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Communication

A Quality Control Assay to Access the HCl Molarity of Radionuclide Solutions

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Abstract: Strontium-82 is produced by proton activation of a rubidium chloride target in an accelerator or cyclotron and purified by ion exchange chromatography. The Strontrium-82 is used in Cardigen generators to produce Rubidium-82 for cardiac imaging. Quality control testing of the purified Strontium-82 is performed with Inductively Coupled Plasma-Optical Emission spectroscopy (ICP-OES) and gamma spectroscopy. To meet Department of Energy specifications for HCl molarity the purified Strontium-82 solution needs to be tested to determine if the isotope is in the 0.05–0.5 M HCl range. This manuscript reports a simple HCl molarity test to determine if the purified Strontium-82 solution meets specifications. Validation of the assay was performed by evaluating all solutions associate with Strontium-82 processing.

Keywords: molarity test; quality control; strontium-82; Sr-82; BromoCresol Purple

1. Introduction

Many radioisotopes manufacturers dissolve radionuclides in dilute HCl to allow easier use in medical applications and environmental applications. One example is Strontium-82 (Sr-82) which is produced in the USA by the isotope production groups at Los Alamos and Brookhaven National Labs [1]. The final Sr-82 is dissolved in 0.1 M HCl [2], shipped to customers that load the isotope on a medical isotope generator, which is marketed as Cardiogen [3,4]. The Sr-82 has a half-life of 25 days and is used in the generator to produced Rubidium-82 which has a half-life of 72 s. The Rubidium-82 mimics potassium in the body, and the isotope is taken up by the heart and used for heart imaging [5]. Many quality control tests are performed on Sr-82 prior to the final product being released for packaging and shipping to customers [6]. In 2013 a technician performing the purification of Sr-82 performed the final dissolution with 4 M hydrochloric acid, the Sr-82 passed all quality control tests involving gamma spectroscopy and ICP-OES analysis. The high hydrochloric acid concentration prevented the customer from loading the Sr-82 solution on a generator for the production of Rubidium-82, and the solution was quarantined in accordance with regulatory policies [7]. One attempt to develop a quick quality control test to determine the HCl molarity of the purified Sr-82 was to dilute the sample with water, determine the pH with pH paper, then calculate the HCl molarity in the original sample. The approach produced varying results and validation of the method was problematic. Checking the HCl molarity using a pH meter can be challenging with 10 µL solutions, as we have found some micro pH probes provide accurate results while others do not reach a stable reading. In this short communication we report a fast quality control test to determine if the HCl molarity of a Sr-82 solution is in the acceptable range. The US Department of Energy specification for HCl molarity of Sr-82 is 0.05–0.5 M HCl, so the test needs to be negative for molarities outside the acceptance range. Titrating the solution to find the exact HCl molarity may take too long and could lead to a higher radiation dose to the technician.

2. Experimental Section

Reagents were purchased from Fisher or Sigma Aldrich. A 1 mg/mL solution of BromoCresol Purple was prepared using 18 MΩ water. For the assay the color of the solution was recorded after each step, and the steps associated with the method are: Step 1) To a 2–5 mL vial or test tube was added 10 µL of the Sr-82 solution, 90 µL of 18 MΩ water and 90 µL of BromoCresol Purple solution. Step 2) Then 49 µL of 0.01 M NaOH, was added. Step 3) Next 465 µL of 0.01 M NaOH was added. The assay was repeated with 10 µL of the following solutions: 0.04, 0.05, 0.1, 0.5, 0.55, 0.6, 1, 4, 6 M HCl, ammonia-ammonium chloride, saturated ammonium chloride and water. Analysis: BromoCresol Purple is yellow below pH 5.2, and the dye is purple above pH 6.8 [8–10]. A yellow colored solution after steps 1 and 2 would pass the test, but a purple colored solution would fail the test. For step 3 a purple colored solution would pass the test, and a yellow colored solution would fail the test.

3. Results and Discussion

Quality control testing of Strontium-82 is typically performed in a four hour time window. The ICP-OES, gamma spectroscopy and other testing must be completed prior to evaluation by the quality assurance unit and subsequent packaging. So a rapid assay is needed that uses minimal solution volume. The assay was setup with three steps, and a Strontium-82 product solution should pass all three steps of the assay in order to contain a HCl molarity between 0.05 and 0.5 M HCl. If the Sr-82 solutions fail any of steps of the assay then the sample fails the quality control test. For regulatory compliance a failed batch should be reprocessed according to previously setup reprocessing methods [11]. In step one the Sr-82 solution is tested to determine if it is not in a basic solution, and step two the assay determined if the HCl molarity of the Sr-82 solution is greater than or equal to 0.05 M HCl. In step 3 the assay determines if the Sr-82 solution is equal to or less than 0.5 M HCl. To pass the assay a yellow solution is required after steps 1 and 2, and a purple solution is required after step 3.

Validation of the assay was performed by testing 10 µL of various solutions, and the results are summarized in Table 1 and supplemental information [12]. The following solutions were chosen because they are used during the purification of Sr-82: 0.1, 0.5, 1, 4, 6 M HCl, ammonia-ammonium chloride, saturated ammonium chloride and water [1,2]. The quality control assay described herein involves the use of a pH indicator to test molarity, and validation of the assay is different than an instrumental method [13]. The range of the assay was evaluated by performing the assay with the following solutions: 0.04, 0.05, 0.5, 0.55 and 0.06 M HCl. The 0.5, 0.55, 0.6 M HCl standards were used to test the upper range of the assay, and the 0.55 and 0.6 M HCl standards failed the assay, but the 0.5 M HCl standard passed the assay. The lower range of the assay was established by performing the analysis on 0.04 and 0.05 M HCl standards. As expected the 0.04 M HCl standard failed the assay, and the 0.05 M HCl standard passed the assay.

Step 1 of the assay failed the ammonia hydroxide-ammonium chloride solution. Step 2 of the assay failed the following solutions: molarities less 0.05 M HCl, water and saturated ammonium chloride. Step 3 failed solutions with molarities greater than 0.5 M HCl. BromoCresol Purple was chosen for the assay. Alternatively, Bromothymol blue, which is yellow below pH 6.0 and blue above pH 7.6, could be used as indicator for the assay. Pipettes used for production samples are routinely checked for accuracy and the pipetting errors range from 1.6 to 1.77%. To calculate propagation of error a pipette error of 1.3% has been used [6,14]. For step 1 the propagation of error was calculated using Equation (1),

$$\text{error} = \sqrt{(\sigma)^2 + (\sigma)^2 + (\sigma)^2} \tag{1}$$

where σ corresponds to the error of pipetting each solvent in step 1. A similar equation was used to determine the error in steps 2 and 3 and the total error for each step was determined: step 1 (2.2%), step 2 (2.6%) and step 3 (2.9%).

Table 1. Evaluation of the quality control assay for Sr-82 solutions.

Solution	Step 1 Color	Pass/Fail	Step 2 Color	Pass/Fail	Step 3 Color	Pass/Fail	Accept/Reject	Expected Result
6 M HCl	yellow	pass	yellow	pass	yellow	fail	Reject	Reject
4 M HCl	yellow	pass	yellow	pass	yellow	fail	Reject	Reject
1 M HCl	yellow	pass	yellow	pass	yellow	fail	Reject	Reject
0.6 M HCl	yellow	pass	yellow	pass	yellow	fail	Reject	Reject
0.55 M HCl	yellow	pass	yellow	pass	yellow	fail	Reject	Reject
0.5 M HCl	yellow	pass	yellow	pass	purple	pass	Accept	Accept
0.1 M HCl	yellow	pass	yellow	pass	purple	pass	Accept	Accept
0.1 M HCl	yellow	pass	yellow	pass	purple	pass	Accept	Accept
0.1 M HCl	yellow	pass	yellow	pass	purple	pass	Accept	Accept
0.05 M HCl	yellow	pass	yellow	pass	purple	pass	Accept	Accept
0.04 M HCl	yellow	pass	purple	fail	N/A		Reject	Reject
NH_4OH-NH_4Cl	Purple	fail	NA		NA		Reject	Reject
Sat. NH_4Cl	yellow	pass	purple	fail	NA		Reject	Reject
water	yellow	pass	purple	fail	NA		Reject	Reject
Sr-82 sample 1	yellow	pass	yellow	pass	purple	pass	Accept	Accept
Sr-82 sample 2	yellow	pass	yellow	pass	purple	pass	Accept	Accept
Sr-82 sample 3	yellow	pass	yellow	pass	purple	pass	Accept	Accept

4. Conclusions

The assay determines if a Sr-82 solution is in the acceptable HCl molarity range 0.05–0.5 M HCl, and the assay will prevent shipments of Sr-82 solutions in the incorrect matrix. The rapid test can be performed with minimal radiation exposure to the technician and can be adapted for quality control testing of other isotopes. The assay can be used for isotopes that are shipped in HCl solutions such as: Y-88, Sr-82, Ho-166, Pm-149, Tc-95m, As-72, Ge-68, Cu-67, Fe-52, and Mg-28 [15].

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Conflicts of Interest: The authors declare no conflict of interest.

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