The Separation of Bismuth-213 from Actinium-225 and the Ion Exchange Properties of the Alkali Metal Cations with an Inorganic Resin

A Dissertation Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Mark Alan Moore
December 2017

Acknowledgements

This research was funded by a research grant from the National Nuclear Security Administration (NNSA) Stewardship Science Academic Alliances (SSAA) Program. All views expressed here are those of the author and do not necessarily reflect those of the NNSA or the SSAA.

Abstract

Interest in the use of alpha radiation emitters in radio immunotherapy is due to the high linear energy transfer and short range of alpha radiation. These properties enable the targeting of single tumor cells with diminished risk of damaging the surrounding tissue. Significant research has been done in the separation of the alpha emitter Bismuth-213 from its parent solution of Actinium-225 using organic resins. Due to radiolytic damage to the resin emphasis in the research has focused on the rapid elution of Bismuth-213 or storage of the parent Actinium-225 solution on a more robust resin. Inorganic ion exchange resins have shown a greater resistance to radiolytic damage than organic resins. If an inorganic resin could retain its structural integrity then Actinium-225 could be loaded on an inorganic resin bed with a clinical dose of Bismuth-213 eluted from the column when needed. The performance of two inorganic ion exchange resins, Isolute SCX and Isolute SCX-2, were compared to the performance of the organic resin AG-50X8 in the separation of the radionuclide Bismuth-213 from its parent solution of Actinium-225. Performance was based on the percent of Bismuth-213 available eluted, and the breakthrough of Actinium-225. It was found that Isolute SCX and Isolute SCX-2 produced less of the Bismuth-213 available on the column. The breakthrough of the Actinium-225 for all three columns was well below the toxicity level. Further tests showed that Isolute SCX and Isolute SCX-2 suffered less apparent damage from radiation generated *in situ*.

A comparison of the ion exchange properties of the inorganic resin Isolute SCX-2 with alkali metal cations, including francium, to several better known organic resins is also presented. With hydrophobic organic ion exchange resins the selectivity of alkali metal cations tends to increase as the mass of the ion increases while the selectivity's for the less hydrophobic Isolute SCX-2 increased from francium to cesium to potassium to sodium. Lithium had the lowest selectivity, likely due to the strong hydration of the ion, and rubidium did not follow the selectivity trends of the other alkali ions.

Table of Contents

List of Figures

INTRODUCTION

Scope

The purpose of this work is to report on the performance of ion exchange resins with alkali metal cations, the separation of ^{213}Bi from ^{225}Ac and the ability of three resins to withstand radiation generated *in situ*. The material is organized into three sections. Chapter 1 presents the results of ion exchange studies between Isolute SCX-2 and alkali metal cations. These results are compared with literature values using Dowex 50X8 with an emphasis on how the polarity of the resin structure affects the exchange with alkali metal cations.[1, 2] The performance of Isolute SCX and Isolute SCX-2 in the separation of ^{213}Bi from its parent nuclide ^{225}Ac is presented in Chapter 2. The results focus on the production of ^{213}Bi when "milking" the ^{225}Ac "cow" and the breakthrough of ^{225}Ac. Chapter 3 shows the effects of radiation generated *in situ* on Isolute SCX, Isolute SCX-2 and AG-50X8 by examining the migration of radionuclides down the volume of the resin bed over time, the ability of the resin to retain the radionuclides and microscopic pictures of the resin beds.

The nature of alpha radiation, its usefulness in cancer treatment and the use of ^{213}Bi as an alpha emitter is included in the background information. The background information also contains an overview of ion exchange between ionic liquids and solid resins, the ion exchange resins used in these experiments and how gamma spectroscopy is used to identify radionuclides.

Background

Alpha Radiation and its Use in Cancer Treatment

The potential of alpha radiation in cancer treatment lies in the short range and high linear energy transfer (LET) of alpha particles.[3] Alpha particles are emitted from an unstable heavy nucleus and consist of a combination of 2 protons and 2 neutrons. An alpha particle has a positive charge and as it propagates through a material it interacts electromagnetically with the negatively charged electrons in the material.[4] This interaction transfers energy from the alpha particle to the many electrons with which it is interacting. This interaction simultaneously decreases the velocity of the alpha particle and raises the electron to a higher-lying shell or ionizes it completely.[4] Because the alpha particle interacts with so many electrons simultaneously the rate of energy transfer is high, which gives the alpha particle a short

range. The short range and the high LET insures that much of the energy of the particle will be transferred into the targeted cell. These properties make alpha particles useful in the treatment of micrometastatic disease, leukemia, and lymphoma.[5]

^{213}Bi

A wide range of alpha emitting radionuclides has been studied for medical treatments, including ^{213}Bi.[3, 5-7] ^{213}Bi is one of six daughters of ^{225}Ac that are in the decay chain of ^{233}U. Figure 1 shows the half-lives and method of decay for the ^{233}U decay chain. A system for labeling monoclonal antibodies with ^{213}Bi is established but the relatively short half-life of 45 minutes for ^{213}Bi means the process of separating ^{213}Bi from other radionuclides and labeling the antibodies must be rapid.[8, 9] With half-lives of 10 days for ^{225}Ac and 45 minutes for ^{213}Bi secular equilibrium is reached in approximately 5 hours, allowing ^{225}Ac to be used as a source of ^{213}Bi and "milked" for ^{213}Bi up to twice daily. This provides a reusable and ready source of alpha emitters that can quickly be prepared for clinical use.

Using an ^{225}Ac column as a source to produce ^{213}Bi presents certain challenges, however. If the resin is loaded directly onto the column the ^{225}Ac loads on a thin layer at the top of the resin bed.[10] The intensity of the alpha radiation concentrated in this small volume of the bed may damage the resin, decreasing its capacity and causing premature failure of the column. The greater stability of inorganic resins when subjected to radiation may mitigate this damage and provide a means for more robust ^{213}Bi sources.[11] The ability of the inorganic resins Isolute SCX and Isolute SCX-2 to replace a historically utilized organic resin (AG-50X8) in a ^{213}Bi generator was measured by adding the ^{225}Ac to the column and eluting the ^{213}Bi over several days. The performance of two Isolute resins, SCX and SCX-2, are compared in this study with that of AG-50X8, a resin commonly used for this type of separation.

Francium

^{225}Ac decays by emitting an alpha particle to become ^{221}Fr, an unstable radionuclide with a half-life of about 5 minutes. The most stable of all the francium isotopes is ^{223}Fr, with a half-life of about 22 minutes. These short half-lives have made it one of the least studied elements. The laboratory work that

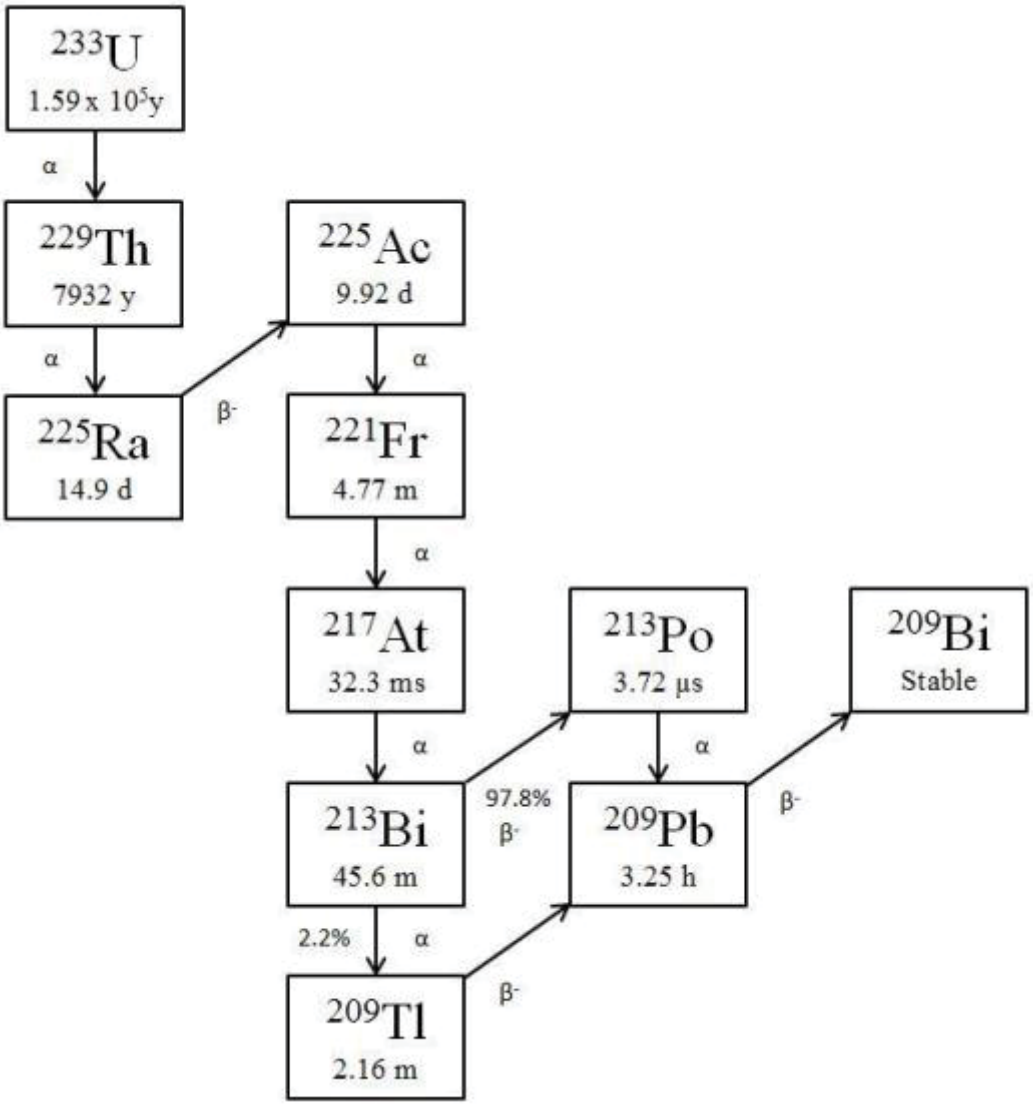

Figure 1. Decay chain for ^{233}U.[12]

has been done with francium includes studies on the selectivity of cesium selective calix[4]arenecrown-6 in the complexation of francium and the hydration energy, the energy of partitioning and the thermodynamic radius of francium.[13, 14] Because they are both in the decay chain for ^{233}U, working with ^{225}Ac presents an opportunity to determine ion exchange properties of ^{221}Fr as well. The research presented here focused on the behavior of ^{221}Fr with an inorganic ion exchange resin and how that compares with the other alkali metals.

The Isolute SCX-2 has little non-polar character, making it less hydrophobic than historically used organic resins.[1] A series of batch ion exchange tests was conducted in a range of concentrations for each of the stable alkali metals. Ion exchange tests between Isolute SCX-2 and ^{221}Fr were also conducted. Because the short half-life of the ^{221}Fr limited its use in a batch method, the francium measurements were made using ^{221}Fr generated *in situ* from ^{225}Ac. In all the experiments, the concentration of the alkali metal was kept well below the resin capacity and the concentration of H^+ in the solution. The results of these experiments are compared to results from data reported in the literature.

AG-50X8, Isolute SCX, Isolute SCX-2

AG-50X8 is a strong acid cation exchange resin with a styrene divinylbenzene copolymer lattice structure. While AG-50X8 is available in sodium and ammonium forms, it was used in these studies in its hydrogen form. Isolute SCX and Isolute SCX-2 are inorganic strong acid cation exchange resins with a silica structure. Isolute SCX is functionalized with a benzene sulfonic acid bonded to the silica while Isolute SCX-2 is functionalized with a propylsulfonic acid. Both Isolute resins were used in their hydrogen form. The structure of the resins are shown in Figure 2.

The interest in the inorganic Isolute resins is their potential to resist the damage caused by the alpha decay of radionuclides used in these studies. Radiolytic effects on organic ion exchange resins include breaking of the bond between the functional group and the structure, formation of free radicals, the rupture of functional groups in the structure of the resin and their formation into gaseous products.[11] Inorganic resins have shown a greater resistance to radiation than organic resins.[11] If an inorganic resin

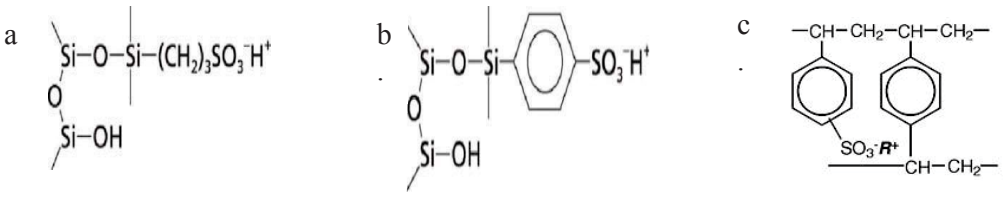

Figure 2. The chemical structure of (a) Isolute SCX-2, (b) Isolute SCX and (c) AG-50X8.

could resist radiolytic damage when loaded with ^{225}Ac a dose of ^{213}Bi could be eluted from the column periodically when needed.

For this study, the stability and performance of an inorganic and 2 organic resins were investigated while being subjected to an *in situ* radiation source of ^{225}Ac over a period of days. Microfluidic beds of the inorganic resins Isolute SCX and Isolute SCX-2 and the organic resin AG-50X8 were loaded with a 100 μCi solution of ^{225}Ac and its daughters. Photographs and radiation images were taken over 2 weeks to monitor the damage to the different resins. The resin beds were washed with 0.1 M HNO_3 periodically. The washes were collected and analyzed with a high purity germanium detector (HPGe) after 4 weeks.

Ion Exchange

The ion exchange processes conducted in these studies consisted of the transfer of cations between an aqueous solution and an organic or inorganic resin. The exchange processes used in these studies for univalent ions can be described by the equation:

$M^+ + HR \leftrightarrow MR + H^+$

where M^+ represents an alkali metal cation, H^+ is a proton, and R is the resin. When the ion exchange process reaches equilibrium the extent to which the resin takes up ions is called the loading of the resin. The resin loading (q) is the number of cations exchanged per gram of resin and is reported in millimoles per gram. The charge of the ion and its concentration in solution help determine the affinity it will have for the resin. The extent of the affinity an ion has for a resin is referred to as the ions selectivity for the resin. The selectivity is measured by the distribution coefficient (K_D) and can be calculated by the following equation:

$$K_D = \frac{q_i}{a_i}$$

where q_i is the loading of component in mmol/g and a_i is the activity of component in mmol/ml.

Gamma-Rays and Gamma-Ray Spectroscopy

Gamma-rays are photons emitted from a nucleus that is in an excited state, usually after radioactive decay. The difference in energy between the excited state and the ground state is discrete, making radionuclides identifiable by the energy of their gamma-ray emission.[15] In these studies, a high-purity germanium gamma detector (HPGe) was used with CANBERRA's Genie software to analyze the ion exchange chromatography fractions collected during the elution process. The activity of the radionuclides analyzed with the HPGe was corrected for the efficiency of the detector and the decay occurring between the collection and analysis of the sample. The eluent flowing from the columns was analyzed with a Kromek GR1 CZT inline detector with Multispect software.

The HPGe and Kromek GR1 CZT gamma detectors are semiconductor diode detectors. Like any crystalline material, the energy of the electrons in semiconductors are restricted to bands. Semiconductors have a valence band that contains the outer-shell electrons binding the different atoms of the semiconductor together, and a conduction band that contains electrons that are free to move around the material.[4] The difference in the energy levels between the conduction band and the valence band is called the bandgap. When a gamma ray photon deposits its energy in the semiconductor diode of a detector the energy is transferred to an electron in the valence band. If this energy allows the electron to overcome the bandgap, then the electron moves to the conduction band. A potential difference provided by a bias voltage sweeps the electrons to a collecting electrode.[4]

In this study, the fractions were analyzed for 10 minutes with the HPGe using the energy peak at 440 KeV to determine the activity of the ^{213}Bi in the fraction. The samples were analyzed again several days later after the ^{213}Bi eluted from the column had decayed. The activity detected at 440 KeV could then be attributed to the ^{213}Bi created from the decay of ^{225}Ac, which would have the same activity as ^{213}Bi due to the radionuclides being in secular equilibrium. Activity of the radionuclides was reported by

the HPGe in counts per second with an error equal to the square root of the total count. The elution curves of the columns were plotted using the data gathered from the Kromek inline detector.

References

1. *Method Development in Solid Phase Extraction using Isolute SCX and SCX-3 SPE Columns for the Extraction of Aqueous Samples*. 2004, Biotage.
2. Diamond, R.M., *Factors influencing ion exchange equilibrium in concentrated solutions: Behavior of the alkaline earth and alkali ions*. J. Am. Chem. Soc., 1954. **77**.
3. Mirzadeh, S., *Generator-produced alpha-emitters*. Appl. Radiat. Isot., 1998. **49**: p. 345-349.
4. Knoll, G.F., *Radiation Detection and Measurement*. 3rd ed. 2000, New York: John Wiley & Sons. 802.
5. Imam, S., *Advancements in Cancer Therapy with Alpha-Emitters: A Review*. Int. J. Radiat. Oncol. Biol. Phys., 2001. **51**(1): p. 271-278.
6. Aghevlian, S., A.J. Boyle, and R.M. Reilly, *Radioimmunotherapy of cancer with high linear energy transfer (LET) radiation delivered by radionuclides emitting alpha-particles or Auger electrons*. Adv Drug Deliv Rev, 2017. **109**: p. 102-118.
7. Jurcic, J., et al., *Targeted alpha particle immunotherapy for myeloid leukemia*. Blood, 2002. **100**.
8. Dangshe, M., et al., *Rapid preparation of short-lived alpha particle emitting radioimmunopharmaceuticals*. Appl Radiat Isotopes, 2001. **55**: p. 463-470.
9. Geerlings, M.W., *Method for preparing 213Bi for therapeutic use*. 1997, Akzo Nobel N.V.
10. McDevitt, M.R., et al., *An 225Ac/213Bi generator system for therapeutic clinical applications: construction and operation*. Appl Radiat Isot, 1999. **50**: p. 895-904.
11. Pillay, S., *Review of the radiation stability of ion exchange materials*. J Radioanal Nucl Ch, 1986. **102**(1): p. 247-268.
12. Beck, R., et al., *213Bi-radioimmunotherapy defeats early-stage disseminated gastric cancer in nude mice*. Cancer Sci, 2007. **98**(8): p. 1215-22.
13. Haverlock, T.J., S. Mirzadeh, and B.A. Moyer, *Selectivity of calix[4]arene-bis(benzocrown-6) in the complexation and transport of francium ion*. J Am Chem Soc, 2003. **125**(5): p. 1126-7.
14. Delmau, L.H., et al., *First experimentally determined thermodynamic values of francium: hydration energy, energy of partitioning, and thermodynamic radius.* J Phys Chem B, 2013. **117**(31): p. 9258-61.
15. Turner, J.E., *Atoms, Radiation, and Radiation Protection*. 2007: Wiley.

CHAPTER I: THE ION EXCHANGE PROPERTIES OF THE ALKALI METAL CATIONS INCLUDING FRANCIUM WITH AN INORGANIC RESIN

Abstract

A comparison of the ion exchange properties of the inorganic resin Isolute SCX-2 with alkali metal cations, including francium, to better known organic resins is presented. With hydrophobic organic ion exchange resins the selectivity of alkali metal cations tends to increase as the mass of the ion increases while the selectivity's for the less hydrophobic Isolute SCX-2 increased from francium to cesium to potassium to sodium.

Introduction

Background

The selectivity of the stable alkali metal cations with organic resins in an HCl solution increases as the ionic mass increases.[1-3] Ion exchange studies between the alkali metals and Duolite C-3, an organic resin, in HCl show increasing selectivity's for the alkaline metal ions as the ionic mass increases, with $^{221}Fr^{+}$ having the highest selectivity.[4] This increase in the selectivity is likely caused by the level of hydration of the cations interacting with the hydrophobic resin. The smaller and denser alkali metal cations strongly orient water molecules around them while the larger more polarizable alkali metal cations are less able to form these strong hydration shells.[5] The interaction between the larger hydration shells and the hydrophobic resin decreases the selectivity of the denser alkali metal cations.[6].

If the selectivity is impacted by the hydrophobicity of a resin and the hydration of the ions, then the selectivity for the more hydrophilic Isolute SCX-2 resin should differ from the more hydrophobic organic resins. Raman Spectroscopy on the Isolute SCX-2 suggests this by showing no significant frequency shifts for the SO_3 functional group regardless of the hydration state.[7]

Objective

The goal of this part of the dissertation is to investigate the effects of hydrophobicity of a resin on its selectivity of alkali metal ions. To achieve this goal, a series of experiments were conducted to measure the distribution coefficients of several stable alkali metal ions with Isolute SCX-2 cation exchange resin. Concentrations of alkali metal ions ranged from 2 to 200 mmol/l. These experiments were performed in batch mode (which will be described in the experimental section). Studies were

extended to include cation exchange behavior of ^{221}Fr in Isolute SCX-2 as well. Because of the short half-life of the ^{221}Fr ($t_{1/2}$= 4.8 min), the distribution constants were measured by column techniques (as will be detailed in the experimental section), and ^{221}Fr generated *in situ* from decay of ^{225}Ac. In all the experiments, the concentration of the alkali metal was kept well below the concentration of the hydrogen cation in the solution. The results of these experiments are compared to results from data reported in the literature.[3, 4]

Theory

The equation for ion exchange for the singly charged alkali metal cations is:

$M^+ + HR \leftrightarrow MR + H^+$

where M^+ is the metal cation, H^+ is the hydrogen ion and R is the ion exchange material. The distribution coefficient (K_D) is defined as the ratio of the concentration of the metal ion in the resin to the concentration of the metal ion in the solution at equilibrium. In theory, the distribution coefficients should remain constant and independent of the cation ion concentration if the concentration of the metal ion is kept low compared to the capacity of ion exchanger.[8] The loading of the alkali metal on the resin was plotted as a function of the equilibrium concentration and the equation for the linear best fit line was calculated. The slope of the best fit line was taken as the K_D value.

Experimental

Lithium nitrate, cesium chloride, sodium nitrate, rubidium nitrate and potassium sulfate salts were used as received from Fisher Scientific. The cation exchange resins Isolute SCX-2 and AG-50X8 resins as well as standard solutions of 1000 ppm lithium, cesium, sodium, rubidium and potassium were obtained from Fisher Scientific. 2 and 5 M HCl were prepared from 12.1 M HCl by dilution with deionized water. The ^{225}Ac used to generate the ^{221}Fr was provided by Dr. Rose Ball at Oak Ridge National Laboratory. It was received as a dry nitrate and dissolved in 0.1 M HNO_3. Samples of the results from the ion exchange tests with the stable alkali metal cations were analyzed with a PerkinElmer Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES). The ICP-OES was calibrated using the alkali metal cation standards diluted with 0.5 M HCl.

Method for Stable Alkali Metal Cations

To ensure that the Isolute SCX-2 was in hydrogen form it was treated with 2 M HCl acid. Typically, 7 grams of Isolute SCX-2 was stirred for an hour on a magnetic stir plate in 150 ml of 2 M HCl. The acid was decanted and the resin washed with deionized water and then dried in a vacuum oven at 80° C for 2 hours.

To determine the distribution coefficients with the Isolute SCX-2, cesium chloride, lithium, sodium, potassium, and rubidium nitrate feed solutions were prepared in 0.5 M HCl. The initial concentrations were: 200 mmol/l of lithium nitrate, 50 mmol/l of sodium nitrate, 3 mmol/l of potassium sulfate, 7 mmol/l of rubidium nitrate and 5 mmol/l of cesium chloride. Five samples for ion exchange were made for each alkali metal cation. The concentration of the first sample was the initial concentration with sample 2 diluted to 80% of the initial concentration, sample 3 to 60%, sample 4 to 40% and sample 5 to 20%. The resin was added to each of the samples, the samples were then stirred on a magnetic stir plate for one hour. After mixing the solution was vacuum filtered to remove the resin, diluted with 0.5 M HCl and analyzed with the ICP-OES. Each of the 5 samples used in the ion exchange were divided into 3 aliquots for analysis by the ICP-OES. The ICP-OES analyzed each aliquot 3 times, giving a total of 9 concentration estimations for each sample. The standard deviation of these 9 estimations was used as the error.

The loading of the resin (q) is the number of millimoles of the alkali cation exchanged divided by the mass of dry resin in grams. This was plotted vs the equilibrium concentration of the solution in mmol/l (see Figures 3-7). K_D was determined by linear regression to find the slope of the best fit line for the plot.

Method for ^{221}Fr

The batch method used for the stable alkali metal cations could not be used with ^{221}Fr, the hour spent mixing would represent 12 half-lives of the alkali metal. Instead, the ^{221}Fr was generated *in situ*

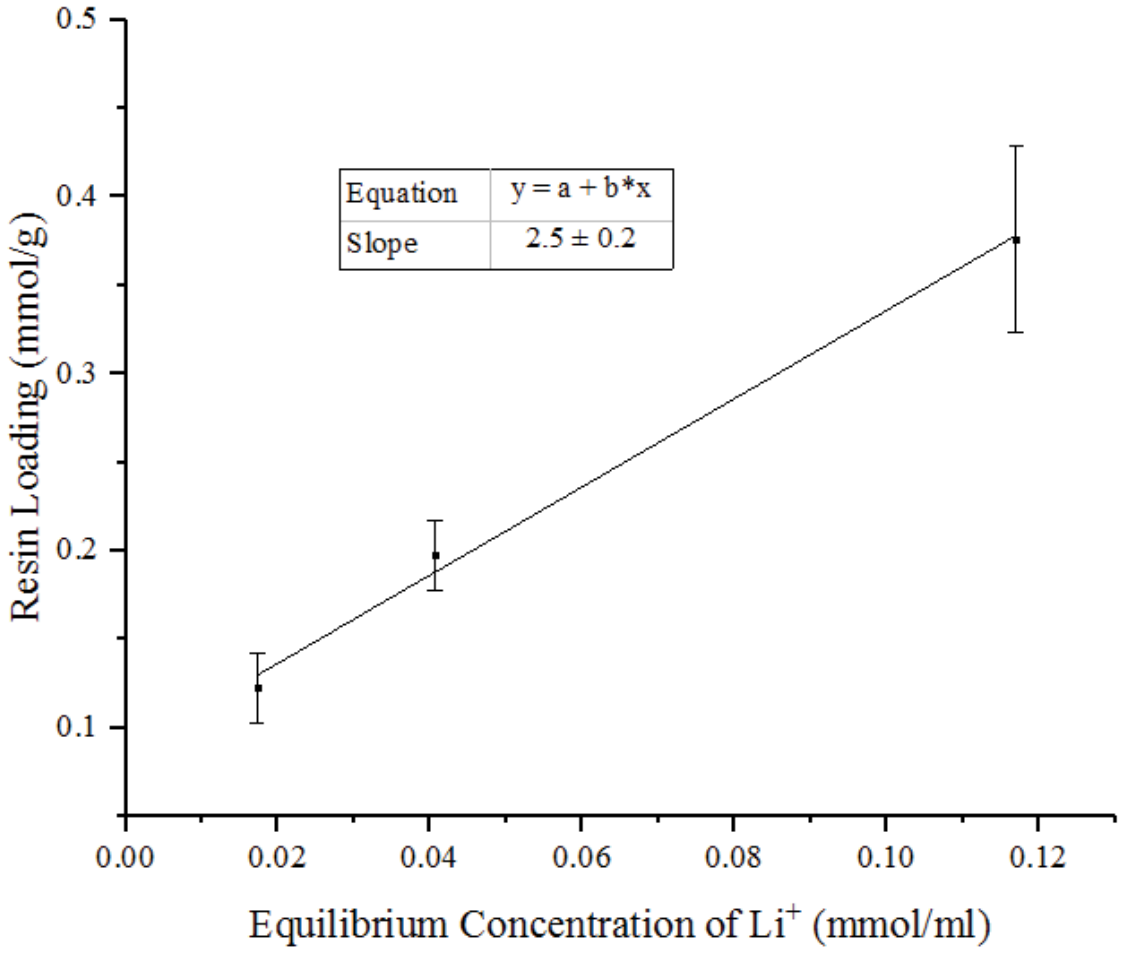

Figure 3. Plot and slope of the best fit line for the equilibrium concentration of the Li ion vs the loading of the resin after ion exchange.

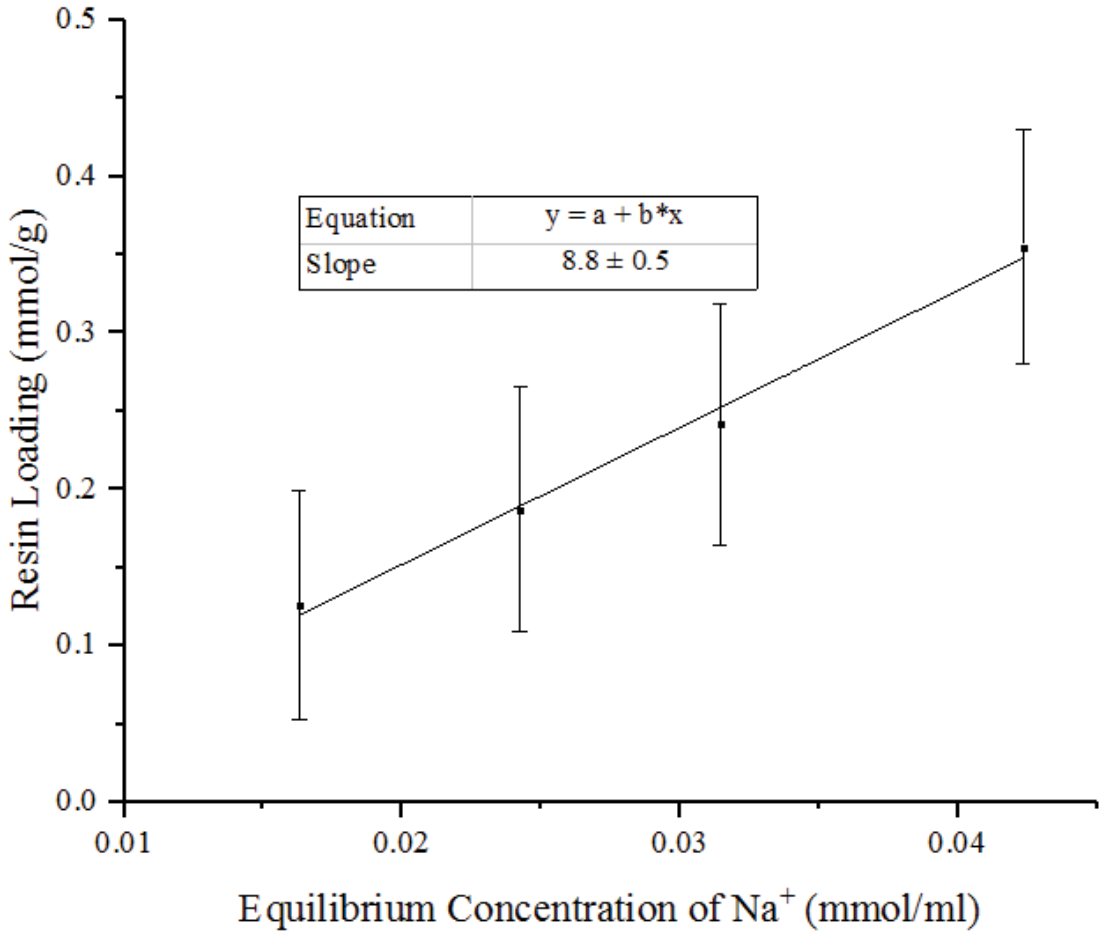

Figure 4. Plot and slope of the best fit line for the equilibrium concentration of the Na ion vs the loading of the resin after ion exchange.

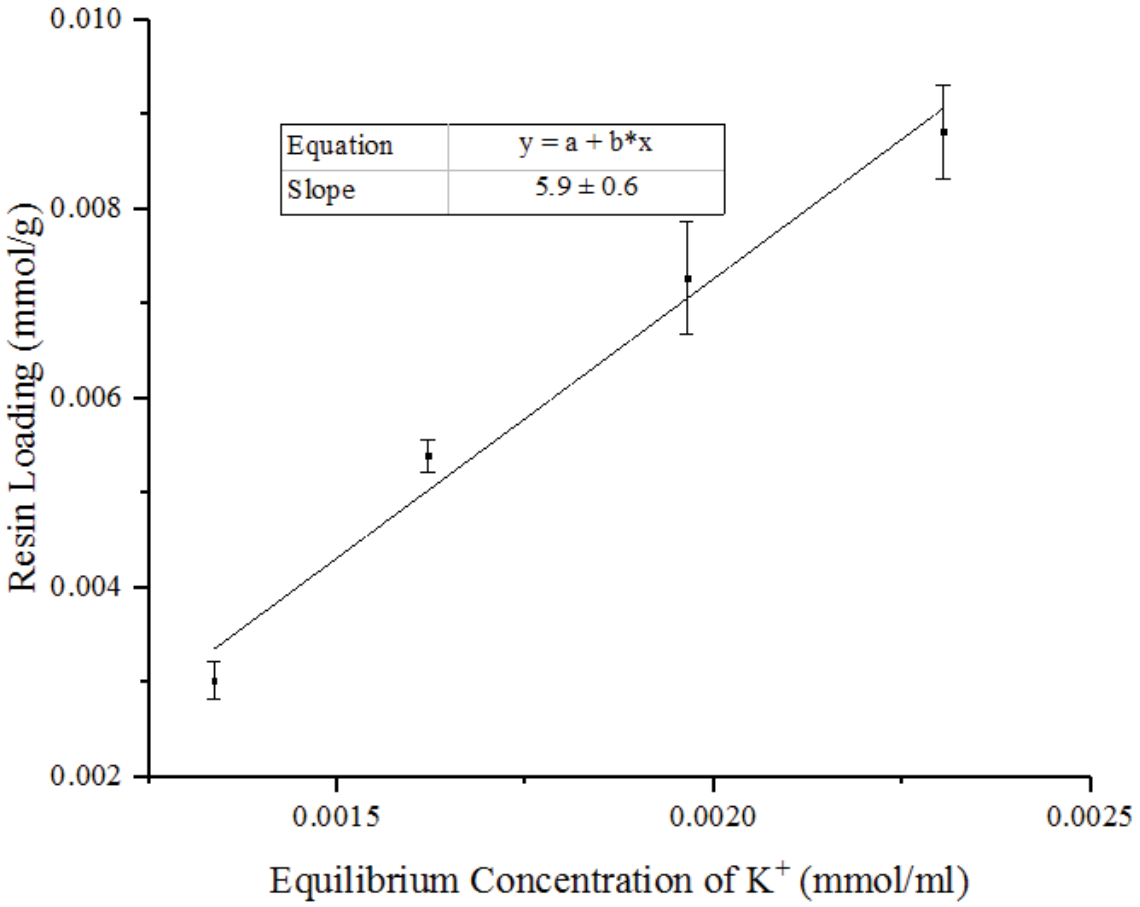

Figure 5. Plot and slope of the best fit line for the equilibrium concentration of the K ion vs the loading of the resin after ion exchange.

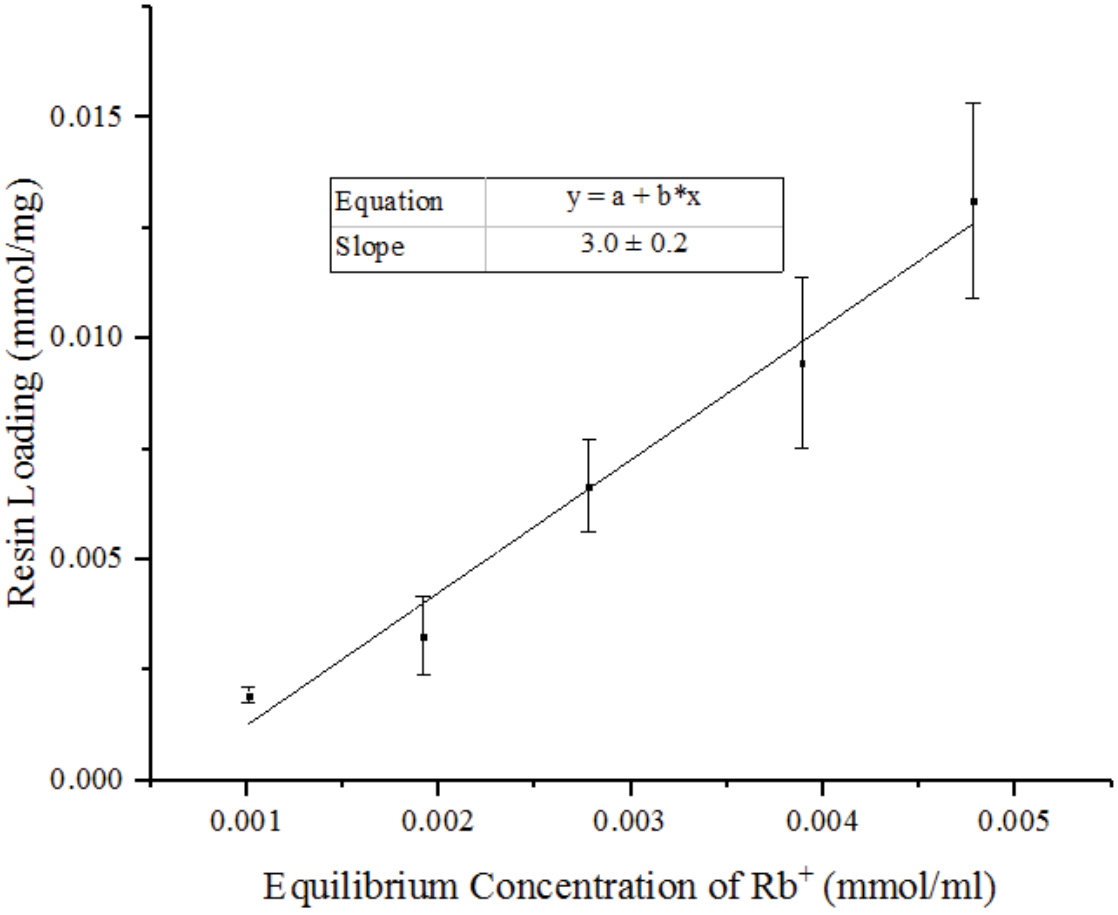

Figure 6. Plot and slope of the best fit line for the equilibrium concentration of the Rb ion vs the loading of the resin after ion exchange.

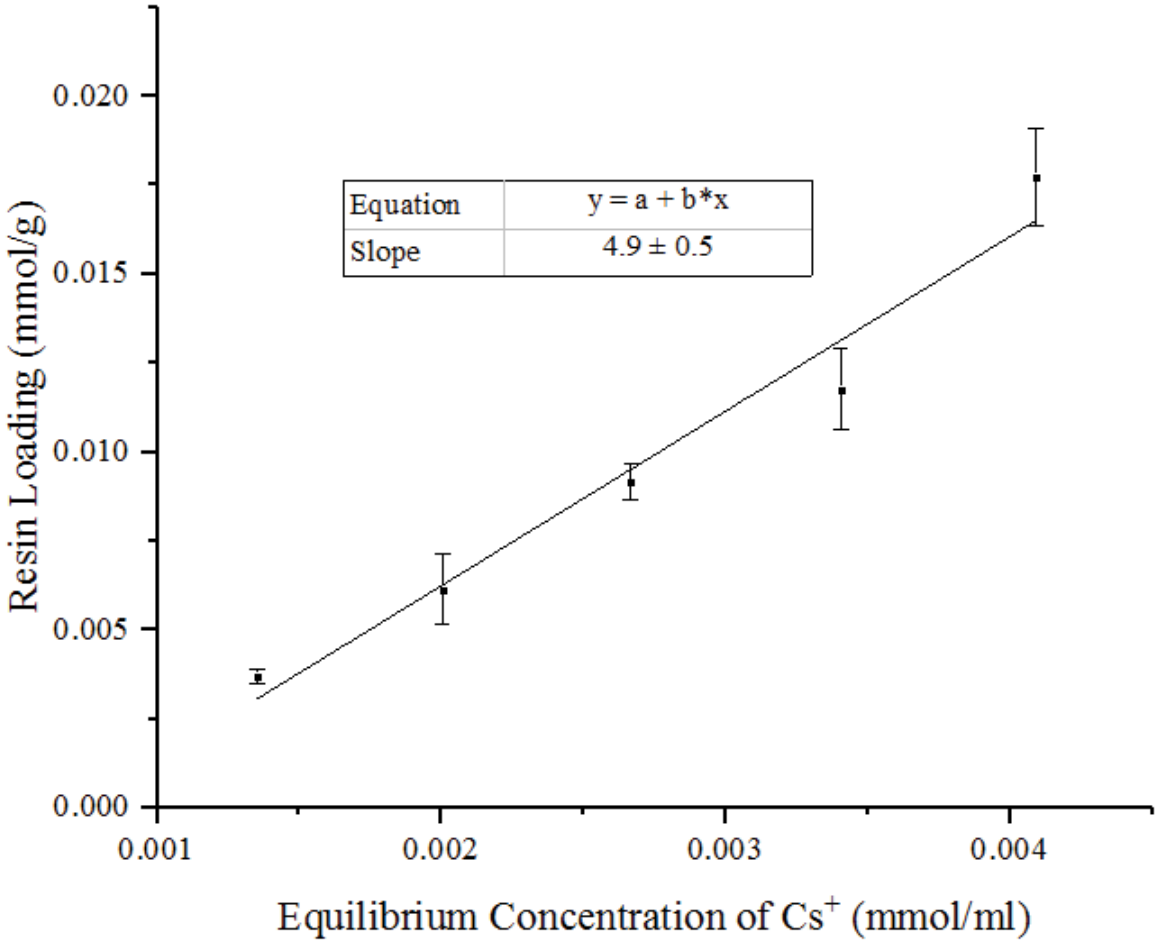

Figure 7. Plot and slope of the best fit line for the equilibrium concentration of the Cs ion vs the loading of the resin after ion exchange.

from the decay of ^{225}Ac in a column and eluted with 0.5 M HCl. ^{225}Ac has the decay chain $^{225}Ac \rightarrow {}^{221}Fr \rightarrow {}^{217}At \rightarrow {}^{213}Bi$ with the ^{225}Ac and the ^{221}Fr reaching secular equilibrium in about 20 minutes. To prepare the column of Isolute SCX-2 the resin was mixed with Milli-Q water and pipetted into the column to a bed volume of 0.5 mL. Using manufacturer recommendations, the bed was conditioned with 4 mL of 1 M Acetic Acid that was followed by a wash of 4 mL of Milli-Q water. A volume of 0.35 mL of the resin was removed from the bed, mixed with 200 μCi of ^{225}Ac on a rocker for 25 minutes, then pipetted back into the column.

BioRad AG-50X8 resin was mixed with Milli-Q water and pipetted into a column to a bed volume of 0.6 mL then conditioned with 4 mL of 8 M HNO_3 followed with several bed volumes of water to remove the strong acid. A volume of 0.4 mL of the resin was mixed with 200 μCi of ^{225}Ac in the same procedure as the Isolute SCX-2. To generate the ^{221}Fr the columns were eluted, by gravity flow, with 0.1 M KI/HCl to remove both ^{213}Bi and ^{221}Fr. After one hour, the ^{225}Ac had reached secular equilibrium with the ^{221}Fr and the columns were washed with 0.6 mL of 0.5 M HCl. The fractions were analyzed with a HPGe gamma detector for 10 minutes immediately after collection. The decay of the ^{221}Fr after collection of the fraction and during analysis was calculated and added to the final activity. The distribution coefficient was calculated by dividing the concentration of the $^{221}Fr^{+}$ in the bed volume by the concentration of the $^{221}Fr^{+}$ in the wash. The concentration of the $^{221}Fr^{+}$ in the wash was calculated with the activity of the $^{221}Fr^{+}$ in all the fractions divided by the volume of HCl used to wash the column.

Results

The K_D values for the stable alkali metal cations for Isolute SCX-2 in HCl media are summarized in Table 1. The first column of Table 1 shows the results of this study. The values of K_D were calculated as the slope of the best fit line of the resin loading vs the equilibrium concentration plots. The concentration of the alkali metal cation remaining in the solution after exchanging with the resin was read 3 times with the ICP-OES from each of 3 aliquots taken from every ion exchange sample. The K_D values in the table were calculated from the average of these 9 values, with the error calculated from the standard

Table 1. K_D values for the alkali metal cations exchanged with Isolute SCX-2 and data found in the literature for Dowex 50WX8.

	Isolute SCX-2 K_D (ml/g)	Dowex 50WX8 Kim K_D (ml/g)	Dowex 50WX8 Nelson K_D (ml/g)
Li^+	2.5 ± 0.2	2.97	3.18
Na^+	8.8 ± 0.5	5.26	5.38
K^+	5.9 ± 0.6	13.0	11.5
Rb^+	3.0 ± 0.3	--	14.5
Cs^+	4.9 ± 0.5	--	17.5
Fr^+	3.5		

deviation of the 9 values. In the second column are the K_D values for Dowex 50W-X8 200-400 mesh reported by Kim et al., and in the third column are the K_D values for Dowex 50WX8 400 mesh reported by Nelson.[3, 4]

The Dowex 50WX8 values show a trend of increasing selectivity as the atomic mass of the alkali metal ion increases. The trend in the selectivity of the Isolute SCX-2 for the alkali metal ions is different than that of the Dowex 50WX8, with the trend in the selectivity being $Li^+ < Rb^+ < Fr^+ < Cs^+ < K^+ < Na^+$. The distribution coefficient between ^{221}Fr and the Isolute SCX-2 was 3.5 mL/g. The intensity of the gamma radiation for the ^{221}Fr eluted from the AG-50X8 resin was below the limit of detection for the HPGe detector, which suggests a very high K_D value.

Discussion

The K_D value for the Fr^+ is the ratio of the concentration of the Fr^+ cation in the stationary phase (the resin) to the concentration of the Fr^+ cation in the mobile phase at equilibrium. The exchange of the Fr^+ between the mobile phase and the stationary phase at equilibrium is a stochastic process, with some of the Fr^+ cations retained on the resin longer than others. As with any random process this can be described with a Gaussian distribution. An elution curve that exhibits the symmetry of a Gaussian distribution then describes a process that is in equilibrium. The elution curve obtained for the Fr^+ is shown in Figure 8. A common method for testing the symmetry of an elution curve is the tailing factor.[9] The tailing factor is the ratio of the back width of the curve to the front width of the curve at 10% peak height, a value close to 1 indicating symmetry. Another measure of symmetry is the skewness of a curve, with a value close to 0

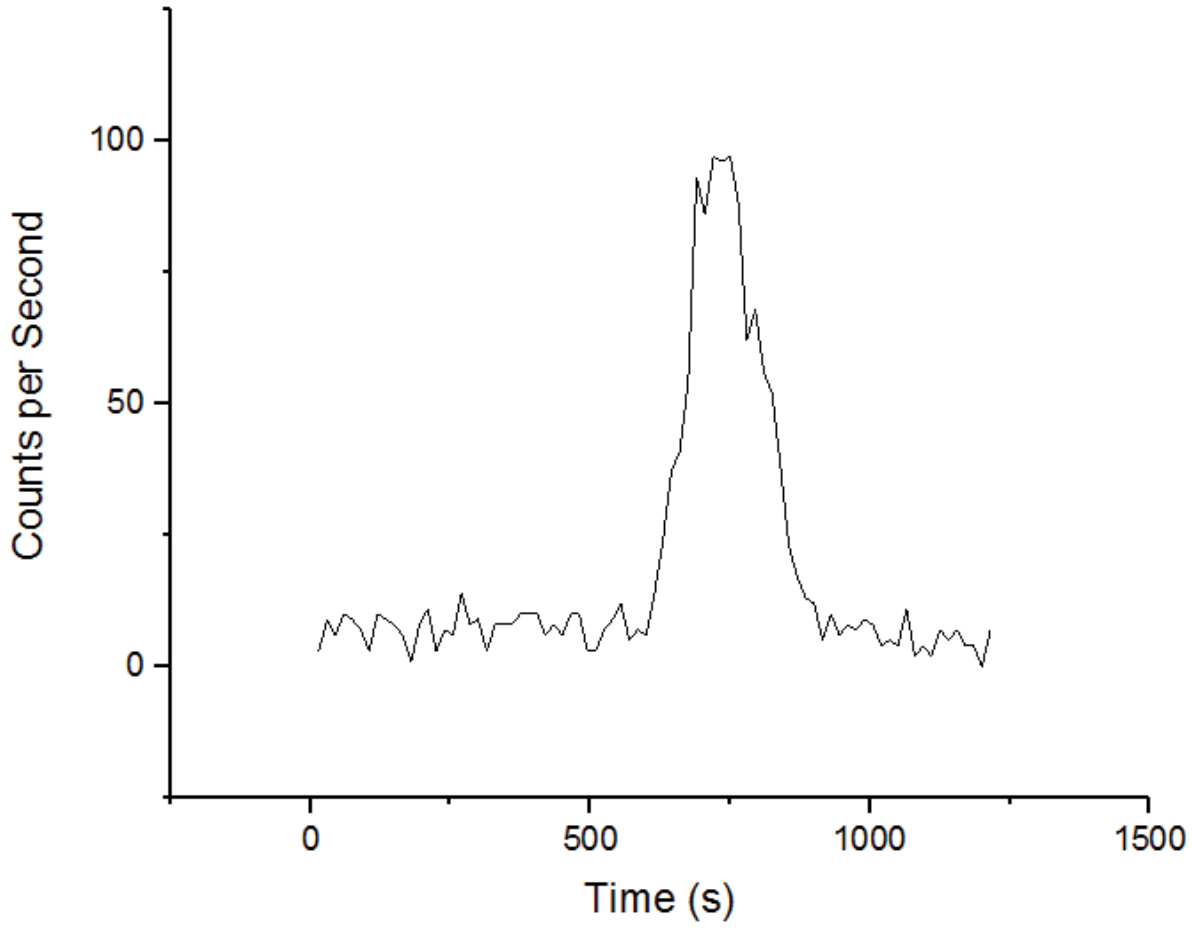

Figure 8. The elution curve of the ^{221}Fr for the Isolute SCX-2 column when washed with 0.5 M HCl. The data was collected with a Kromek GR1 CZT detector inline with flow out of the column. The discontinuity in the tail of the curve was created when the column flow was stopped to change fractions.

indicating symmetry. The tailing factor for the elution of Fr^+ curve in Figure 8 is 1.16 and the skew of the curve is 0.082. Because of the symmetry of the elution curve it was assumed that the Fr^+ was in equilibrium with the resin during the elution.

The organic ion exchange materials exhibited increasing K_D values as the ions increased in atomic number, showing the pattern for the distribution coefficients to be $Li^+<Na^+<K^+<Rb^+<Cs^+$. This result can be explained by the complexation of the alkali metals cations by water. The smaller and denser alkali metal cations strongly orient the water molecules around them.[5] The larger more polarizable alkali metal cations are unable to form these strong hydration shells. These weaker hydration shells can have two effects. The smaller number of water molecules and the relative weakness with which they orient around the cations allow the larger alkali metal cations to have a greater attraction to the ion exchange sites on the resin than the smaller ions with strongly oriented hydration shells.[6] The highly hydrated smaller alkali metal cations may also have difficulty entering into the resin to gain access to the ion exchange sites due to being rejected by the hydrophobic properties of the polystyrene structure. This effect can be compounded by the inability of the crosslinked resin to swell and allow access to the hydrated cations. Without the ability to gain access to the ion exchange sites the cations are not retained by the resin.

In contrast to the organic resins the K_D values for the ion exchange between the alkali metal cations and Isolute SCX-2 ranged from 2.5 to 8.8 mL/g, with the selectivity's in the order: $Li^+<Rb^+<Fr^+<Cs^+<K^+<Na^+$. This is similar to the results using a high-charge-density fluorophlogopite mica, Na-4-mica resin which had selectivity's in the order: $Li^+<Cs^+<K^+<Na^+$.[10] Selectivity increased from Fr^+ to Cs^+ to K^+ to Na^+ as the density of the ion increased. Li^+ had the lowest selectivity for the resin suggesting the high level of hydration could be too much even for a hydrophilic resin. Rb^+ did not follow the overall trend shown by the other alkali metals, which is likely due to an unknown error in the procedure. The hydrophilic nature of the resin allows the hydrated ions entrance into the resin giving access to the ion exchange sites. Without the effect of a hydrophobic resin repelling the hydration shells this trend follows the "hard/soft" acid base concept with SO_3^- exchange site acting as a hard base.

Conclusion

The differences in the selectivity's between the alkali metals and the two resins can be explained by the interaction between water and the resins. The hydrophobic resins show consistently lower selectivity for the cations as the hydration level increases. This is not the case for this hydrophilic resin, that show an increase in selectivity going from Fr^+ to Cs^+ to K^+ to Na^+ as the cations increase in density.

References

1. Yeager, H.L. and A. Steck, *Ion Exchange Selectivity and Metal Ion Separations with a Perfluorinated Cation-Exchange Polymer*. Anal Chem, 1979. **51**(7).
2. Strelow, F.W.E., *Quantitative Separation of the Alkali Metals by Cation Exchange Chromatography with BIO-REX 40 Resin*. Anal Chem Acta, 1968. **43**: p. 465.
3. Kim, D.W., et al., *Ion exchange behavior of alkali and alkaline earth metal ions with a sulfonated polystyrene and a novel triazacrown cation exchanger*. Bull. Korean Chem. Soc., 1995. **16**(8).
4. Nelson, F., et al., *Ion exchange procedures VII: Separation of alkali metal ions*. Journal of Chromatography, 1965. **20**.
5. NIghtingale, E.R., *Phenomenological Theory of Ion Solvation. Effective Radii of Hydrated Ions*. J. Phys. Chem, 1959. **63**(9): p. 1381.
6. Fritz, J.S., *Factors affecting selectivity in ion chromatography*. Journal of Chromatography A, 2005. **1085**(1): p. 8-17.
7. Orendorff, C.J., *Structure-Function Relationships in Chromatographic Stationary Phases: Characterization of Existing Phases and Improved Strategies for Materials Fabrication*, in *Chemistry*. 2003, University of Arizona. p. 644.
8. Watson, J.S., *Separation Methods for Waste and Environmental Applications*. 1999, New York: Marcel Dekker, Inc.
9. Hinshaw, J.V., *How Do Your Peaks Measure Up?* LCGP Europe, 2013. **26**(10).
10. Kodama, T. and S. Komarneni, *Alkali metal and alkaline earth metal ion exchange with Na-4-mica prepared by a new synthetic route from kaolinite*. J. Mater. Chem., 1999. **9**: p. 2475-2480.

CHAPTER II: THE PERFORMANCE OF TWO SILICA BASED ION EXCHANGE RESINS IN THE SEPARATION OF ^{213}BI FROM ITS PARENT SOLUTION OF ^{225}AC

Abstract

The performance of two inorganic ion exchange resins, Isolute SCX and Isolute SCX-2, were compared to the performance of the organic resin AG-50X8 in the separation of the radionuclide bismuth-213 from its parent solution of actinium-225. Performance was based on the percent of bismuth-213 available eluted, and the breakthrough of actinium-225. It was found that Isolute SCX and Isolute SCX-2 produced less of the bismuth-213 available on the column. The breakthrough of the actinium-225 for all three columns was well below the toxicity level.

Introduction

Background

The high linear energy transfer (LET) and short range of alpha particle emissions has potential for use in radioimmunotherapy. The short range allows individual cancer cells to be targeted without damaging the surrounding tissue while the high LET insures that much of the energy of the particle will be transferred into the targeted cell. These properties provide potential for use in the treatment of micrometastatic disease, leukemia, and lymphoma.[1] Because of this a wide range of alpha emitting radionuclides have been studied for medical treatments,[2-4] of particular interest is ^{213}Bi.[5-8] ^{213}Bi is one of six daughters of ^{225}Ac, decaying by an 8.4 MeV alpha particle.[2]

The radiolytic damage done to resins can decrease the activity of the desired radionuclide produced by damaging the structure of the resin.[9] The breakdown of the structure comes through bond breakage, oxidation, and gaseous product formation by ionizing radiation.[10] While a number of studies have been conducted separating ^{213}Bi with organic resins such as AG-50X8,[7-9, 11] an inorganic resin could potentially show greater resistance to radiolytic damage.[10] An ion exchange column could act as a generator of ^{213}Bi by storing ^{225}Ac for several days or weeks with the elution of ^{213}Bi when needed. A generator that stored the ^{225}Ac on Eichrom Silica Actinide Resin was developed by Wu et al. to minimize the radiolytic damage to the resin.[12] The ^{213}Bi was eluted with 1.0 M HCl only to be re-adsorbed onto an AG-50X8 column in series with the Silica Actinide Resin column. An inorganic resin that withstood

radiolytic effects and provided similar performance to AG-50X8 could be used as a generator of ^{213}Bi without the need for a second column.

Objective

The goal of this study was to establish if the inorganic resins Isolute SCX and Isolute SCX-2 could be used in place of AG-50X8 to establish an ^{213}Bi generator by adding the ^{225}Ac to the resin column and eluting the ^{213}Bi over several days. The secular equilibrium time for ^{225}Ac and ^{213}Bi is less than 5 hours, therefore it is possible to elute the generator multiple times per day. The performance of two Isolute resins, SCX and SCX-2 are compared in this study with that of AG-50X8.

Experimental

Materials

Isolute SCX and SCX-2 are strong cation exchange resins containing a silica structure. Isolute SCX is functionalized by benzenesulfonic acid bonded to the silica while SCX-2 is functionalized by propylsulfonic acid. Both Isolute resins were purchased from Fisher Scientific. AG-50X8 is a strong cation exchange resin containing a styrene divinylbenzene structure functionalized with sulfonic acid ion exchange sites and was purchased from BioRad.

The ^{225}Ac used in this study was provided courtesy of Dr. Rose Boll at Oak Ridge National Laboratory (ORNL). The ^{225}Ac was received dry and dissolved in 0.1 M HNO_3.

Method

The Isolute SCX-2 column was prepared by mixing the resin with deionized water and pipetting the mixture into the column to a bed volume of 0.5 mL. The resin was conditioned with 4 mL of 1 M Acetic Acid followed by a wash of 4 mL Milli-Q water to the manufacturers recommendations. When the resin is loaded directly with ^{225}Ac it deposits in a layer at the leading edge of the bed subjecting a small volume of resin to intense alpha radiation. The radiolytic damage from the alpha particles can cause the column to clog, leading to failure of the column in 1 to 2 days.[5, 8] To prevent any damage to the resin bed a method similar to that outlined by McDevitt was used.[8] A volume of 0.35 mL of the SCX-2 resin was pipetted out of the column and mixed with 200 μCi of the ^{225}Ac solution and 0.8 mL of

0.1 M HNO_3. The SCX-2 resin and the ^{225}Ac were mixed on a rocker for 25 minutes. The supernatant was then removed and the resin was loaded onto the column and washed with 3 bed volumes of Milli-Q water. The resin in the column was stored overnight in 1 mL of deionized water.

The Isolute SCX resin was received in a 3-mL column with a bed volume of 0.5 mL. The SCX resin was conditioned with 4 mL of 1 M acetic acid then washed with 4 mL of deionized water. A volume of 0.35 mL of the resin was then mixed with 200 μCi of ^{225}Ac in the same procedure as the Isolute SCX-2. The column was washed with 3 bed volumes of deionized water and stored overnight in 1 mL of deionized water.

The column containing the AG-50X8 column was prepared by mixing the resin with deionized water and pipetting the mixture into the column to a bed volume of 0.6 mL. The resin was conditioned with 4 mL of 8 M HNO_3. A volume of 0.4 mL of the resin was mixed with 200 μCi of ^{225}Ac in the same procedure as the Isolute SCX and SCX-2. The column was washed with 1.5 mL of deionized water and stored overnight in 1 mL of water.

The ^{213}Bi in the Isolute SCX-2 column was eluted with 1 bed volume of 0.1 M KI/HCl in the mornings of the 1st and 4th days after adding the ^{225}Ac. Additional elution's of ^{213}Bi with 0.1 M KI/HCl were done in the afternoon of the 2nd and 3rd days after the column had reached secular equilibrium. The ^{213}Bi in the Isolute SCX and the AG-50X8 were eluted with 0.1M KI/HCl once per day over 4 consecutive days. All elution's were by gravity flow and the volume of the fractions collected were 0.5 mL. The samples were analyzed with a Kromek GR1 CZT inline detector with Multispect software while being eluted and a high-purity germanium gamma detector (HPGe) with Genie software immediately after elution. The fractions collected were analyzed for 10 minutes with the HPGe using the gamma energy peak at 440 KeV to determine the activity of the ^{213}Bi in the fraction. The ^{225}Ac breakthrough in the peak fractions were analyzed several days after the elution when the ^{213}Bi eluted from the column had decayed. The activity of the ^{213}Bi in secular equilibrium with the ^{225}Ac was analyzed with the HPGe detector and the ^{225}Ac breakthrough at the time of the elution was calculated with the exponential decay equation.

Table 2. The average production of 213Bi, breakthrough of 225Ac, distribution coefficients of ^{213}Bi and the percent of ^{213}Bi eluted in the two peak fractions.

Resin	Isolute SCX-2	Isolute SCX	AG-50X8
^{213}Bi Recovered	67% ± 9%	72% ± 1%	85% ± 6%
^{225}Ac Breakthrough	0.002% ± 0.002%	0.002% ± 0.002%	0.01% ± 0.02%
K_D of ^{213}Bi (mL/g)	1.6 ± 0.6	1.20 ± 0.09	0.4 ± 0.2
^{213}Bi in the two peak fractions	96% ± 5%	94% ± 1%	96% ± 1%

Results and Discussion

^{213}Bi Production

Table 2 shows the production of ^{213}Bi (activity of ^{213}Bi eluted from column) over several days for Isolute SCX-2, Isolute SCX and AG-50X8. The production is given as the percent of the ^{213}Bi available on the column that was eluted. The ^{213}Bi was generated *in situ* from the ^{225}Ac on the column. An average of 67% ± 9% of the ^{213}Bi in secular equilibrium with the ^{225}Ac on the column was eluted from the Isolute SCX-2 column, an average of 72% ± 1% from the Isolute SCX column and an average of 85% ± 6% from the AG-50X8 column. The uncertainties here and in subsequent paragraphs are the standard deviation between the different values in the fractions.

The clinical dose of ^{213}Bi necessary for treatment is dependent on the treatment. A study by Beck et al. found a dose of 1.85 MBq (50 μCi) to be the most effective in treating gastric cancer in nude mice while Aghevlian et al. extended the survival of mice with disseminated 5T33 myeloma cells with doses of 3.7 or 7.4 MBq (100 or 200 μCi).[13, 14] Assuming an average mass of the mice to be 25 grams this dose equates to 2 mCi/kg for the Beck study and 5 or 10 mCi/kg for the Aghevlian study. Leukemia patients were treated with 10.4 to 37.0 MBq/kg (280 μCi/kg to 1 mCi/kg) in a trial by Jurcic.[15] Due to the differences in these values an activity of 24 mCi is used as the basis for production, which is based on work by McDevitt.[8] To produce an average activity of 24 mCi of ^{213}Bi Isolute SCX-2 would require 34.8 mCi of ^{225}Ac on the column, the Isolute SCX would require 34.3 mCi and the AG-50X8 would require 28.6 mCi.

Breakthrough of ^{225}Ac

The breakthrough of ^{225}Ac during the separation process presents several potentially negative effects. The ^{225}Ac will compete with the ^{213}Bi during the radiolabeling process. If administered to the patient the decay of ^{225}Ac could break the chemical bond attaching it to the targeting antibody.[16] Without this antibody for targeting cancer cells the daughter radionuclides of ^{225}Ac could distribute throughout the body, potentially causing harm. The nonchelated ^{225}Ac injected could distribute to the liver and skeleton where it will undergo a series of radioactive decays, potentially causing damage to its surroundings.[17] The predicted administered dose of ^{225}Ac causing toxicity was estimated by Sgouros to be 2-3 mCi.[16] The breakthrough of the ^{225}Ac is shown in Table 2. The average breakthrough for Isolute SCX-2 was 0.002% ± 0.002% of what was on the column, the average for Isolute SCX was 0.002% ± 0.002% and the average for the AG-50X8 was 0.01% ± 0.02%. Using the maximum of the uncertainty in the averages an Isolute SCX-2 column producing a dose of 24 mCi of ^{213}Bi would have an ^{221}Ac breakthrough of 1 μCi, an Isolute SCX column would have a breakthrough of 80 μCi and an AG-50X8 would have a breakthrough of 8 μCi.

Distribution Coefficients and Separation Factors

The distribution coefficient (K_D) is defined as the concentration of the ion on the resin divided by the concentration in the solution. Ions that remain attached to the resin will have a higher K_D value while ions that tend to remain in the liquid will have a lower K_D value. In most cases a value of $K_D > 1{,}000$ indicates the ion is retained by the resin while a value of $K_D < 1$ indicates the removal of the ion from the resin.[18] The K_D values for the elution of ^{213}Bi can be seen in Table 2. The average K_D value for Isolute SCX-2 was 1.6 ± 0.6 mL/g, the average for Isolute SCX was 1.20 ± 0.09 ml/g and the average for AG-50X8 was 0.4 ± 0.2 mL/g.

The separation factor (α) between two ions is the ratio between the distribution coefficients and is the relative retention value between the two ions.[19] Values of $\alpha > 10^4$ show a sharp separation between two ions. The α values between ^{225}Ac and ^{213}Bi were on average 4.22×10^5 for Isolute SCX-2, 1.68×10^6 for Isolute SCX and 3.74×10^4 for AG-50X8.

Elution Curves

Typical elution curves for Isolute SCX-2, Isolute SCX and AG-50X8 using gravity flow can be seen in Figures 9, 10, and 11. The curves were produced from data taken by a Kromek GR1 CZT gamma detector inline with the flow out of the column. The activity of the ^{213}Bi is shown by the ordinate while the abscissa represents the time elapsed from opening of the stopcock of the column. The elution curves show little activity of ^{213}Bi outside of the peak. This was confirmed by the analysis of the column fractions with the HPGe detector that showed most of the ^{213}Bi eluted was contained in two fractions. The percentage of all the ^{213}Bi eluted found in the two peak fractions is in Table 2 for each resin. Over all the elution's the Isolute SCX-2 averaged 96% ± 5% of the ^{213}Bi in the two peak fractions, the Isolute SCX averaged 94% ± 1% and the AG-50X8 averaged 96% ± 1%.

Conclusion

The goal of the study was to ascertain if Isolute SCX-2 and Isolute SCX could be used to separate ^{213}Bi from its parent ^{225}Ac solution for radioimmunotherapy. The two inorganic resins would require 20% more ^{225}Ac to produce a clinical dose of 24 mCi of ^{213}Bi. The breakthrough of the ^{225}Ac was orders of magnitude less than the toxicity level and there was a high level of separation between the ^{225}Ac and ^{213}Bi for all the resins used. The Isolute SCX and Isolute SCX-2 have proven capable of producing ^{213}Bi for clinical use. Future work will focus on if the Isolute SCX-2 and Isolute SCX resins show greater resistance to radiolytic damage than AG-50X8.

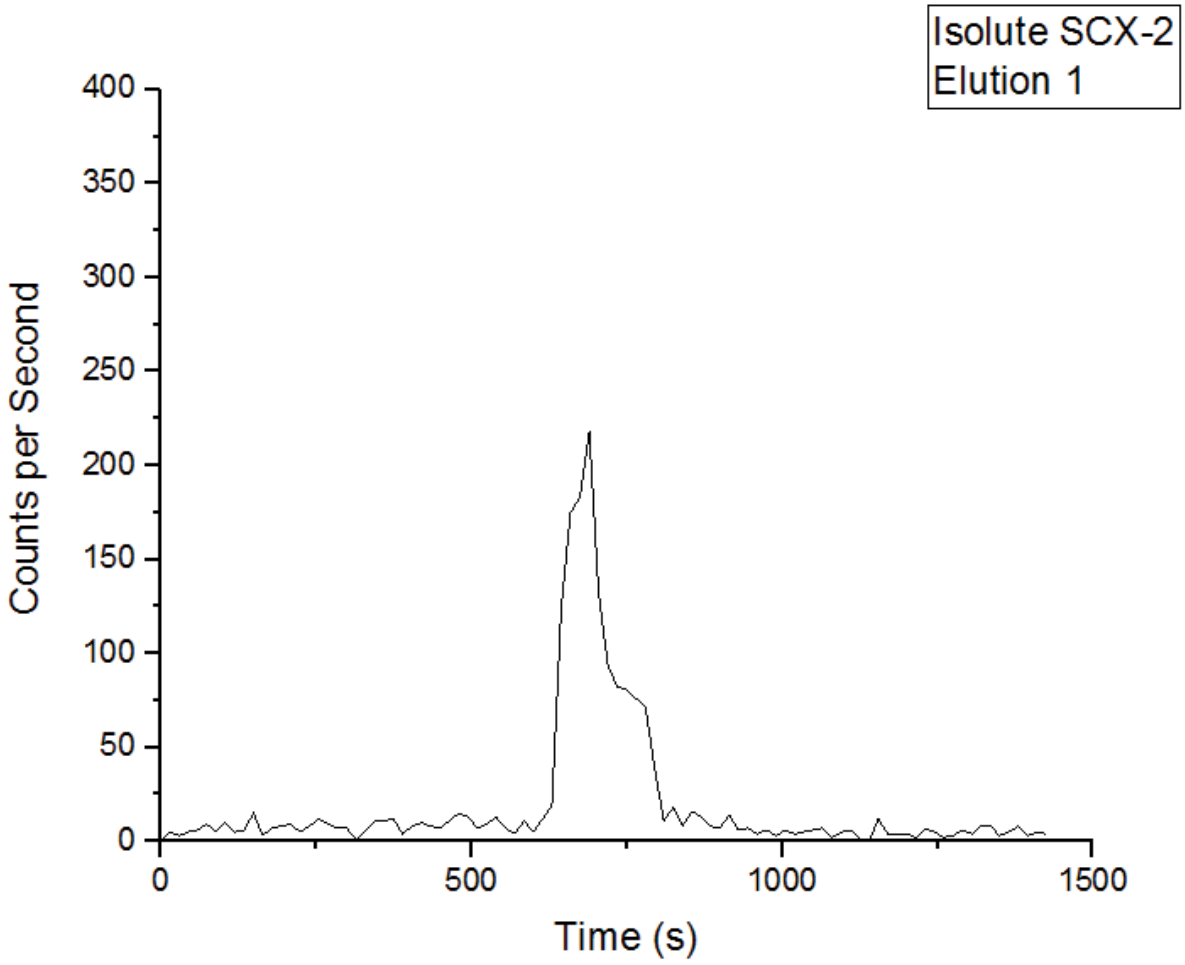

Figure 9. Typical elution curve for the Isolute SCX-2 taken with a Kromek GR1 CZT detector inline with flow out of the column. The discontinuity in the tail of the curves was created when the column flow was stopped to change fractions.

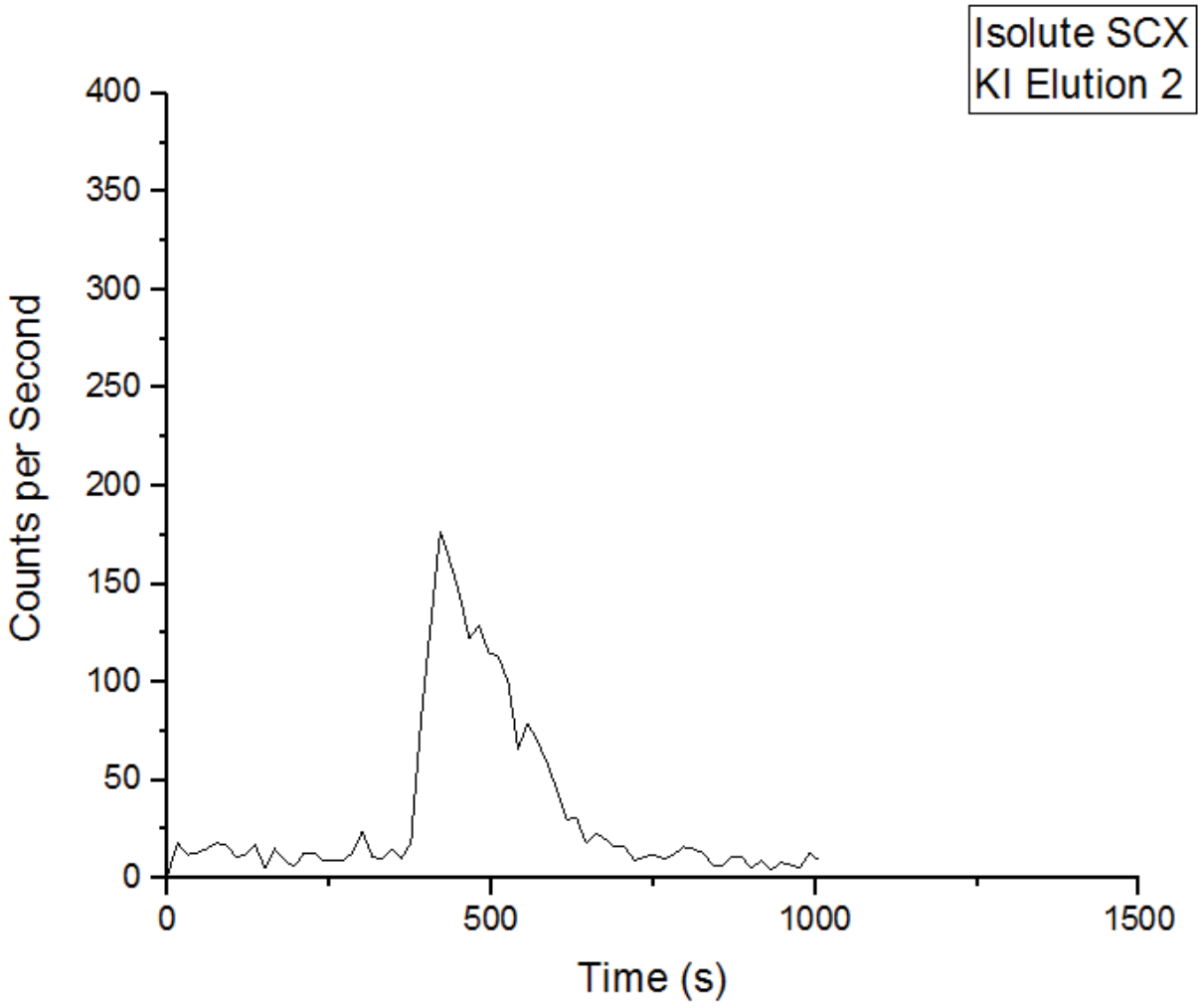

Figure 10. Typical elution curve for the Isolute SCX taken with a Kromek GR1 CZT detector inline with flow out of the column. The discontinuity in the tail of the curves was created when the column flow was stopped to change fractions.

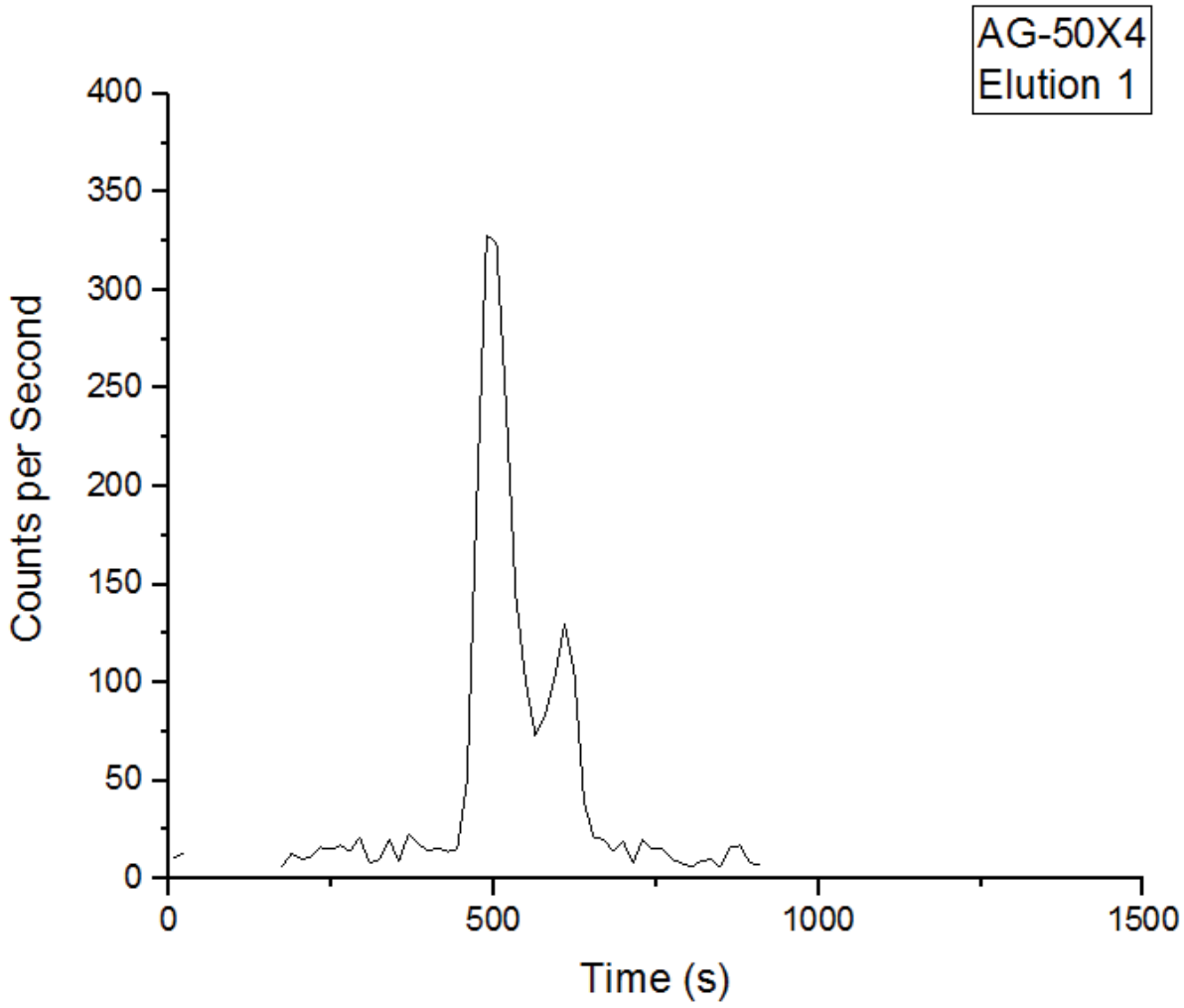

Figure 11. Typical elution curve AG-50X8 column taken with a Kromek GR1 CZT detector inline with flow out of the column. The discontinuity in the tail of the curves was created when the column flow was stopped to change fractions.

References

1. Imam, S., *Advancements in Cancer Therapy with Alpha-Emitters: A Review*. Int. J. Radiat. Oncol. Biol. Phys., 2001. **51**(1): p. 271-278.
2. Mirzadeh, S., *Generator-produced alpha-emitters*. Appl. Radiat. Isot., 1998. **49**: p. 345-349.
3. Feinendegen, L. and J. McClure, *Alpha-Emitters for Medical Therapy - Workshop of the United States Department of Energy*. Radiat. Res., 1996. **148**.
4. Huneke, R., et al., *Effective Alpha-Particle-mediated Radioimmunotherapy of Murine Leukemia*. Cancer Res., 1992. **52**: p. 5818-5820.
5. Bray, L.A., et al., *Development of a unique bismuth automated generator*. Ind. Eng. Chem. Res., 2000(39): p. 3189-3194.
6. Geerlings, M.W., *Method for preparing 213Bi for therapeutic use*. 1997, Akzo Nobel N.V.
7. Guseva, L.I. and N.N. Dogadkin, *Development of a tandem generator system 229Th/225Ac/213Bi for repeated production of short-lived α-emitting radionuclides*. Radiochemistry, 2009. **51**(2): p. 169-174.
8. McDevitt, M.R., et al., *An 225Ac/213Bi generator system for therapeutic clinical applications: construction and operation*. Appl Radiat Isot, 1999. **50**: p. 895-904.
9. McAlister, D.R. and E. Philip Horwitz, *Automated two column generator systems for medical radionuclides*. Appl Radiat Isot, 2009. **67**(11): p. 1985-91.
10. Pillay, S., *Review of the radiation stability of ion exchange materials*. J Radioanal Nucl Ch, 1986. **102**(1): p. 247-268.
11. Dangshe, M., et al., *Rapid preparation of short-lived alpha particle emitting radioimmunopharmaceuticals*. Appl Radiat Isotopes, 2001. **55**: p. 463-470.
12. Wu, C., M. Brechbiel, and O. Gansow, *An Improved Generator for the Production of 213Bi from 225Ac*. Radiochim Acta, 1997. **79**(2).
13. Beck, R., et al., *213Bi-radioimmunotherapy defeats early-stage disseminated gastric cancer in nude mice*. Cancer Sci, 2007. **98**(8): p. 1215-22.
14. Aghevlian, S., A.J. Boyle, and R.M. Reilly, *Radioimmunotherapy of cancer with high linear energy transfer (LET) radiation delivered by radionuclides emitting alpha-particles or Auger electrons*. Adv Drug Deliv Rev, 2017. **109**: p. 102-118.
15. Jurcic, J., et al., *Targeted alpha particle immunotherapy for myeloid leukemia*. Blood, 2002. **100**.
16. Sgouros, G., *Long-lived Alpha Emitters in Radioimmunotherapy: The Mischievous Progeny*. Cancer Biother Radio, 2000. **15**(3): p. 235-244.
17. Davis, I.A., et al., *Comparison of 225Actinium Chelates Tissue Distribttion and Radiotoxicity*. Nucl Med Biol, 1999. **26**.
18. Dudas, F.O. *Ion Exchange Chromatography*. MIT OpenCourseWar 2011 [cited 2017 April 18]; Available from: https://ocw.mit.edu/courses/earth-atmospheric-and-planetary-sciences/12-119-analytical-techniques-for-studying-environmental-and-geologic-samples-spring-2011/labs/MIT12_119S11_Ion_Exchange.pdf.
19. Ettre, L.S., *Nomenclature for chromatography*. Pure & Appl. Chem., 1993. **65**(4).

CHAPTER III: A COMPARISON OF THE STABILITY OF AG-50X8, ISOLUTE SCX AND ISOLUTE SCX-2 ION EXCHANGE RESINS WHEN SUBJECTED TO *IN SITU* RADIATION FROM AN ^{225}AC SOLUTION.

Abstract

A study on the radiolytic damage suffered by ion exchange resins when loaded with actinium-225. Tests showed that Isolute SCX and Isolute SCX-2 suffered less apparent damage from radiation generated *in situ* than AG-50X8. Discoloration due to radiation damage was more apparent with the AG-50X8 resin than the Isolute SCX or Isolute SCX-2 resin beds. Radiation imaging of the resin beds also showed a greater migration of the radionuclides down the beds of the Isolute resins.

Introduction

Studies using ion exchange resins for the separation of radionuclides show promise for their use in radiotherapy. The short range and high linear energy transfer of alpha particles are particularly useful for the targeting of individual cancer cells.[1-5] One of the challenges associated with the use of organic ion exchange resins in the separation of alpha emitters is the damage to the resins from the radiation, which could lead to a decrease in yield and can limit the capacity of the generator.[6] Ion exchange resins consist of an inert material (the structure) to which is bonded a functional group that participates in the ion exchange. The structure of the ion exchange resin typically marketed as small, spherical beads.[7] Radiolytic effects on organic ion exchange resins include breaking of the bond between the functional group and the structure, formation of free radicals, chain scission and chain crosslinking.[8, 9] The rupture of functional groups in styrene divinylbenzene by radiation causes weight loss due to the evolution of gaseous products.[8] Radiolytic damage to the resin beads result in the darkening of their color going from amber to brown, dark red and eventually black.[8]

Damage to silica from radiation occurs on the surface as well as in the lattice structure itself. Particle radiation of sufficient energy can displace silicon atoms from its lattice structure, creating a vacancy/interstitial pair.[10] Ionizing radiation can also displace electrons in silica, forming electron/hole pairs.[11] The defect centers from displaced silicon atoms and electron/hole pairs can cause paramagnetic centers to be produced, alter the thermal conductivity, and change the density of the silica.[11] Kazansky et. al reported formation of stable hydrogen atoms on the surface layer of silica-gel caused by the scission of OH bonds by gamma radiation.[12] While inorganic resins have proven to be

more resistant to radiation than organic resins, damage to inorganic resins can occur from pH changes and radiolytic products caused by radiolysis of other materials.[8]

The purpose of this study was to examine the stability and performance of inorganic and organic resins when subjected to an *in situ* radiation source over a period of days. Microfluidic beds (described in the experimental section) of the inorganic resins Isolute SCX and Isolute SCX-2 and the organic resin AG-50X8 were loaded with a 100 μCi solution of ^{225}Ac and its daughters. Photographs and radiation images were taken over 2 weeks to monitor the damage to the different resins. After the resin beds were washed with 0.1 M HNO_3 periodically. The washes were collected and analyzed with a high purity germanium detector (HPGe) after 4 weeks.

Experimental

Isolute SCX and SCX-2 are strong cation exchange resins containing a silica structure, AG-50X8 is a strong cation exchange resin with a styrene-divinylbenzene structure. Isolute SCX is functionalized by benzenesulfonic acid, Isolute SCX-2 with propylsulfonic acid and the sulfonic acid is bonded directly to the structure in AG-50X8. The microfluidic devices (MFD) consist of a 10 μL channel molded into polydimethylsiloxane (PDMS) that is in turn bonded to a glass slide. To prepare the resin beds each of the resins was mixed with deionized water and pipetted into a MFD. The Isolute SCX and Isolute SCX-2 have an average particle size of 50 μm and the AG-50X8 resin used was 200-400 mesh. The resins used were each separated with a sieve to give particle sizes between 40 and 70 μm.

The ^{225}Ac was obtained from Dr. Rose Ball at Oak Ridge National Laboratory. The ^{225}Ac was received as a dry nitrate and dissolved in 0.1 M HNO_3. Each MFD was loaded with approximately 100 μCi of the ^{225}Ac solution. The absorbed dose of radiation for the MFD resin beds was approximately 3 Gy/s (3 joules per kilogram per second) when loaded with 200 mCi of ^{225}Ac in secular equilibrium with its daughters. A resin bed comparable to that used by McDevitt et. al to produce a clinical dose of ^{213}Bi would have an absorbed dose of about 21 Gy/s.

Over a two-week period, microscopic images were taken of the resin beds at several different magnifications. Over these two weeks each of the microfluidic devices was put in contact with a

Table 3. The full width at half the maximum of the radiation intensity resin bed curves.

Days after Adding the ^{225}Ac	Isolute SCX	Isolute SCX-2	AG-50X8
3	5.48 mm	4.17 mm	4.13 mm
12			5.07 mm
13	7.45 mm	5.73 mm	

phosphor screen for 5 to 10 minutes. The phosphor screen was processed with a Perkins Elmer Cyclone II Imager to obtain images of the radiation on the MFD resin beds.

Results

The radiation images were taken of the MFD's over the course of 2 weeks. The intensity of the radiation on the MFD beds was recorded as both images and values in digital light units (DLU). The values for the radiation intensity along the length of the bed were plotted and are shown with the images in Figures 12-17. To examine the extent to which the radionuclides migrated down the length of the bed the full width of the curves at half their maximum (FWHM) was calculated. The FWHMs of the curves are in Table 3. The decline in the height of the curves from day 3 to day 12 reflect the loss of radionuclides to decay, the increase in width indicates that the radionuclides tend to migrate down the length of the bed over time.

On the 3rd day after adding the ^{225}Ac, the Isolute SCX MFD had a FWHM of 5.48 mm, the Isolute SCX-2 MFD had a FWHM of 4.17 mm and the AG-50X8 MFD had a FWHM of 4.13 mm. The FWHM for the AG-50X8 increased to 5.07 mm on the 12th day after adding the ^{225}Ac. On the 13th day after adding the ^{225}Ac the FWHM for Isolute SCX and Isolute SCX-2 had increased to 7.45 mm and 5.73 mm, respectively. The difference in the FWHM was 19% for AG-50X8, 27% for Isolute SCX-2 and 26% for Isolute SCX. Some of the dispersion in the Isolute SCX-2 bed is likely attributable to a disturbance in the resin bed that occurred when removing air bubbles.

Microscopic images of the resin beds are shown in Figures 18-28. There is a slight change in color for the Isolute SCX and Isolute SCX-2 MFD resin beds. Discontinuities in the resin bed of the

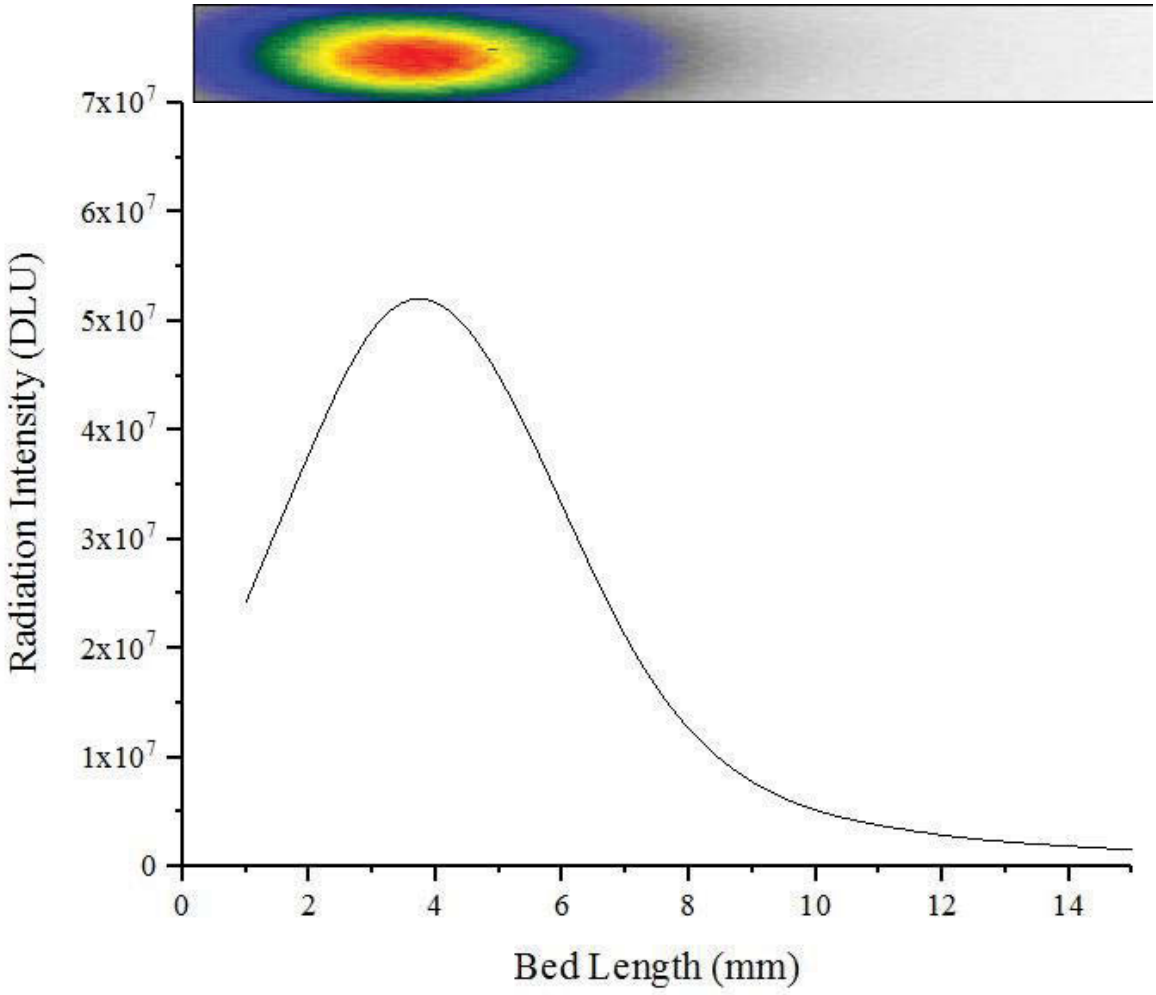

Figure 12. Graph of the radiation intensity along the length of the Isolute SCX MFD on the 3rd day after adding the ^{225}Ac. The image of the radiation intensity is above the graph. The FWHM of the curve is 5.48 mm.

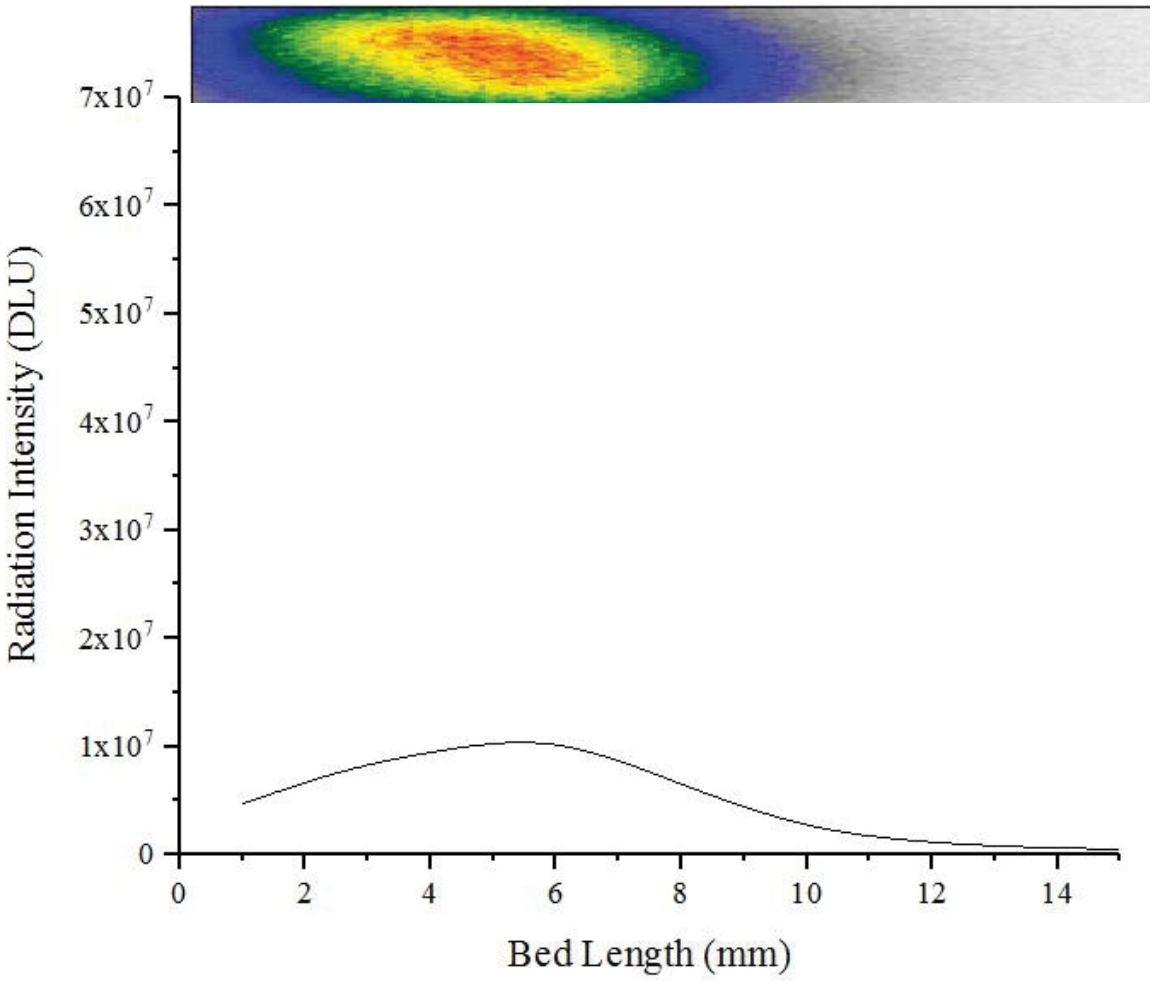

Figure 13. Graph of the radiation intensity along the length of the Isolute SCX MFD on the 13th day after adding the ^{225}Ac. The image of the radiation intensity is above the graph. The loss of activity due to radioactive decay is illustrated by the lower curve peak. The FWHM of the curve is 7.45 mm, indicating migration of some of the radionuclides down the length of the bed.

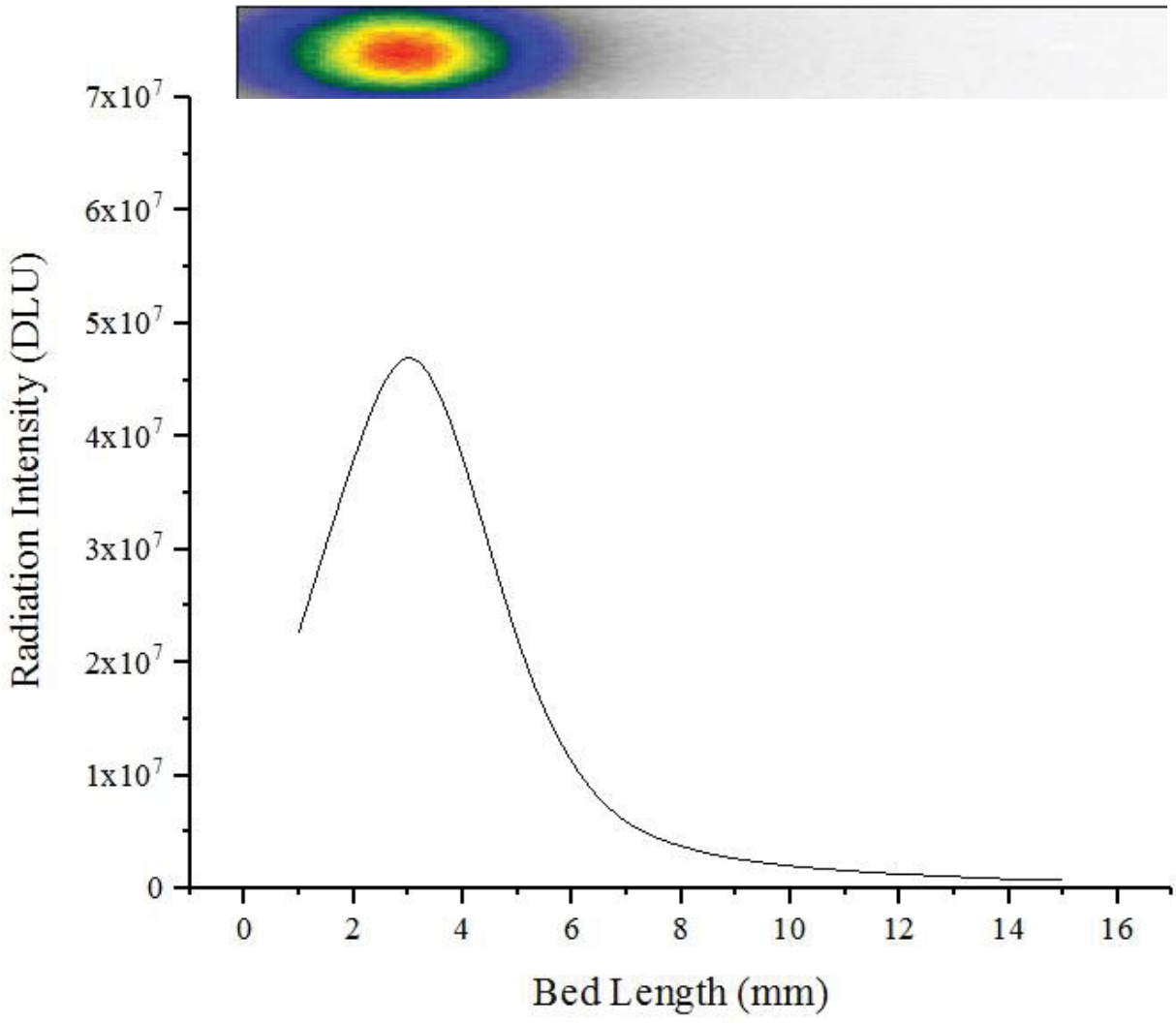

Figure 14. Graph of the radiation intensity along the length of the Isolute SCX-2 MFD on the 3rd day after adding the ^{225}Ac. The image of the radiation intensity is above the graph. The FWHM of the curve is 4.17 mm.

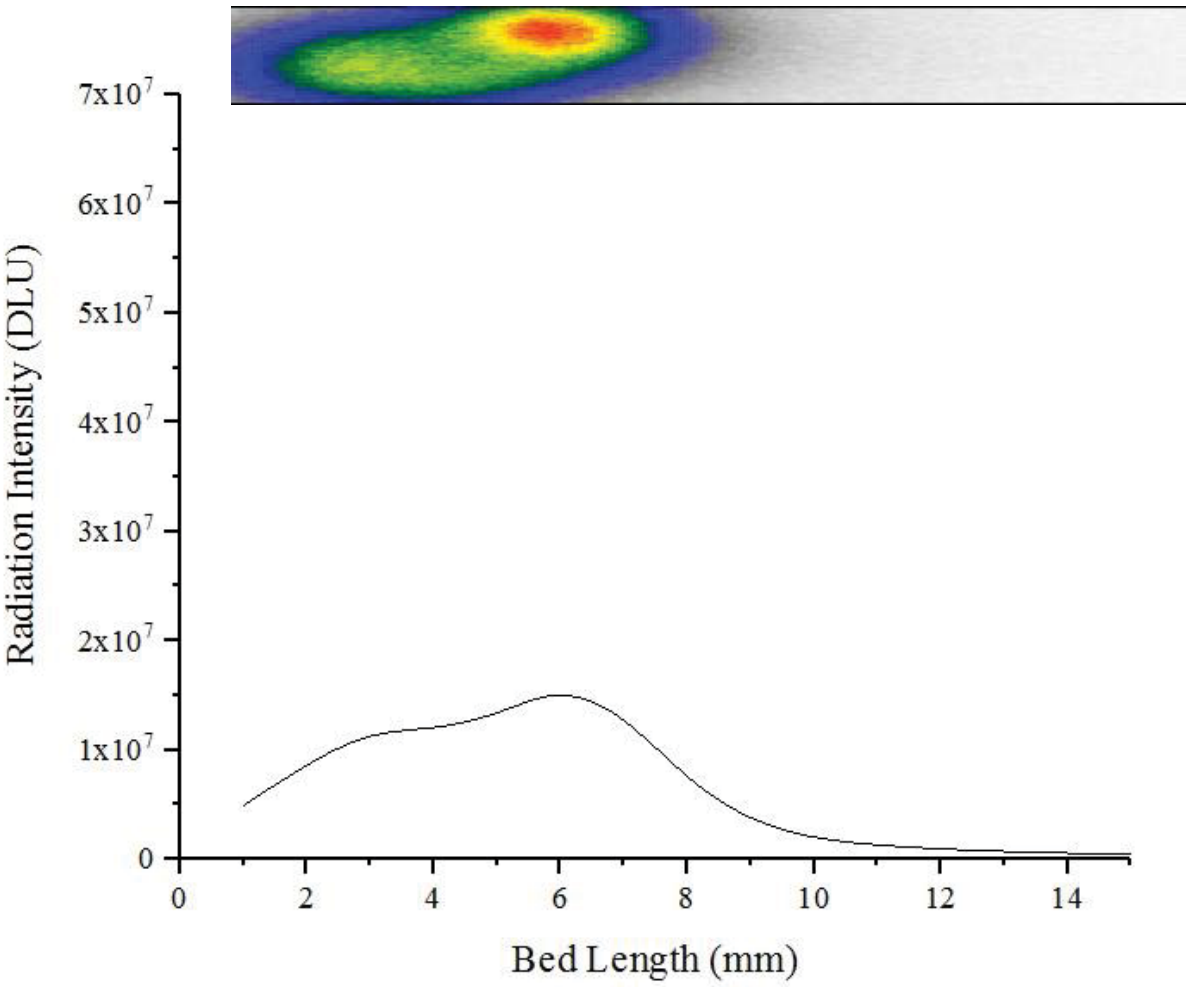

Figure 15. Graph of the radiation intensity along the length of the Isolute SCX MFD on the 13th day after adding the ^{225}Ac. The image of the radiation intensity is above the graph. The discontinuity in the curve is likely caused by disruptions in the resin bed after the removal of air bubbles.

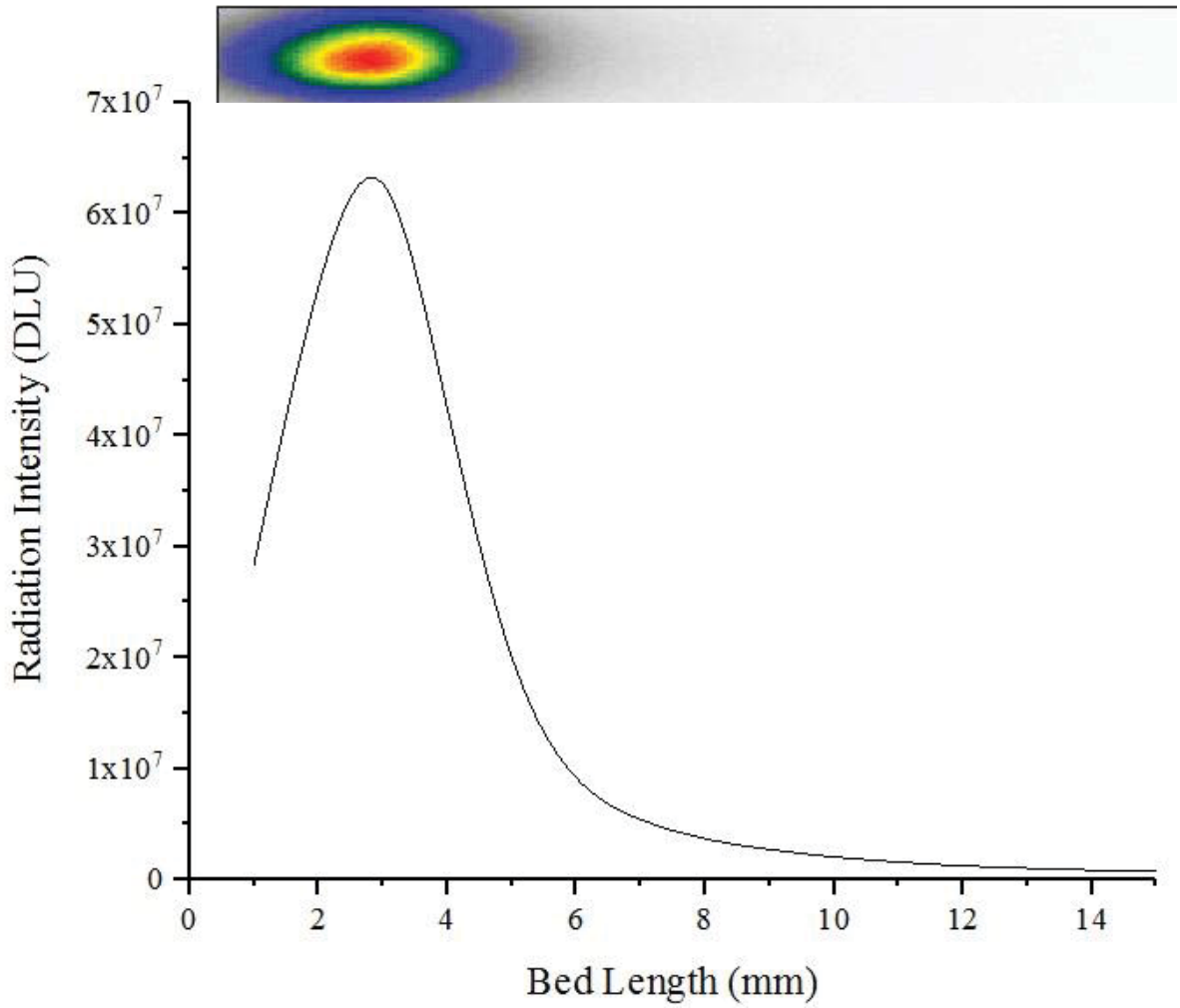

Figure 16. Graph of the radiation intensity along the length of the AG-50X8 on the 3rd day after adding the ^{225}Ac. The image of the radiation intensity is above the graph. The FWHM of the curve is 4.13 mm, lowest among all the MFDs on day 3.

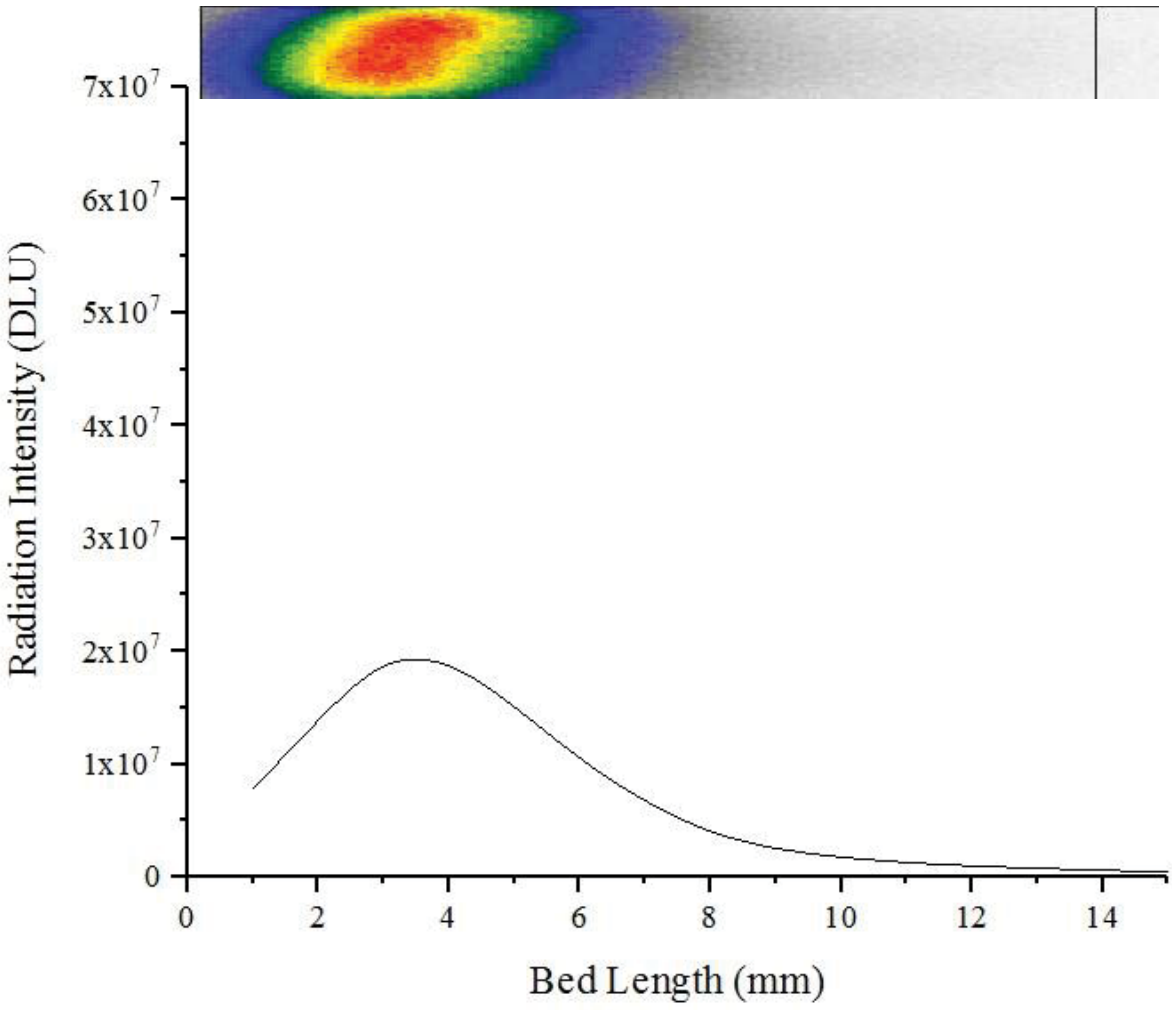

Figure 17. Graph of the radiation intensity along the length of the AG-50X8 MFD on the 12th day after adding the ^{225}Ac. The image of the radiation intensity is above the graph.

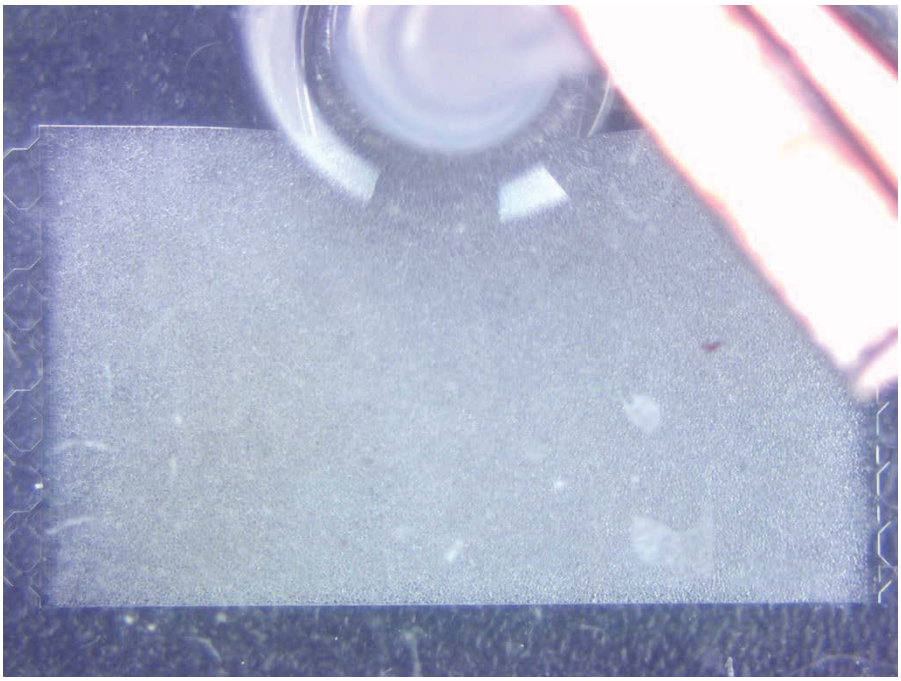

Figure 18. Microscopic picture of Isolute SCX MFD 1 day after adding the ^{225}Ac.

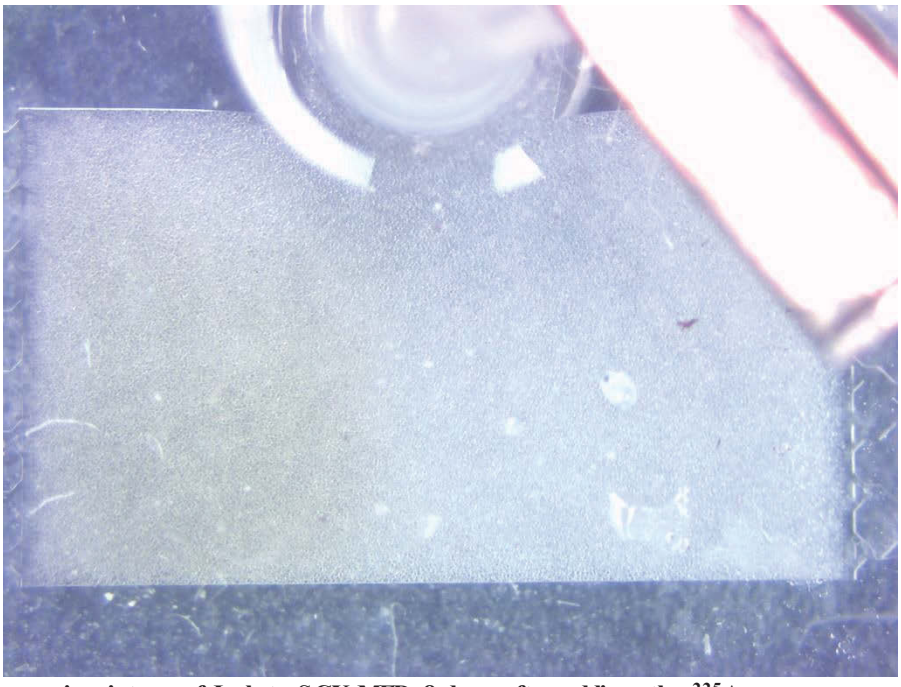

Figure 19. Microscopic picture of Isolute SCX MFD 8 days after adding the ^{225}Ac.

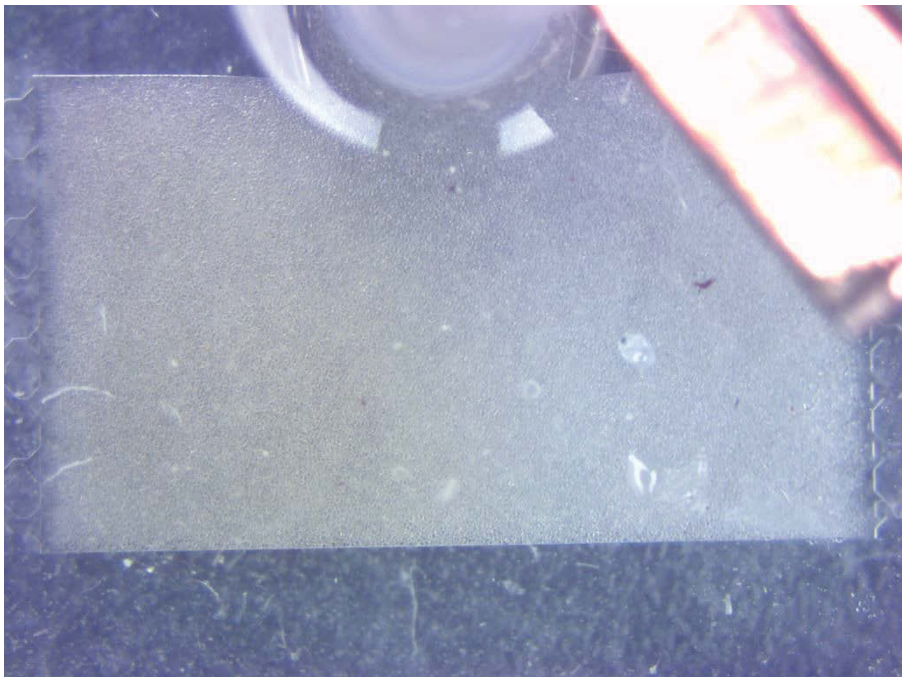

Figure 20. Microscopic picture of Isolute SCX MFD 13 days after adding the ^{225}Ac.

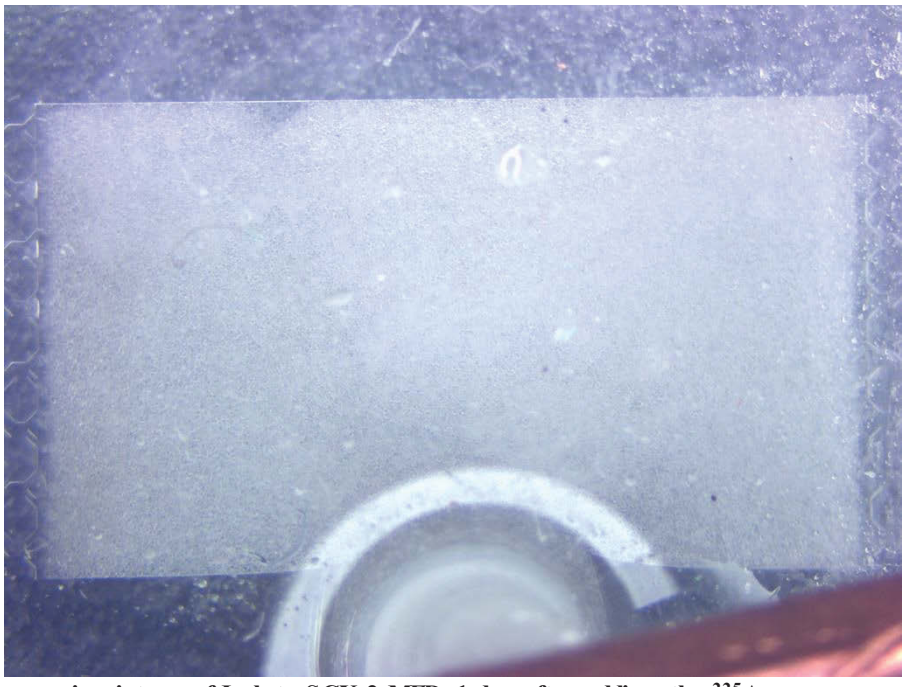

Figure 21. Microscopic picture of Isolute SCX-2 MFD 1 day after adding the ^{225}Ac.

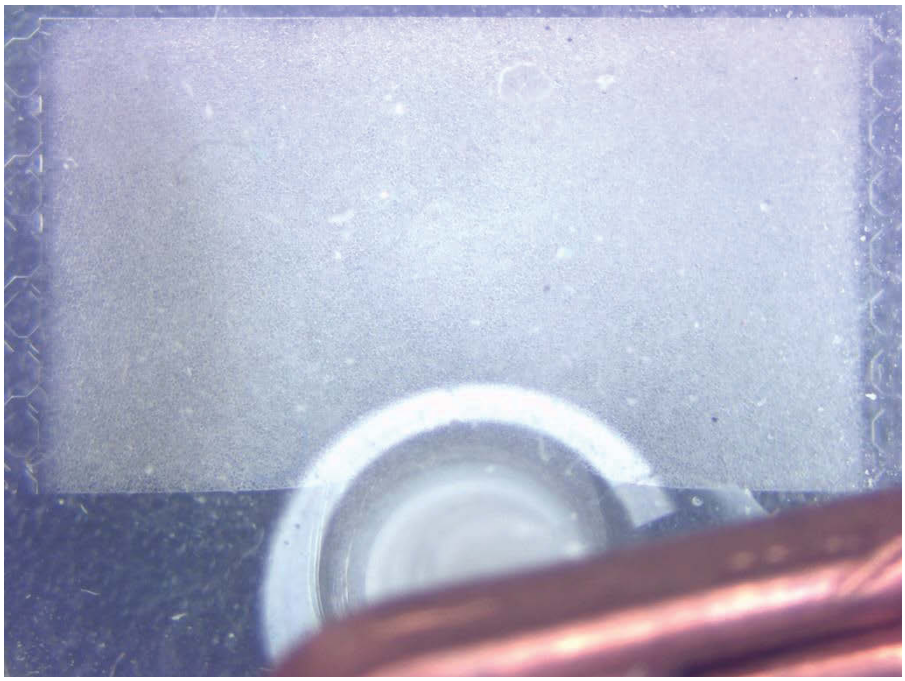

Figure 22. Microscopic picture of Isolute SCX-2 MFD 8 days after adding the ^{225}Ac.

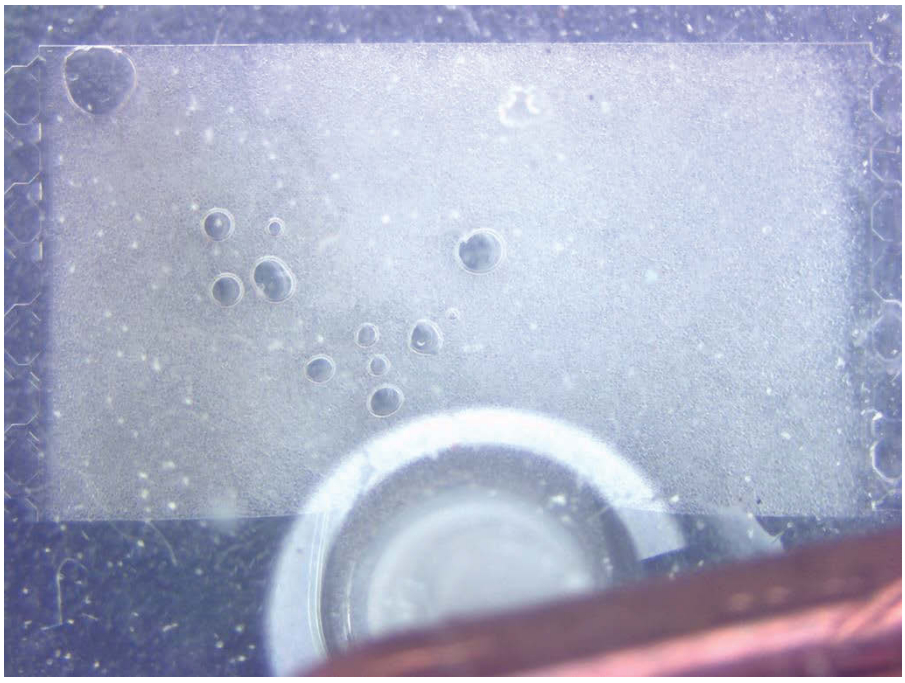

Figure 23. Microscopic picture of Isolute SCX-2 MFD 9 days after adding the ^{225}Ac. Disruptions in the resin bed were created when air bubbles were removed on the 8th day after adding the ^{225}Ac.

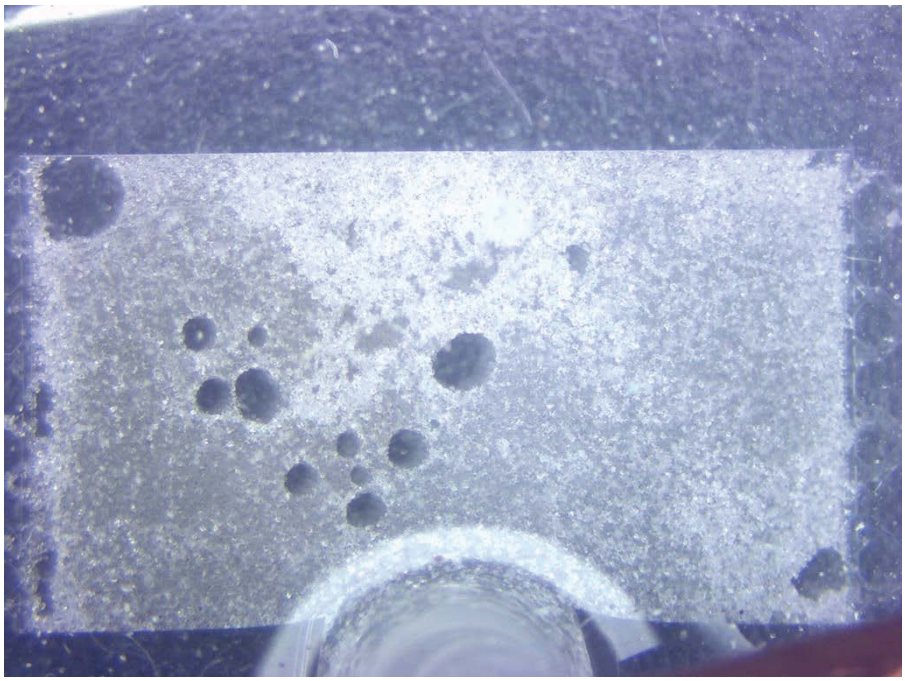

Figure 24. Microscopic picture of Isolute SCX-2 14 days after adding the ^{225}Ac.

Figure 25. Microscopic picture of AG-50X8 1 day after adding the ^{225}Ac.

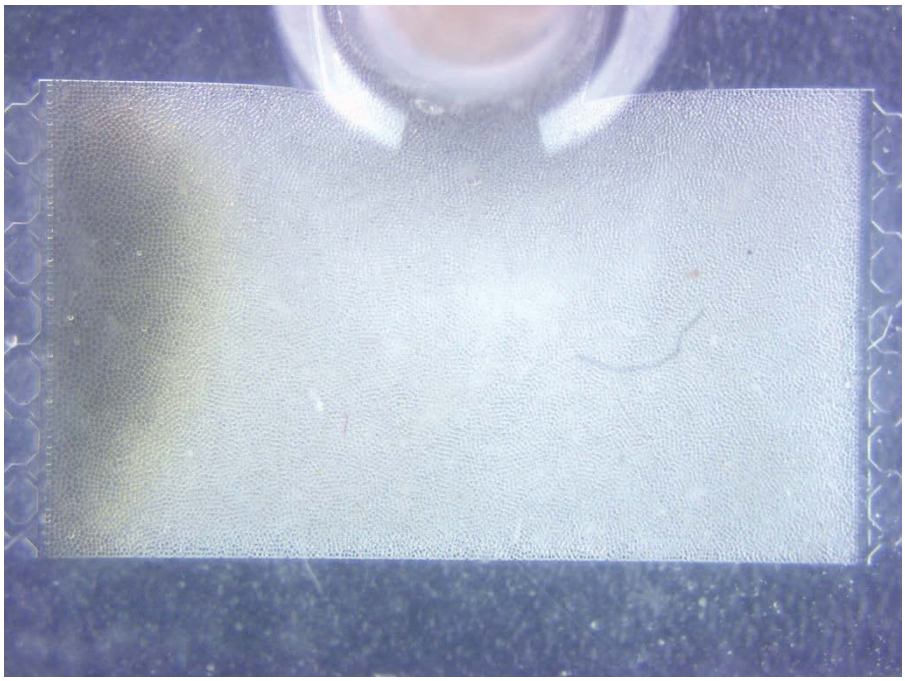

Figure 26. Microscopic picture of AG-50X8 MFD 3 days after adding the ^{225}Ac.

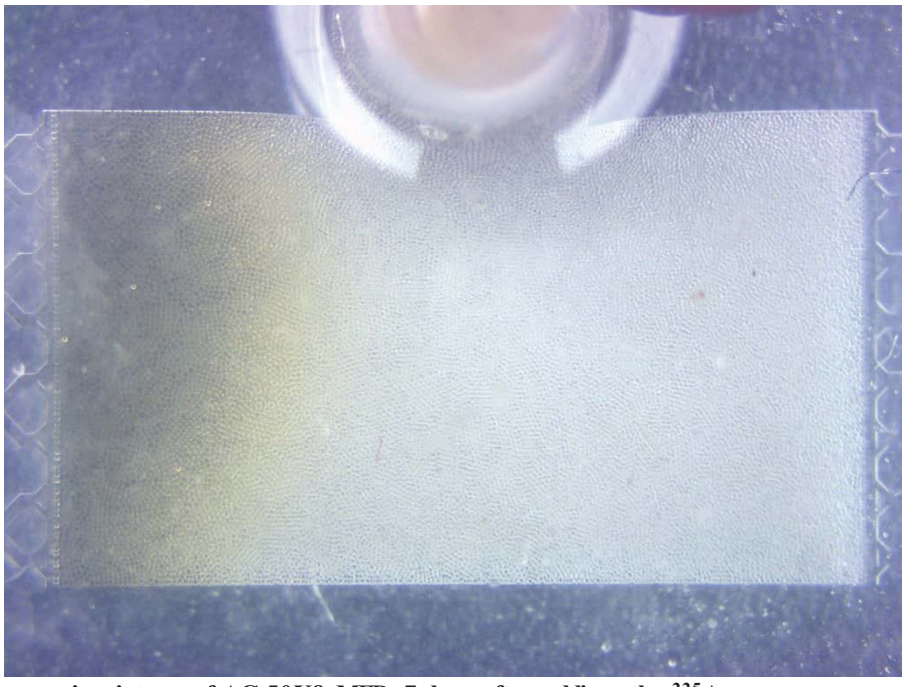

Figure 27. Microscopic picture of AG-50X8 MFD 7 days after adding the ^{225}Ac.

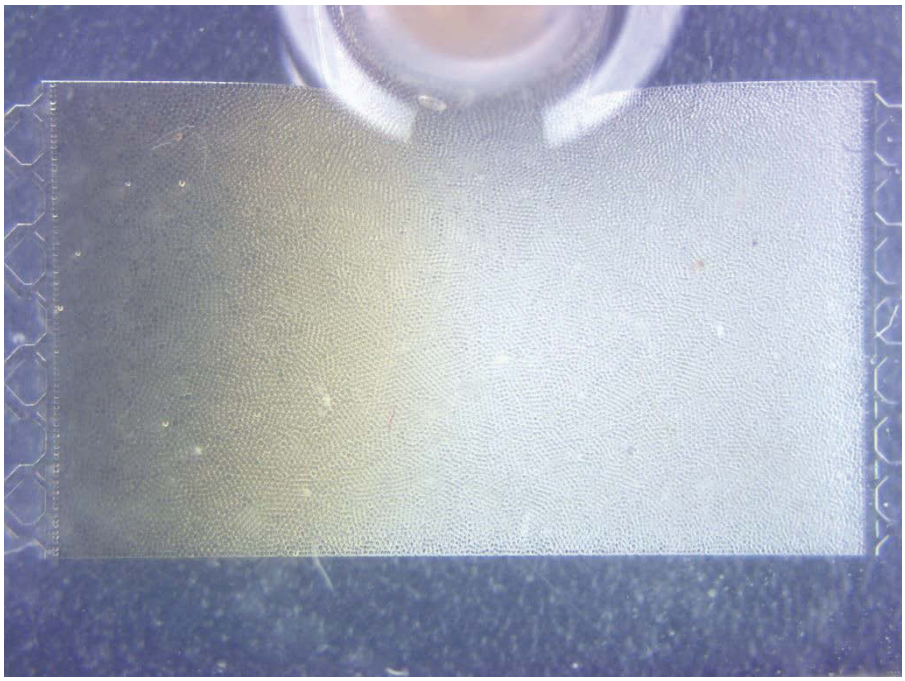

Figure 28. Microscopic picture of AG-50X8 14 days after adding the ^{225}Ac.

Isolute SCX-2 MFD occurred on the 8th day when air bubbles were removed. The MFDs were washed with 1 bed volume of 0.1 M HNO_3 periodically, with the washes collected and analyzed for the activity of ^{213}Bi with the HPGe detector. The results are in Table 4. The ^{225}Ac detected in the wash of the AG-50X8 MFD was less than the lower limit of detection for the HPGe. The Isolute SCX MFD retained 75% of the ^{225}Ac on the bed and Isolute SCX-2 MFD retained 99%. The resin bed of the AG-50X8 MFD shows greater color change than the other two.

Discussion

The larger initial dispersions of the radionuclides on the resin beds of Isolute SCX and Isolute SCX-2 compared to that of AG-50x8 could mitigate the intensity of the radiation that the resin is subjected to. The major source of decay energy for ^{225}Ac and its daughters are alpha particles, which have a high rate of linear energy transfer but short range.[5] This short range limits the volume of resin the radiation energy can reach. If the radionuclides have a wider distribution than the resin beads are less subject to radiation bombardment from multiple sources in the bed. The larger dispersion across the volumes of Isolute SCX and Isolute SCX-2 is likely due to the lower capacity of the inorganic resins. Both Isolute resins have a capacity of 0.6 meq/g while the AG-50x8 has a capacity of 1.7 meq/g.

Table 2. The activity of ^{225}Ac loaded on the resin beds and the ^{213}Bi in the HNO_3 wash 28 days after loading.

	Isolute SCX	Isolute SCX-2	AG-50X8
Activity of ^{225}Ac Loaded on Resin Bed	89.8 μCi	89.8 μCi	92.8 μCi
Activity of ^{225}Ac on Resin Bed Before HNO_3 Wash	19.5 μCi	19.5 μCi	23.2 μCi
Activity of ^{213}Bi in Wash	6.1 μCi	$3.18x10^{-2}$ μCi	0 μCi

The growth in the FWHM of the radiation intensity curves is an indication of the damage done to the resin from the radiation. Damage to the ion exchange site or the structure of the resin bead could cause the radionuclide to detach from the resin and interact with another ion exchange site. Relative to the starting FWHM, the AG-50x8 had the smallest increase in the FWHM. This is likely due to the exchange capacity of the AG-50X8 being almost 3 times that of the two Isolute resins.

The AG-50X8 resin bed showed a greater discoloration than the Isolute SCX or Isolute SCX-2 resin beds. This difference in the tone of the discoloration between the AG-50X8 resin and the Isolute resin could denote greater damage to the structure of the AG-50X8 resin than the Isolute resins. Ultimately, the Isolute SCX-2 performed better than the other two resins. It showed less of a color change in the microscopic images than the AG-50X8, and retained 99% of the radionuclides on the resin.

Conclusion

Isolute SCX and Isolute SCX-2 had a larger dispersion of the radionuclides on the resin which reduces the intensity of the radiation on the resin. They also showed less structural damage than the AG-50X8 resin which had pronounced discoloration. The Isolute SCX resin did not retain ^{213}Bi nearly as well as the Isolute SCX-2 resin, however. With less apparent structural damage than the AG-50X8 resin and better retention of ^{213}Bi the Isolute SCX-2 outperformed the other two resins.

References

1. Imam, S., *Advancements in Cancer Therapy with Alpha-Emitters: A Review*. Int. J. Radiat. Oncol. Biol. Phys., 2001. **51**(1): p. 271-278.
2. Dangshe, M., et al., *Rapid preparation of short-lived alpha particle emitting radioimmunopharmaceuticals*. Appl Radiat Isotopes, 2001. **55**: p. 463-470.
3. Geerlings, M.W., *Method for preparing 213Bi for therapeutic use*. 1997, Akzo Nobel N.V.
4. Guseva, L.I. and N.N. Dogadkin, *Development of a tandem generator system 229Th/225Ac/213Bi for repeated production of short-lived α-emitting radionuclides*. Radiochemistry, 2009. **51**(2): p. 169-174.
5. Mirzadeh, S., *Generator-produced alpha-emitters*. Appl. Radiat. Isot., 1998. **49**: p. 345-349.
6. McAlister, D.R. and E. Philip Horwitz, *Automated two column generator systems for medical radionuclides*. Appl Radiat Isot, 2009. **67**(11): p. 1985-91.
7. Dudas, F.O. *Ion Exchange Chromatography*. MIT OpenCourseWar 2011 [cited 2017 April 18]; Available from: https://ocw.mit.edu/courses/earth-atmospheric-and-planetary-sciences/12-119-analytical-techniques-for-studying-environmental-and-geologic-samples-spring-2011/labs/MIT12_119S11_Ion_Exchange.pdf.
8. Pillay, S., *Review of the radiation stability of ion exchange materials*. J Radioanal Nucl Ch, 1986. **102**(1): p. 247-268.
9. O'Donnell, J.H., *Radiation Chemistry of Polymers*. 1989. **381**: p. 1-13.
10. Honniger, F., *Radiation Damage in Silicon - Defect Analysis and Detector Properties*, in *Physics*. 2007, University of Hamburg: Hamburg, Germany.
11. Arnold, G.W. and W.D. Compton, *Radiation Effects in Silica at Low Temperatures*. Physical Review, 1959. **116**(4): p. 802-811.
12. Kazansky, V.B., G.B. Parisky, and V.V. Voevodsky, *Radiation-Induced Proceses on the Silica-Gel Surface*. Discuss. Faraday Soc., 1961. **31**: p. 203-208.

CONCLUSION

The goal of the study was to ascertain if Isolute SCX-2 and Isolute SCX could be used to separate ^{213}Bi from its parent ^{225}Ac solution for radioimmunotherapy and to determine sorption properties of Fr^+, an important species in the decay chain leading to ^{213}Bi.

In contrast to the organic resins the K_D values for the ion exchange between the alkali metal cations and Isolute SCX-2 ranged from 2.5 to 8.8 L/kg, with the selectivity's in the order: $Li^+<Rb^+<Fr^+<Cs^+<K^+<Na^+$. This is similar to the results using a high-charge-density fluorophlogopite mica, Na-4-mica resin which had selectivity's in the order: $Li^+<Cs^+<K^+<Na^+$.[1] Selectivity increased from Fr^+ to Cs^+ to K^+ to Na^+ as the electron density of the ion increased. Li^+ had the lowest selectivity for the resin suggesting the high level of hydration could be too much even for a hydrophilic resin. Rb^+ did not follow the overall trend shown by the other alkali metals, which is likely due to an unknown error in the procedure. Without the effect of a hydrophobic resin repelling the hydration shells this trend follows the "hard/soft" acid base concept with SO_3^- exchange site acting as a hard base.

The differences in the selectivity between the alkali metals and the resins can be explained by the interaction between water and the resins. The hydrophobic resins reject the cations that are hydrated, showing consistently lower selectivity for the cations as the hydration level increases. This is not the case for a hydrophilic resin, who showed an increase in selectivity going from Fr^+ to Cs^+ to K^+ to Na^+ as the cations increase in electron density.

The two inorganic resins tested (Isolute SCX and Isolute SCX-2) would require 20% more ^{225}Ac to produce a clinical dose of 24 mCi of ^{213}Bi when compared with currently used options. The breakthrough of the ^{225}Ac was orders of magnitude less than the toxicity level and there was a high level of separation between the ^{225}Ac and ^{213}Bi for all the resins used. The Isolute SCX and Isolute SCX-2 have proven capable of producing ^{213}Bi for clinical use. Future work will focus on if the Isolute SCX-2 and Isolute SCX resins show greater resistance to radiolytic damage than AG-50X8.

The Isolute resins showed less apparent structural damage in the microscopic images, with the AG-50x8 resin showing a starker color change. The structural damage to the Isolute resins could have been mitigated by the wider dispersion of the radionuclides across the volume of the resin bed, as seen in

the phosphorus radiation images. The AG-50x8 retained 99% of the radionuclides on the resin bed, likely because the radionuclides moved down the bed to exchange with undamaged sites. This is shown in the increase in the FWHM of the radiation intensity graphs. The Isolute SCX only retained 74% of the radionuclides on the bed, but the Isolute SCX-2 retained 99%. Ultimately, the Isolute SCX-2 performed better than the other two resins. It showed less radiolytic damage in the microscopic images than the AG-50x8 and retained 99% of the radionuclides on the resin. This study has shown the inorganic resins tested (Isolute SCX and Isolute SCX-2) to have acceptable qualities to replace those currently used for capturing and retaining ^{213}Bi.

References

1. Kodama, T. and S. Komarneni, *Alkali metal and alkaline earth metal ion exchange with Na-4-mica prepared by a new synthetic route from kaolinite*. J. Mater. Chem., 1999. **9**: p. 2475-2480.

VITA

Mark Moore was born in Nashville, Tennessee in 1972. He graduated from Oak Ridge High School in Oak Ridge, Tennessee in 1990. Starting in the fall of 1990 he attended the University of Tennessee and received his bachelor's degree in Logistics and Transportation. He returned to the University of Tennessee in 2009 to pursue a degree in Chemical Engineering. As an undergraduate in the Chemical Engineering Department he began work as a research assistant estimating the capital costs of Vanadium Redox-Flow Batteries. He continued this research as a graduate student, receiving his Master of Science in Chemical Engineering in 2014. To complete his studies for his Doctor of Philosophy in Chemical Engineering he partnered with the Nuclear Engineering department under a grant from the National Nuclear Security Administration Stewardship Science Academic Alliances Program researching ion exchange chromatography.