of the calibration source and all working samples consisted of 20 mL of dilute acid solution in a plastic scintillation vial. Samples were positioned at a distance from the detector, beyond which cascade-summing effects were negligible. Dead time was kept below 2.0%.

Actinium-225 spectra were analyzed by using the Apex Gamma software package (Mirion Technologies). Gaussian curves were fitted to all peaks and compared against γ emission libraries built using nuclear data from the Decay Data Evaluation Project.[38]

Mass Spectrometry. Two instruments were used in this study: Thermo Scientific iCAP TQe (triple quadrupole ICP-MS) and Thermo Scientific iCAP RQPlus (single quadrupole ICP-MS). The purpose of using two ICP-MS instruments was to evaluate the reproducibility of the methodology. Daily tuning was performed with NIST-traceable, vendor-recommended tuning solutions. Instrument operating parameters are given in Table 1. An internal standard solution was used containing: Tl, Pt, In, Tb, Be, Sc, and Ge.

Table 1. Typical ICP-MS Operating Parameters

	RQPlus ICP-MS	TQe ICP-MS
quadrupole	single	triple
collision/reaction gas	none	none
dwell time, s	0.02	0.02
replicates	5	5
sweeps	50	50
spray chamber temp., °C	2.7	2.7
nebulizer gas, L min^{-1}	tuned[a]	tuned[a]
lens voltages	tuned[a]	tuned[a]
nebulizer type	0.4 mL min^{-1} glass concentric	0.4 mL min^{-1} glass concentric
sampler cone	nickel	nickel
skimmer cone	nickel	nickel

[a]Parameters tuned to maximize signal while maintaining $^{140}Ce^{16}O^+/^{140}Ce^+ < 3\%$ and $^{137}Ba^{2+}/^{137}Ba^+ < 5\%$

Sample Preparations. All sample solutions were prepared using Fisher Chemical TraceMetal Grade acids (HCl or HNO_3) and deionized water (Avidity Science, 18.2 MΩ). Individual sample solutions were prepared by serial dilution from the ^{225}Ac Stock Solution and the ^{227}Ac SRS. All sample solutions had known ^{225}Ac and ^{227}Ac concentrations (Table 2) that were decay corrected to a common experimental calibration time. The uncertainties of the known ^{225}Ac and ^{227}Ac concentrations were obtained by propagating the uncertainties of the preparation steps with the uncertainties of the respective stock solution concentrations. The ^{225}Ac concentrations were fixed at 85.4 MBq L^{-1} (39.5 ng L^{-1}), while the ^{227}Ac concentrations varied from 0 to 5.35×10^3 Bq L^{-1} (0.025 to 2 ng L^{-1}) with a low-level spike of 66.8 Bq L^{-1} (0.025 ng L^{-1}). The ^{225}Ac concentrations were chosen to reflect the expected quality requirements and working sample concentrations, while the ^{227}Ac spike concentrations were chosen near the instrumental detection limits.

Data Collection. The measured count rates were background corrected using the average count rates from blank responses ($n = 6$). All sample solutions were analyzed at least once on each instrument. Replicate measurements ($n = 6$) were made of the Level 3 sample solutions on both instruments. Count rate data was collected for both analyte masses (m/z = 225, 227) and nonanalyte masses (m/z = 4.5, 5.0, 215, 226). The purpose of monitoring the nonanalyte masses was to evaluate the impact of α-decay on instrument background.

Statistical Analyses. The uncertainty in measured concentrations was determined using the Guidelines for Uncertainty in Measurement (GUM)[39] and reported at the 1σ level (68% confidence level, coverage factor $k = 1$).

Acceptance Criteria. The purpose of this method is to quantify ^{227}Ac in ^{225}Ac produced for use as an active pharmaceutical ingredient (API). The experiments reported herein were designed in view of guidance from the United States Pharmacopeia (USP) and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). The data was evaluated against acceptance criteria given in USP Chapters 233[40] and 730,[41] and the ICH Harmonized Guideline ICHQ2(R2).[42]

RESULTS

Methodology. Radioactive decay is a first-order reaction such that the decay rate is directly proportional to the number of radioactive atoms present in a given source. The activity, A, is directly proportional to the number of atoms, N, of nuclide present:

$$A = N\lambda \tag{1}$$

The decay constant, λ, has units of reciprocal time (s^{-1}) and is a unique constant for each radionuclide.

Eq 1 can be used to create unique expressions for the ^{225}Ac and ^{227}Ac content in a sample:

$$A_{225} = N_{225} \times \lambda_{225} \tag{2}$$

$$A_{227} = N_{227} \times \lambda_{227} \tag{3}$$

Table 2. Composition of ^{225}Ac/^{227}Ac Working Solutions

	^{225}Ac		^{227}Ac	
level	MBq L^{-1}	ng L^{-1}	Bq L^{-1}	ng L^{-1}
0	85.4 ± 2.2	39.5 ± 1.0	–	–
1	85.4 ± 2.2	39.5 ± 1.0	66.8 ± 1.7	0.0250 ± 0.0006
2	85.4 ± 2.2	39.5 ± 1.0	267 ± 7	0.100 ± 0.003
3	85.4 ± 2.2	39.5 ± 1.0	$(1.34 \pm 0.03) \times 10^3$	0.500 ± 0.013
4	85.4 ± 2.2	39.5 ± 1.0	$(5.35 \pm 0.12) \times 10^3$	2.00 ± 0.05

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where the subscripts 225 and 227 refer to ^{225}Ac and ^{227}Ac, respectively. These expressions can be combined to express the activities of ^{225}Ac and ^{227}Ac as a ratio (eq 4).

$$\frac{A_{225}}{A_{227}} = \frac{N_{225}}{N_{227}} \times \frac{\lambda_{225}}{\lambda_{227}} \quad (4)$$

The first term in eq 4 is the activity ratio, A_{225}/A_{227}. The second term is the isotope ratio, N_{225}/N_{227}. The isotope ratio is the ratio of the number of nuclei of one isotope (^{225}Ac) to another isotope (^{227}Ac). The third term is the decay constant ratio, $\lambda_{225}/\lambda_{227}$. Eq 4 can be used to interconvert between the activity ratio and the isotope ratio when only one is known.

ICP-MS provides a means for accurately measuring the ^{225}Ac/^{227}Ac isotope ratio. An ICP-MS uses a quadrupole mass spectrometer to filter ions by the mass-to-charge ratio (m/z). Samples may be analyzed at m/z = 225 and m/z = 227 to generate unique responses for ^{225}Ac and ^{227}Ac. These instrument responses (counts per second, cps) will be proportional to the molar concentrations of ^{225}Ac and ^{227}Ac in the sample. Given that ^{225}Ac and ^{227}Ac are isotopes of the same element, their ionization energies, transport efficiency, and mass discrimination by the instrument are practically equivalent.[43] Mass bias effects are negligible for isotopes in this mass range.[44] Therefore, ^{225}Ac and ^{227}Ac will exhibit the same instrument response per molar concentration on ICP-MS. The relative instrument responses for ^{225}Ac (cps_{225}) and ^{227}Ac (cps_{227}) will be equivalent to the relative molar concentrations of ^{225}Ac (M_{225}) and ^{227}Ac (M_{227}) in the sample (eq 5).

$$\frac{cps_{225}}{cps_{227}} = \frac{M_{225}}{M_{227}} \quad (5)$$

The instrument response ratio, cps_{225}/cps_{227}, may be measured by the ratio of the count rate at m/z = 225 to the count rate at m/z = 227. This ratio is directly proportional to the molar concentration ratio of ^{225}Ac and ^{227}Ac, M_{225}/M_{227}. Moles in a given sample are proportional to the number of nuclei. Equation 5 can, thus, be restated in terms of the ^{225}Ac/^{227}Ac isotope ratio:

$$\frac{cps_{225}}{cps_{227}} = \frac{N_{225}}{N_{227}} \quad (6)$$

Equation 6 states that the ^{225}Ac/^{227}Ac isotope ratio for an ^{225}Ac sample is equivalent to the instrument response ratio determined by ICP-MS. If eqs 4 and 6 are combined, then the ^{225}Ac/^{227}Ac activity ratio is directly related to the ICP-MS instrument response ratio:

$$\frac{A_{225}}{A_{227}} = \frac{cps_{225}}{cps_{227}} \times \frac{\lambda_{225}}{\lambda_{227}} \quad (7)$$

Equation 7 uses the measured instrument response ratio to give the ^{225}Ac/^{227}Ac activity ratio at the time of the ICP-MS measurement. A standard practice in radiopharmaceutical quality testing is to report all figures of merit at a common calibration time. It is necessary then to incorporate radioactive decay corrections into eq 7 to account for decay between the time of the ICP-MS measurement and the time of calibration for the particular batch. The relationship between the activities at calibration (t_{cal}) to the activities at the time of ICP-MS measurement (t_{ICP}) is given by eqs 8 and 9 for ^{225}Ac and ^{227}Ac, respectively.

$$A_{225}(t_{ICP}) = A_{225}(t_{cal}) \times e^{-\lambda_{225}(t_{ICP}-t_{cal})} \quad (8)$$

$$A_{227}(t_{ICP}) = A_{227}(t_{cal}) \times e^{-\lambda_{227}(t_{ICP}-t_{cal})} \quad (9)$$

The individual expressions for ^{225}Ac (eq 8) and ^{227}Ac (eq 9) decay can be substituted into eq 7. The resulting expression (eq 10) can be solved for the ^{225}Ac/^{227}Ac activity ratio at calibration, $A_{225}(t_{cal})/A_{227}(t_{cal})$. Equation 11 directly relates the measured ICP-MS instrument response ratio to the ^{225}Ac/^{227}Ac activity ratio for a given calibration time.

$$\frac{A_{225}(t_{cal}) \times e^{-\lambda_{225}(t_{ICP}-t_{cal})}}{A_{227}(t_{cal}) \times e^{-\lambda_{227}(t_{ICP}-t_{cal})}} = \frac{cps_{225}}{cps_{227}} \times \frac{\lambda_{225}}{\lambda_{227}} \quad (10)$$

$$\frac{A_{225}(t_{cal})}{A_{227}(t_{cal})} = \frac{cps_{225}}{cps_{227}} \times \frac{\lambda_{225}}{\lambda_{227}} \times \frac{e^{-\lambda_{227}(t_{ICP}-t_{cal})}}{e^{-\lambda_{225}(t_{ICP}-t_{cal})}} \quad (11)$$

Equation 11 can be rearranged to solve for the absolute ^{227}Ac activity at the time of calibration, $A_{227}(t_{cal})$:

$$A_{227}(t_{cal}) = \frac{cps_{227}}{cps_{225}} \times \frac{\lambda_{227}}{\lambda_{225}} \times \frac{e^{-\lambda_{225}(t_{ICP}-t_{cal})}}{e^{-\lambda_{227}(t_{ICP}-t_{cal})}} \times A_{225}\,(t_{cal}) \quad (12)$$

Thus, the absolute ^{227}Ac activity in an ^{225}Ac API may be determined from the ICP-MS count rate ratio and an orthogonal radiometric measurement of ^{225}Ac activity.

Instrumental Response. The isotope ratio measurement relies on an equivalent instrument response for ^{225}Ac and ^{227}Ac. The instrument response equivalency applies only to measurements within a given analysis. Different instruments will exhibit different responses; individual instruments will exhibit day-to-day variability in the response. The instrument response for each isotope was evaluated from the ^{225}Ac/^{227}Ac working solutions (Table 2) in order to demonstrate equivalency. The instrumental response for the two isotopes was compared in units of counts per second (cps) per picomolar (pM) concentration, or cps pM^{-1}. Table 3 gives a comparison of the instrument response on the TQe ICP-MS and a comparison of the instrument response on the RQPlus ICP-MS. The results indicate that the instrumental response for ^{225}Ac and ^{227}Ac was equivalent over all ^{227}Ac concentrations measured. This equivalency was observed for both the TQe ICP-MS analysis and the RQPlus ICP-MS analysis. The RQPlus ICP-MS exhibited greater sensitivity (~132 cps pM^{-1}) than the TQe ICP-MS (~86 cps pM^{-1}). The greater sensitivity of the RQPlus ICP-MS compared to the TQe ICP-MS was expected based on the typical high mass performance of these instruments. Both instruments had installation specifications that included ^{238}U ≥ 330 × 10^3 cps (ng L)$^{-1}$. The actual

Table 3. Comparison of Instrument Response for ^{225}Ac and ^{227}Ac on TQe ICP-MS and RQPlus ICP-MS

	instrument response, cps·pM^{-1}			
	TQe		RQPlus (SQ)	
level	m/z = 225	m/z = 227	m/z = 225	m/z = 227
0	87 ± 3	NA	132 ± 4	NA
1	86 ± 3	70 ± 18	131 ± 4	155 ± 22
2	86 ± 3	89 ± 9	131 ± 4	147 ± 12
3	86 ± 2	86 ± 7	135 ± 4	138 ± 10
4	85 ± 2	86 ± 4	134 ± 5	134 ± 5

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results from installation were 373 × 10^3 cps (ng L)$^{-1}$ for TQe ICP-MS and 702 × 10^3 cps (ng L)$^{-1}$ for RQPlus ICP-MS.

Linearity. Linearity was evaluated with respect to the guidelines in ICH Q2(R2).[42] The linear relationship between ^{227}Ac concentration and instrument response was assessed over the concentration range of 0.025 to 2.00 ng L^{-1} (66.8 to 5.35 × 10^3 Bq L^{-1}). While the isotope ratio method does not require external calibration standards, a calibration curve is a useful tool for assessing the linearity during method development.

A calibration curve for each instrument analysis was generated by plotting the blank corrected instrument response at m/z = 227 against the known ^{227}Ac concentrations (Figure 1). The instrument response showed strong linearity ($R^2 \geq$ 0.9999) on both instruments over the measured concentration range.

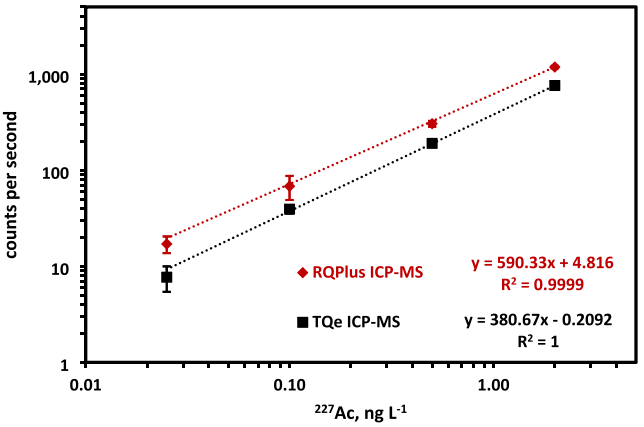

Figure 1. Calibration curves for ^{227}Ac (0.025 to 2.0 ng L^{-1}) on TQe ICP-MS and RQPlus ICP-MS.

Accuracy. Accuracy was evaluated by comparing ^{227}Ac concentrations measured using the isotope ratio method to the known concentrations. The ^{225}Ac/^{227}Ac working solutions (Table 2) were analyzed on both the RQPlus ICP-MS and the TQe ICP-MS. The measured count rates at m/z = 225 and 227 were input into eq 12 in order to obtain measured ^{227}Ac concentrations.

The measured ^{227}Ac concentrations were assessed in terms of spike recovery:

$$\text{spike recovery, \%} = \frac{C_{\text{spiked}} - C_{\text{nonspiked}}}{C_{\text{added}}} \times 100 \quad (13)$$

where C_{spiked} is the measured ^{227}Ac concentration of the spiked solution, $C_{\text{nonspiked}}$ is the measured ^{227}Ac concentration of the nonspiked solution, and C_{added} is the expected ^{227}Ac concentration.

Table 4 includes the results for the spiking study on the TQe ICP-MS. Results are shown in terms of the absolute ^{227}Ac recovery (Bq L^{-1}) and spike recovery (%). The relative uncertainties in the measured ^{227}Ac concentrations were determined using eq 14.

$$\frac{\sigma_{A_{227}}}{A_{227}} = \sqrt{\left(\frac{\sigma_{A_{225}}}{A_{225}}\right)^2 + \left(\frac{\sigma_{cps_{227}}}{cps_{227}}\right)^2 + \left(\frac{\sigma_{cps_{225}}}{cps_{225}}\right)^2} \quad (14)$$

The measured concentrations from the TQe ICP-MS analysis showed excellent agreement (100−101%) with the expected values at ^{227}Ac concentrations of 0.1 ng L^{-1} (267 Bq L^{-1}) and above. The spike recovery for the 0.025 ng L^{-1} (66.8 Bq L^{-1}) ^{227}Ac sample was 74 ± 22% for TQe ICP-MS analysis.

Table 4. Recovery of ^{227}Ac from TQe ICP-MS Analysis of Spiked Solutions

	^{227}Ac concentration, Bq L^{-1}		
level	added	measured	recovery, %
0	0	4.9 ± 3.0	NA
1	66.8 ± 1.7	54.5 ± 14.2	74 ± 22
2	267 ± 7	276 ± 28	101 ± 11
3	(1.35 ± 0.03) × 10^3	(1.35 ± 0.11) × 10^3	100 ± 9
4	(5.35 ± 0.12) × 10^3	(5.41 ± 0.28) × 10^3	101 ± 6

The results for the spiking study on the RQPlus ICP-MS are included in Table 5. The measured concentrations from the RQPlus ICP-MS analysis showed excellent agreement (91−108%) with the expected values for all measured ^{227}Ac concentrations.

Precision. Precision was investigated by using recommended tests for repeatability and intermediate precision. Repeatability was assessed using replicate measurements of the Level 3 sample consisting of 0.5 ng L^{-1} (1.34 × 10^3 Bq L^{-1}) ^{227}Ac spiked into a sample matrix of 39.5 ng L^{-1} (85.4 MBq L^{-1}) ^{225}Ac. The sample was measured six times on the TQe ICP-MS. The count rate data from each measurement were input into eq 12 to determine the measured ^{227}Ac concentrations. The measured ^{227}Ac concentrations from the six replicate measurements were then evaluated in terms of mean, standard deviation (SD), and relative standard deviation (RSD). The RSD for the repeatability assessment on TQe ICP-MS was 3.7% (Table 5).

The repeatability assessment was repeated on a separate day using RQPlus ICP-MS. An identical Level 3 sample was prepared and analyzed six times. The measured ^{227}Ac concentrations were determined from the count rate data of the individual measurements. The RSD for the repeatability assessment on the RQPlus ICP-MS instrument was 4.6% (Table 5).

Intermediate precision was evaluated by combining the repeatability results from the two different instruments. The combined results consist of n = 12 measurements of known 0.5 ng L^{-1} ^{227}Ac concentrations. These 12 measurements come from two identical samples that were analyzed on separate days and on separate instruments. The 12 combined measurements were evaluated for mean, SD, and RSD (Table 5). The RSD was 4.1%, which falls within the acceptance criteria given by USP ⟨233⟩.[40]

Detection Limit and Quantitation Limit. The detection limit (DL) and quantitation limit (QL) were estimated using a signal-to-noise approach as described in ICHQ2(R2).[42] The DL and QL are defined as the minimum ^{227}Ac concentration (Bq L^{-1} or ng L^{-1}) in the ^{225}Ac sample matrix that can be reliably detected or quantified, respectively. The following equations were used:

$$\text{DL} = 3 \times \frac{bkgcps_{227}}{cps_{225}} \times \frac{\lambda_{227}}{\lambda_{225}} \times A_{225} \quad (15)$$

$$\text{QL} = 10 \times \frac{bkgcps_{227}}{cps_{225}} \times \frac{\lambda_{227}}{\lambda_{225}} \times A_{225} \quad (16)$$

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Table 5. Summary of Validation Attributes and Results

attribute	regulatory guidance	evaluation	results		
accuracy	USP ⟨233⟩	multiple levels of ^{227}Ac spiked into ^{225}Ac sample matrix	^{227}Ac, ng L^{-1}	spike recovery, %	
	mean recovery of spiked samples covering the intended range			RQPlus	TQe
			0.025	91 ± 19	74 ± 22
	spike recovery, 70−150		0.100	108 ± 23	101 ± 11
			0.500	103 ± 8	100 ± 6
			2.00	100 ± 5	101 ± 6
precision, repeatability	USP ⟨233⟩	(6) replicate measurements of 0.5 ng L^{-1} ^{227}Ac spiked sample in ^{225}Ac matrix	instrument:	RQPlus	TQe
	spiked sample (n = 6)		replicates, n:	6	6
	RSD NMT 20%		^{227}Ac, ng L^{-1}:	0.513	0.504
			SD, ng L^{-1}:	0.023	0.019
			RSD, %:	4.6%	3.7%
precision, Interm.	USP ⟨233⟩	repeatability performed on a different day and a different instruments	instrument:	RQPlus + TQe	
	spiked samples (n = 12)		replicates, n:	12	
precision	RSD NMT 25%	(12) measurements total of 0.5 ng L^{-1} ^{227}Ac spiked in ^{225}Ac matrix	^{227}Ac, ng L^{-1}:	0.509	
			SD, ng L^{-1}:	0.021	
			RSD, %:	4.1	
specificity	USP ⟨730⟩	demonstrated by meeting accuracy requirement	pass		
	demonstrated by meeting accuracy requirement				
detection	ICH Q2(R2)	eq 15	instrument:	RQPlus	TQe
			DL:	0.037 ng L^{-1}	0.0086 ng L^{-1}
limit	DL = 3 × noise			99 Bq L^{-1}	23 Bq L^{-1}
quantitation	ICH Q2(R2)	eq 16	instrument:	RQPlus	TQe
			QL:	0.123 ng L^{-1}	0.029 ng L^{-1}
limit	QL = 10 × noise			330 Bq L^{-1}	77 Bq L^{-1}
linearity	USP ⟨730⟩	^{227}Ac in ^{225}Ac matrix	instrument:	RQPlus	TQe
	min. two standards + blank (R^2) NLT 0.99	four levels: 0.025 to 2 ng L^{-1} (66.8 to 5.35 × 10^3 Bq L^{-1})	R^2:	0.9999	1.0000
range	USP ⟨730⟩	^{227}Ac	demonstrated 0.025 to 2 ng L^{-1} ^{227}Ac		
	demonstrated by meeting the precision, accuracy, and linearity requirements	0.025 to 2 ng L^{-1} (67 to 5.35 × 10^3 Bq L^{-1})			

Table 6. Comparison of Background Count Rates on the TQe ICP-MS Pre- and Post-Analysis of ^{225}Ac-Containing Samples

	preanalysis			postanalysis					
m/z	n	$\bar{x}_{pre}$, cps	SD, cps	n	$\bar{x}_{post}$, cps	SD, cps	p[a]	$\Delta\bar{x}$, cps	Hedges' g
4.5	6	0.2	0.3	4	3.5	1.1	4.3 × 10^{-3}	3.3 ± 1.1	4.6
5.0	6	0.1	0.2	4	4.3	0.9	1.1 × 10^{-3}	4.2 ± 0.9	7.4
215	6	0.1	0.2	4	4.8	1.0	9.9 × 10^{-4}	4.7 ± 1.0	7.3
225	6	0.2	0.2	4	5.5	0.7	1.9 × 10^{-4}	5.3 ± 0.7	12.5
226	6	1.0	0.4	4	5.2	1.5	5.2 × 10^{-3}	4.2 ± 1.6	4.3
227	6	0.1	0.5	4	4.9	0.7	1.2 × 10^{-4}	3.8 ± 0.8	6.9

[a]Significant at $p < 0.01$.

where $bkg\ cps_{227}$ is the m/z = 227 count rate for blank responses (n = 6), cps_{225} is the m/z = 225 count rate for the sample matrix, and A_{225} is the ^{225}Ac activity concentration of the sample matrix.

The blank responses at m/z = 227 provide a measure of baseline noise. By multiplying the baseline noise by appropriate signal-to-noise ratios (i.e., 3 for DL, or 10 for QL), we established the minimum detectable and quantifiable signals for m/z = 227. These signal limits were converted to ^{227}Ac concentration limits using eq 12.

The calculations for DL and QL are directly stated by eqs 15 and 16. The blank samples consisted of 3% HCl/1% HNO_3 with no added ^{227}Ac or ^{225}Ac. The DL and QL for ^{227}Ac on TQe ICP-MS were 23 Bq L^{-1} (0.0086 ng L^{-1}) and 77 Bq L^{-1} (0.029 ng L^{-1}), respectively. The DL and QL for ^{227}Ac on RQPlus ICP-MS were 99 Bq L^{-1} (0.037 ng L^{-1}) and 330 Bq L^{-1} (0.123 ng L^{-1}), respectively.

Instrument Background. The instrument background was monitored throughout the course of this study using blank sample measurements. Blank samples were analyzed for analyte masses (m/z = 225 and m/z = 227), where residual carryover of ^{225}Ac and ^{227}Ac could contribute to the instrument response, as well as for nonanalyte masses (m/z = 4.5, 5.0, 215, 226) where atomic or molecular ions were not expected to contribute to the instrument response. Prior to the start of these experiments, the TQe ICP-MS exhibited near zero background for the analyte masses and nonanalyte masses (0−1 cps for m/z = 4.5, 5.0, 215, 225, 226, 227), while the RQPlus ICP-MS exhibited significantly elevated background (7−14 cps

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Table 7. Comparison of Background Count Rates on the RQPlus ICP-MS Pre- and Post-Analysis of ^{225}Ac-Containing Samples

	preanalysis			postanalysis					
m/z	n	$\bar{x}_{pre}$, cps	SD, cps	n	$\bar{x}_{post}$, cps	SD, cps	p^a	$\Delta\bar{x}$, cps	Hedges' g
4.5	6	6.6	0.9	5	15.5	2.6	4.1×10^{-4}	8.9 ± 2.7	4.9
5.0	6	6.2	1.3	5	11.9	1.6	1.3×10^{-4}	5.7 ± 2.1	4.0
215	6	5.7	1.4	5	14.2	1.2	9.2×10^{-7}	8.6 ± 1.9	6.4
225	6	5.8	1.7	5	16.6	3.7	7.3×10^{-4}	10.8 ± 4.1	3.9
226	6	5.8	1.0	5	14.4	2.8	7.5×10^{-4}	8.6 ± 3.0	4.2
227	6	8.0	3.2	5	16.8	3.7	1.5×10^{-3}	8.8 ± 4.9	2.6

[a]Significant at $p < 0.01$.

for m/z = 4.5, 5.0, 215, 225, 226, 227) from previous analyses of ^{225}Ac.

The instrument background data was evaluated by comparing the count rates for blank samples run before the analysis of the ^{225}Ac/^{227}Ac working solutions to those run after the analysis of the ^{225}Ac/^{227}Ac working solutions. The aim was to determine whether the analysis of samples containing α-emitting radionuclides led to a statistically significant increase in the instrument background. Table 6 gives a statistical comparison of the two blank sample groups for TQe ICP-MS analysis. Six blank samples were run before the analysis of the ^{225}Ac/^{227}Ac working solutions. Four blank samples were run after the analysis of the ^{225}Ac/^{227}Ac working solutions. The two groups were compared using an unequal variances t-test (Welch's t-test). A unique t-test was performed for each m/z value. Since the predicted effect was an increase in instrument background, the one-tailed p-value was reported. The effect size for all m/z values was calculated using both the mean difference ($\Delta\bar{x}$) and Hedges' g.[45] The statistical comparison was repeated for the blank sample groups on RQPlus ICP-MS (Table 7).

Specificity. A preliminary study was performed to identify potential polyatomic interferences. The count rates at m/z = 225 and 227 were measured for a set of multielement standards containing: U, Eu, Nd, Ce, and La (10−70 ng L^{-1}); Bi, Pb, Hg, W, Sm, Sb, Cd, and Mo (100−700 ng L^{-1}); and Ba (1−7 μg L^{-1}). No signal was observed above the background at m/z = 227, while a linear response (R^2 = 0.99) was observed at m/z = 225. The linear response was attributed to the formation of ^{209}Bi^{16}O. The nominal instrument response at m/z = 225 was 2.7×10^{-3} cps (pM Bi)$^{-1}$.

The internal standard (Tl, Pt, In, Tb, Be, Sc, Ge) solution was analyzed in order to evaluate the potential formation of polyatomic interferences from these elements—particularly ^{192}Pt^{35}Cl. No instrument response was observed at m/z = 225 or 227 from the internal standard solution.

DISCUSSION

Methodology. The isotope ratio method works by using ICP-MS count rate data to determine the relative ^{225}Ac and ^{227}Ac activities in a sample. Equation 4 shows the relationship between the isotope ratio and activity ratio for ^{225}Ac and ^{227}Ac. The isotope ratio is measured using ICP-MS as the ratio of instrument responses (cps) for ^{225}Ac and ^{227}Ac (eq 6). The instrument response ratio is defined as the ratio of the count rates at m/z = 225 and m/z = 227 for a given ^{225}Ac sample. Thus, the only data required to measure the ^{225}Ac/^{227}Ac activity ratio in a sample is the count rates for two m/z values with no need to relate these count rates to an external calibration curve. A significant benefit of this approach is that ^{227}Ac standards are not required for routine analysis. Rather, ^{227}Ac standards are only needed for initial method validation. Thus, the routine use of this method does not generate new ^{227}Ac waste streams or create added risks for occupational exposure to ^{227}Ac.

Eq 12 demonstrates that an absolute ^{227}Ac activity can be obtained by combining the ICP-MS data with an orthogonal measurement of the sample ^{225}Ac activity. γ spectrometry is the most straightforward method for obtaining this activity, since the technique is routinely used in ^{225}Ac quality testing.

Instrument Response. The isotope ratio method depends on an equivalent instrument response for ^{225}Ac and ^{227}Ac. The instrument response equivalency was demonstrated by evaluating samples with known molar concentrations of ^{225}Ac and ^{227}Ac using the following units: cps pM^{-1}. Table 3 shows the instrument responses for ^{225}Ac and ^{227}Ac on the two instruments. The responses for ^{225}Ac and ^{227}Ac on a given instrument were equivalent within the measurement uncertainty.

Linearity. Actinium-227 standard solutions of increasing concentration yielded proportional increases in instrument response, as indicated by very strong coefficients of determination (R^2). The evaluated linear range was 0.025 to 2 ng L^{-1} (66.8 to 5.35 x10^3 Bq L^{-1}) for ^{227}Ac. Validation criteria for linearity of quantitative impurities per USP ⟨730⟩ is R not less than (NLT) 0.99. The calibration curves reported herein show R^2 values of ≥ 0.9999.

Accuracy and Precision. Accuracy was assessed using a spike recovery study. Actinium-227 was added at different levels (0 to 2 ng L^{-1}, 0 to 5.35×10^3 Bq L^{-1}) to an ^{225}Ac sample matrix (85.4 MBq L^{-1}). The spiked samples were analyzed; the measured ^{227}Ac concentrations were determined using eq 12. The measured ^{227}Ac concentrations agreed with the known concentrations within uncertainty (Table 4). The uncertainties of the measured ^{227}Ac concentrations (eq 14) incorporates the uncertainties of the m/z = 225 and 227 count rates and the uncertainty of the orthogonal ^{225}Ac measurement. The uncertainties in the measured ^{227}Ac concentrations are driven by the uncertainties of the m/z = 227 count rate since the samples contain ^{227}Ac at concentrations close to the true detection limit.

The measured ^{227}Ac concentrations were evaluated in terms of spike recovery. The acceptance criteria for spike recovery is 70−150% per USP ⟨233⟩.[40] This criterion was met for all measured ^{227}Ac concentrations on both instruments (Table 5). The 0.025 ng L^{-1} (66.8 Bq L^{-1}) ^{227}Ac spike recoveries were 74 ± 22% and 91 ± 19% for TQe ICP-MS and RQPlus ICP-MS, respectively. The large uncertainties for the 0.025 ng L^{-1} spike recoveries are expected given that the spiked ^{227}Ac

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concentrations are less than the measured QLs of 0.029 ng L^{-1} (TQe ICP-MS) and 0.123 ng L^{-1} (RQPlus ICP-MS).

Precision is demonstrated by meeting separate acceptance criteria for repeatability and intermediate precision. To assess repeatability, a midlevel ^{227}Ac spike at 0.5 ng L^{-1} was injected six times on the TQe ICP-MS. The ^{227}Ac concentration was calculated for each injection using eq 12. The RSD for the replicate measurements was determined. The repeatability assessment was repeated on the RQPlus ICP-MS. The two data sets combined to provide a measure of intermediate precision. The acceptance criteria for repeatability and intermediate precision given by USP ⟨233⟩ are RSD not more than (NMT) 20% and 25%, respectively.[40] Table 5 shows that the acceptance criteria for repeatability and intermediate precision was met.

Detection and Quantitation Limit. The DL and QL for ^{227}Ac concentration will vary from analysis to analysis. These limits are dependent on both the instrument background and the elemental sensitivity. Increasing instrument background will raise the lower range limits, which can be seen from eqs 15 and 16. The DL and QL are proportional to the background signal at m/z = 227. Therefore, maintaining a low background is critical for achieving low and consistent limits. Increasing the instrument sensitivity will decrease the lower range limits. This can be done through proper instrument selection and performance optimization. Table 3 shows that the RQPlus ICP-MS exhibited a higher instrument response than the TQe ICP-MS. Based on these results, the RQPlus ICP-MS should have exhibited a lower DL and QL than the TQe ICP-MS. However, this was not the case. The lower limits measured for the TQe ICP-MS reflect the lower background count rate at m/z = 227 for the TQe ICP-MS ($\bar{x}$ = 1.1 cps, n = 6) compared to the RQPlus ICP-MS ($\bar{x}$ = 7.3 cps, n = 6).

Instrument Background. An increase in the instrument background has been observed since the introduction of α-emitting samples (e.g., ^{223}Ra, ^{226}Ra, ^{225}Ac, and ^{227}Ac) to the ICP-MS instruments. If the instruments are not used to analyze α-emitting samples, the instrument background is observed to decrease at a nominal rate corresponding to the half-lives of the shorter-lived radionuclides (i.e., ^{223}Ra, ^{225}Ac). The effect of α-emitting radionuclides on instrument background was quantitatively evaluated as part of the present study. A series of blank samples were analyzed before and after analysis of the ^{225}Ac/^{227}Ac working samples. Count rate data was collected for both analyte masses (m/z = 225 and 227) and nonanalyte masses (m/z = 4.5, 5.0, 215, 226). It was observed that the instrument background increased after the analysis of the ^{225}Ac/^{227}Ac working samples (Tables 6 and 7). For the TQe ICP-MS analysis, a statistically significant (p < 0.01) increase in instrument background was observed for all measured m/z values (Table 6). For the RQPlus ICP-MS analysis, a statistically significant increase in the instrument background was observed for all measured values (Table 7). Large effect sizes (g > 1) were observed on both instruments for both analyte masses and nonanalyte masses. The observation of statistically significant increases in instrument background at both analyte masses and nonanalyte masses suggests that the background increase for analyte masses was not due to carryover of ^{225}Ac or ^{227}Ac. The similar mean differences for analyte and nonanalyte masses on a given instrument suggest a common underlying mechanism.

It is hypothesized that α-emitting radionuclides are being deposited on the ICP-MS detector face as an unavoidable consequence of the analysis. These deposited radionuclides continuously emit α particles which are equivalent to He^{2+} ions. The ICP-MS detector itself does not discriminate between ions of different m/z. It is the quadrupole upstream of the detector that separates ions of a given m/z. If α-emitting radionuclides are deposited in the instrument downstream of the quadrupole, the α-particles (and associated recoil daughters) produced through radioactive decay can potentially strike the detector. These interactions would be registered as counts, irrespective of what m/z is being selected for at a given time in the analysis. Thus, an increase in instrument background would be expected at all measured m/z values, not just those corresponding to the α-emitters routinely analyzed by the instrument. This hypothesis aligns with our previous observations and the statistical evaluations included in this study. Previous ICP-MS studies with long-lived α-emitters have shown a trend of increasing signal intensity with repeated analyses.[46,47] The unique feature of this study was the inclusion of a short-lived α-emitting radionuclide in the analysis.

The effect of internal α contamination on the instrument background has implications for instrumental detection limits. Equations 15 and 16 established that the instrumental limits are proportional to the instrument background at m/z = 227. Maintaining low instrument background is critical to maintaining low detection limits. The results suggest that controlling the total activity of α-emitting radionuclides introduced to the instrument is critical to maintaining low instrument background. This could be done in several ways: limiting sample ^{225}Ac concentrations, minimizing sample quantities, reducing acquisition times, allowing for radioactive decay between analyses, or frequently replacing instrument hardware.

Another approach to maintaining low detection limits could be to perform the ^{227}Ac/^{225}Ac isotope ratio analysis on a multicollector ICP-MS (MC-ICP-MS) rather than a quadrupole ICP-MS. A MC-ICP-MS allows for the simultaneous measurement of analytes on independent detectors.[48] If the ^{227}Ac/^{225}Ac isotope ratio method were performed on MC-ICP-MS, ^{227}Ac and ^{225}Ac would be analyzed on separate detectors. This could significantly reduce the instrument background at m/z = 227 caused by the ^{225}Ac decay. The reduction in the instrument background would lead to improved accuracy and precision for routine measurements of ^{227}Ac in the presence of ^{225}Ac. Additional improvements in accuracy and precision would be expected from using a MC-ICP-MS due to the reduction of temporal noise. A MC-ICP-MS has been used for the analysis of ^{227}Ac by isotopic dilution with ^{225}Ac in seawater samples.[36] The reported instrumental detection limits were 1.5 × 10^{-5} ng kg^{-1} when using MC-ICP-MS in addition to a high-sensitivity desolvation sample introduction system.

Specificity. Specificity is the ability of a method to unequivocally assess an analyte in the presence of components that may be expected to be present. The purpose of the isotope ratio method is to measure ^{227}Ac in ^{225}Ac produced as an active pharmaceutical ingredient. Thus, specificity was evaluated as the ability of the method to assess ^{227}Ac in a representative ^{225}Ac sample matrix (i.e., dilute acid). According to the USP ⟨730⟩, specificity is demonstrated by meeting the acceptance criteria for accuracy.[41] Since the accuracy requirement was met, specificity was also demonstrated.

There are a number of possible interferences for ^{225}Ac and ^{227}Ac.[49] Interferences at m/z = 227 will have a greater impact

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Table 8. Comparison of Methods for the Quantification of ^{227}Ac in ^{225}Ac-Containing Samples

technique	refs	sample type	result time	IDL ^{227}Ac concentration	demonstrated ^{227}Ac/^{225}Ac (%)
DES	34	^{225}Ac	6 d	not reported	0.14
α-srp	33	^{225}Ac	83−107 d	not reported	2.00×10^{-4}
ICP-MS	13	^{225}Ac	<1 d	<0.1 ng L^{-1}	$<7.1 \times 10^{-5}$
ICP-MS isotope ratio	this work	^{225}Ac	<1 d	8.6×10^{-3} ng L^{-1}	$<2.7 \times 10^{-5}$
MC-ICP-MS isotope dilution	36	10−30 L seawater	2−3 weeks	1.5 × 10−5 ng L^{-1}	NA

on the method since the m/z = 227 count rates are expected to be significantly lower than those for m/z = 225. The most significant potential polyatomic interferences for ^{227}Ac include: $^{192}Pt^{35}Cl$, $^{187}Re^{40}Ar$, $^{187}Os^{40}Ar$, $^{209}Bi^{18}O$, and $^{226}Ra^{1}H$. The elements Pt, Re, Os, and Ra are not likely to be present in the ^{225}Ac API. The separation methods employed in the production of ^{225}Ac APIs are highly selective for Ac and would remove these elements.[10,13,17] Bismuth-209 will be present in the ^{225}Ac API samples since it is the ultimate decay product of ^{225}Ac. However, the separation methods used for ^{225}Ac API production would remove Bi, so the only ^{209}Bi present at the time of analysis would be that which forms between ^{225}Ac API generation and quality testing. The slow ingrowth of ^{209}Bi combined with the low natural abundance of ^{18}O (0.2%) makes $^{209}Bi^{18}O$ an unlikely interference. Platinum is a common material of construction in ICP-MS interface cones. Thus, the $^{192}Pt^{35}Cl$ is a potential polyatomic interference irrespective of the metallic purity of the ^{225}Ac API. The ICP-MS interface cones used in this study were Ni; however, the internal standard included approximately 2.5 μg L^{-1} Pt and the sample diluent contained 3% HCl. So there was the ability to form the $^{192}Pt^{35}Cl$ ion in the analysis. The m/z = 227 count rates on TQe ICP-MS were near zero prior to the introduction of ^{225}Ac. Therefore, it is concluded that no detectable $^{192}Pt^{35}Cl$ was present. Rhenium will produce a significant signal at m/z = 227 due to the formation of $^{187}Re^{40}Ar$, so Re should be excluded from any internal standard solution.[49]

The most significant interferences for ^{225}Ac are ^{225}Ra, $^{185}Re^{40}Ar$, and $^{209}Bi^{16}O$. Rhenium is not likely to be present in the ^{225}Ac API. Small quantities of ^{209}Bi will be present in the ^{225}Ac API at the time of analysis. Since ^{225}Ac is the major component of the sample, the signal m/z = 225 signal from ^{225}Ac will overwhelm any signal from $^{209}Bi^{16}O$. When ^{209}Bi samples (100−700 ng L^{-1}) were analyzed on the RQPlus ICP-MS in the absence of ^{225}Ac, an instrument response of ∼2.7 × 10^{-3} cps (pM Bi)$^{-1}$ was observed at m/z = 225. The instrument response for ^{225}Ac on RQPlus ICP-MS was ∼133 cps pM^{-1} (Table 3). Radium-225 is a potential isobaric interference since it will produce a signal at m/z = 225. Several ^{225}Ac production routes rely on ^{229}Th or ^{225}Ra generators to yield ^{225}Ac through radioactive decay. The ^{225}Ac used in this study had a radionuclidic purity of >99.9%. which is typical for ^{225}Ac produced as an API.[50] The potential 0.1% ^{225}Ra radionuclidic impurity corresponds to a potential 0.15% impurity by mass. Since the potential ^{225}Ra impurity was significantly lower than the uncertainties for the m/z = 225 count rates (0.7 to 2.1% RSD), the impact of ^{225}Ra was not a concern to the study presented herein. The same logic applies to ^{225}Ac APIs generally. Radionuclidic purity standards preclude the presence of ^{225}Ra in quantities that could significantly influence the m/z = 225 signal.

The isobaric interference of ^{225}Ra with ^{225}Ac becomes relevant if the isotope ratio method is applied to the analysis of ^{227}Ac in samples with high ^{225}Ra content—^{229}Th or ^{225}Ra generator solutions. In these cases, ^{225}Ra would be expected to be present in quantities that significantly interfere with the ^{225}Ac signal at m/z = 225. A suitable strategy would need to be employed to eliminate the interference: Ra/Ac separation as part of the sample preparation or use of a reaction gas that exhibits selectivity for Ac or Ra. Since the focus of this work was on the analysis of ^{225}Ac APIs, these strategies were not rigorously investigated or incorporated into the methodology.

Method Comparison. The isotope ratio method can be compared to the other ^{227}Ac quantification methods discussed in the Introduction section (Table 8). The ICP-MS-based methods do not require ^{225}Ac decay or ^{227}Ac daughter ingrowth. Actinium-225 API samples may be analyzed by these methods immediately following purification. Sample preparation involves simple dilution of the ^{225}Ac API sample into dilute acid. Typical ICP-MS analyses take less than 2 h and can be performed concurrently with other quality tests (e.g., radionuclidic purity, radionuclidic identity, elemental purity). The quantification time for the ICP-MS methods can be conservatively estimated as less than 1 day post ^{225}Ac API purification, which is a significant advantage over the radiometric methods. The isotope ratio method has an achievable DL of 0.0086 ng L^{-1} (23.0 Bq L^{-1}), which is superior to the DL reported by Robertson et al.[13] Neither the DES method nor the α-srp method reports a DL in terms of the ^{227}Ac concentration. The DES method reports DL in terms of the ^{225}Ac/^{227}Ac activity ratio, while the α-srp has no reported DL. The four methods can be compared in terms of their demonstrated ^{227}Ac/^{225}Ac activity ratio. The isotope ratio method has the lowest reported ^{227}Ac/^{225}Ac activity ratio. This value was taken by dividing the DL of TQe (23.0 Bq L^{-1}) by the ^{225}Ac activity in the evaluated samples (85.4 MBq L^{-1}). While the ^{227}Ac/^{225}Ac ratio allows all four methods to be compared against common criteria, it is not the most useful comparison. For the ICP-MS methods, the lowest reportable activity ratio is dependent on the instrumental detection limit for ^{227}Ac and the ^{225}Ac activity used in a given analysis. Assuming that the true ^{227}Ac concentration remains below the instrumental detection limit, the reportable ^{227}Ac/^{225}Ac activity ratio could be lowered by simply analyzing higher activities of ^{225}Ac. For the DES method, the lowest reported ^{227}Ac/^{225}Ac activity ratio is the detection limit. Analyzing samples with ^{225}Ac activity will not improve the lowest reportable ^{225}Ac/^{227}Ac activity ratio. Table 8 includes the work of Levier et al., who used MC-ICP-MS and isotope dilution to quantify ^{227}Ac in 10−30 L seawater samples.[36] The method takes 2−3 weeks to perform owing to lengthy preconcentration and chemical separation steps.[36] While the Levier method is not focused on the analysis of ^{225}Ac APIs, it does highlight the potential sensitivity gains that can be achieved by the use of

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MC-ICP-MS and a high-sensitivity desolvation sample introduction system. The downside of MC-ICP-MS is the high cost and lack of industry use compared to quadrupole-based instruments. Quadrupole-based ICP-MS instruments are commonly used to quantify elemental impurities in radionuclides produced for pharmaceutical use. Institutions that produce ^{225}Ac likely have access to quadrupole ICP-MS instruments and use them for stable metal analysis. Thus, the implementation of the isotope ratio method for ^{227}Ac quantification could be as simple as adding m/z = 225 and 227 measurements to existing ICP-MS methods for stable metal analysis.

CONCLUSION

A method has been described herein for the quantification of ^{227}Ac in ^{225}Ac APIs using isotope ratio analysis and ICP-MS. The relationship between ICP-MS count rate data and the ^{225}Ac/^{227}Ac activity ratio was developed mathematically and then demonstrated through the course of the study. It was shown that the instrument responses (cps pM^{-1}) for ^{225}Ac and ^{227}Ac were equivalent. Thus, the ratio of count rate at m/z = 225 and m/z = 227 could provide a direct measure of the relative molar concentrations of ^{225}Ac and ^{227}Ac in a sample. It was further shown that ^{227}Ac concentrations measured using the isotope ratio method matched the values expected based on sample preparation. The methodology was evaluated against validation criteria for accuracy, precision, linearity, detection limits, quantitation limits, and specificity, showing excellent performance. When compared to other methods for ^{227}Ac quantification in ^{225}Ac APIs, the isotope ratio method shows lower detection limits and shorter analysis times required to produce reportable results. Actinium-227 quantification can be completed in less than 1 day, independent of ^{225}Ac decay or ^{227}Ac daughter in-growth. Furthermore, the method uses analytical equipment (ICP-MS, HPGe) that is commonly used for medical radionuclide quality control testing. Given the sensitivity, timing, and ease of operation, the isotope ratio method can be implemented as a standard technique for ^{225}Ac API quality control. The implementation of this method by ^{225}Ac API producers will help radiopharmaceutical manufacturers and clinical sites demonstrate regulatory compliance and maintain high standards of occupational safety.

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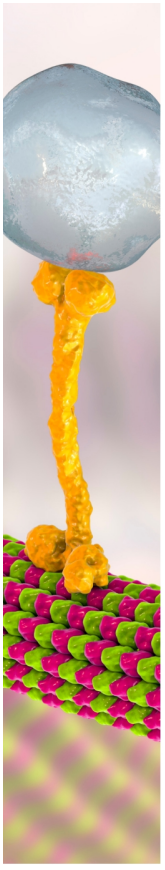
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