Applied Physics Research; Vol. 7, No. 1; 2015
ISSN 1916-9639 E-ISSN 1916-9647
Published by Canadian Center of Science and Education

Recovery Profiles of Molybdate Solutions Through Varying Dowex™-1 Resin Amounts, and Translation to Mo99/Tc99m Separation

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Received: October 9, 2014 Accepted: November 4, 2014 Online Published: January 21, 2015

doi:10.5539/apr.v7n1p72 URL: http://dx.doi.org/10.5539/apr.v7n1p72

Abstract

The influence of molybdenum concentration and resin amount on the retention of molybdenum in 5M NaOH on Dowex™-1 columns with successive elutions of saline and tetrabutylammonium bromide (TBAB) was investigated. Studies were performed with 45, 75, 125, 175, or 250 mg of resin and at 100 and 250 mg/mL molybdenum concentrations. Initial pass-through molybdenum recoveries from the column were 97.8% at 100 mg/L and 97.8% at 250 mg/mL (n=3 at each resin amount). Molybdenum breakthrough into TBAB solvent was low for all five resin amounts. Values for the 100mg/mL solution were 0.33 – 3.73 ppm, representing 0.0002 - 0.0014% of the original molybdenum load; and were 0.96 - 11.27 ppm for the 250 mg/mL solution, equivalent to 0.0002 – 0.0027%. Breakthrough into TBAB is generally higher with higher resin amounts for both the 100 mg/ml and 250 mg/mL molybdenum concentrations. The resin can be used for high molybdenum loads, with care taken to optimize the relative resin-solute amounts.

Keywords: column separation, Dowex, molybdenum, specific activity, technetium

1. Introduction

We and collaborators are developing linear accelerator technology for a viable long-term production alternative for the current ageing medical isotope reactor production of molybdenum-99 (Mo99), and in line with the global transition to technologies that are more environmentally sustainable (Canadian Light Source, 2012; International Atomic Energy Agency, 2013; Kobes et al., 2010; Mang'era et al., 2011; Natural Resources Canada, 2012; Prairie Isotope Production Enterprise, 2010; Uvarov et al., 1998). As the target material for accelerator production is an isotope of molybdenum and the conversion, the radioactive product Mo99 product is intrinsically of low-to-medium specific activity, and the high relative molybdenum chemical loads mean that the traditional alumina column used separation of the daughter radionuclide technetium-99m (Tc99m) from Mo99 is not viable. Capacity of alumina is limited to 2-20 mg Mo/g alumina (Chattopadhyay & Das, 2008; Dash et al, 2013). Solvent-solvent extraction and solid-phase affinity chromatography (including use of Dowex™-1 resin) are two techniques that have been applied to successfully separate technetium-99m (Tc99m) and molybdenum-99m (Mo99) from stocks of low-specific activity Mo99 of the type that is obtained by linear accelerator production (International Atomic Energy Agency, 1995; Kanpp & Mirzadeh, 1994). In Dowex™-1 separations, Mo99 is not retained appreciably by the resin and the procedure involves quantitative pass-through of the molybdenum and retention of the Tc99m. The Tc99m is subsequently recovered, usually with the solvent tetrabutyl ammonium bromide (TBAB), and it is critical for clinical use that minimal Mo99 breakthrough into the TBAB eluate is seen.

Publications that report separations utilizing Dowex™-1 resin have usually employed very similar parameters, including concentration of solvent base (NaOH) used to dissolve molybdenum (Chattopadhyay & Das, 2008; Chattopadhyay et al., 2008; Morley et al., 2012). The goal of this investigation is to evaluate the Dowex™-1 system under various parameters that would be applicable to the very low specific activity Mo99 relevant to linear accelerator production technology. We spiked the molybdenum mixtures with Tc99m and report on Tc99m extraction efficiency. We extrapolate on the implications for product quality of any molybdenum retention on the

resin or elution into the solvents and report the effects of changing the concentration of the sodium molybdate solution and the amount of Dowex^{TM}-1 used on the molybdenum breakthroughs and Tc99m extraction efficiencies.

2. Materials and Methods

Molybdenum(IV)oxide powder, sodium hydroxide, Dowex^{TM}-1x8 (200-400 Mesh Cl), dichloromethane, TBAB, nitric acid (70%), and molybdenum AA/ICP calibration/check standard used in ICP-OES analysis (1005 ppm in H_2O) were obtained from Sigma-Aldrich (St. Louis, MO.) 0.9% Saline for injection was obtained from Baxter Corporation (Alliston, ON). Separation spin columns with screw cap (900µL) were obtained from Thermo Scientific Inc. (Rockford, IL.). Tc99m was obtained from the Winnipeg Health Sciences Centre Radiopharmacy (eluted from a Technekow^{TM} Mo99/Tc99m generator, Mallinckrodt Pharmaceuticals, St. Louis, MO) and the radioactive quantities were assayed using a CRC-55tR Dose Calibrator (Capintec Inc., Ramsey, NJ). ICP-OES analysis was performed using a 730 Series ICP-OES system (Agilent Technologies, Mississauga, ON).

2.1 Column Separation Procedure

Separation columns were prepared by transferring slurry of the Dowex^{TM}-1 resin in water to the spin column and washing successively with 5 mL normal saline and 5 mL water. Solutions equivalent to 100 and 250 mg/mL molybdenum were prepared by dissolving MoO_3 powder in 5M NaOH to 150 and 375 mg/mL, respectively. 50µL was sampled from these stock solutions for inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis. Each solution was dispensed into five 10mL aliquots and the aliquots were passed through separate freshly-prepared Dowex^{TM}-1 columns containing the five different resin weights. Eluents were collected in pre-weighed vials (Figure 1, Step 1), 50 µL sample from each run was set aside for ICP-OES analysis, and the columns were washed with 0.9% saline (Step 2) and then eluted using 5 mL of TBAB in dichloromethane (1 mg TBAB/5 mL CH_2Cl_2, Step 3). A 50 µL sample was taken from the saline wash solution for ICP-OES analysis.

Two additional replicates of the separation process were obtained by sequentially re-running the sodium molybdate solution collected in Step 3 (minus the 50 µL analysis sample) through freshly prepared columns and repeating the saline wash and TBAB elution steps.

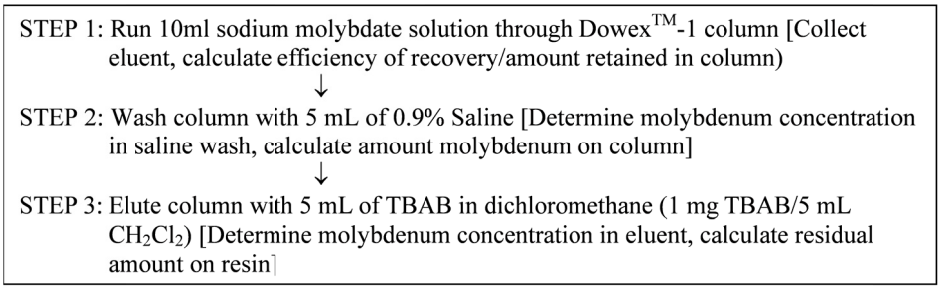

Figure 1. Stepwise procedure for evaluation of molybdenum retention on a Dowex^{TM}-1 column

2.2 Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) Analysis

The molybdenum concentration in the TBAB eluate was determined with ICP-OES. The TBAB/ CH_2Cl_2 solvents were evaporated to incipient dryness and the residue was re-dissolved with 29 mL of 2% nitric acid. For ICP-OES analyses for molybdenum concentration in the TBAB eluate, the TBAB/CH_2Cl_2 solvents were evaporated off and residue dissolved to 20 mL in 2% nitric acid.

The dilution factors of the 50 µL samples of the test solutions were diluted by a factor of $1.6x10^5$ for the sodium molybdate stock solution, and a factor of 400 for the saline wash and TBAB solutions. The ICP-OES determinations were performed against a linear calibration curve obtained from a set of nine standards ranging in concentration from 0.1-2.5 ppm. The 20 mL standards were prepared from a common 100 ppm stock solution obtained by dilution of the 1005 ppm molybdenum standard.

2.3 Mo99/Tc99m Separation Simulation

For evaluation of Tc99m extraction efficiency, the sodium molybdate solution was spiked with 150-300MBq Tc99m-sodium pertechnetate (<0.15mL) and the solution evaluated through the Dowex^{TM}-1 column following the steps represented in Figure 1. All solutions and columns were assayed for Tc99m activity and the Tc99m extraction efficiency was calculated as the proportion of total radioactivity that was recovered in the TBAB eluent.

To determine the elution profile of Tc99m into TBAB, after passing the 250 mg/mL molybdenum solution was separately passed through the lowest (45 mg) and the highest Dowex™-1 amounts (250 mg) and the Tc99m eluted using 10mL of TBAB in 15 aliquots, initially in 0.5 mL aliquots during the first 5 mL volume and then 1 mL aliquots for the latter 5 mL solvent.

3. Results and Discussion

Table 1 shows elution recoveries and retentions of molybdenum on Dowex™-1 columns following the three steps of the separation. Percentages of residual molybdenum retained on the column after Step 1 that are then eluted in Step 2, and residual after Step 2 that are then eluted in Step 3 are also provided. Table 1 shows that the molybdenum recoveries are high after the solution is run through Dowex™-1 in Step 1, with the amount of the stock molybdenum retained on the column at less than 4% in all cases.

Table 1. Average percent of molybdenum retained on a Dowex™-1 column and subsequent distribution of retained molybdenum

Amount of Dowex™-1 (mg)		**45**	**75**	**125**	**175**	**250**
STEP 1						
% of stock molybdenum retained on column	**100 mg/mL (A)**	0.83	0.83	3.46	2.52	3.56
	250 mg/mL (A)	2.17	2.50	2.49	3.52	2.75
STEP 2						
% of retained Mo after Step 1 that is washed out in Saline in Step 2	100 mg/mL	56.05	61.64	27.36	48.81	75.63
	250 mg/mL	14.45	9.46	28.49	54.31	69.53
Calculated % of stock Mo on column after saline wash (A-B)	**100 mg/mL**	0.16	0.00	1.90	0.57	0.96
	250 mg/mL	1.71	1.87	1.36	1.10	1.18
STEP 3						
Concentration in ppm of Mo eluted in TBAB	100 mg/mL	0.33	0.44	1.57	2.51	3.73
	250 mg/mL	1.82	0.96	2.71	2.92	11.27
% of Mo on column after Step 2 that is eluted in TBAB Step 3	100 mg/mL	0.06	0.07	0.02	0.08	0.86
	250 mg/mL	0.01	0.00	0.02	0.22	0.33
Mo eluted in TBAB expressed as % of original stock soln x10^{-2}	**100 mg/mL**	0.02	0.03	0.09	0.14	1.13
	250 mg/mL	0.04	0.02	0.07	0.07	0.27

Note. Molybdenum retained on a Dowex™-1 column from passed through sodium molybdate solutions equivalent to 100 mg/mL and 250 mg/mL molybdenum (Step 1), and subsequent distribution of retained molybdenum into saline wash (Step 2) and TBAB eluate for five different amounts of Dowex™-1 resins (Step 3) (n=3).

The saline washes in Step 2 effectively reduce the retained molybdenum to < 2% in all cases (highest retained is 1.9% at 100 and 250 mg/mL), with the relative percentages washed off variable between 9 – 76 % of the small amounts on the column after Step 1. The magnitude of molybdenum recovered in the wash is higher with higher amounts retained on the column after Step 1. Logically, the washed-out portion at Step 2 seems to have been loosely retained on the column. Although there is some pattern showing higher molybdenum retention with increasing resin amounts after Step 1, the apparently more effective subsequent wash with saline in Step 2 means that after Step 2, especially with the 250 mg/mL molybdenum concentration a consistent residual content on the column of 1.4 ± 0.3% is obtained for all samples at this concentration.

For clinical products in which the key process is the separation of Tc99m from Mo99 and where Tc99m purity is the key parameter, the relative amount of radioactive Mo99 to the Tc99m ("Mo99 breakthrough") constitutes the principal radionuclidic impurity, and relative amount of total molybdenum mass (all isotopes, radioactive and non-radioactive) eluted into the Tc99m extract constitutes the principal chemical impurity. The effectiveness of Step 3 separation is therefore crucial in a clinical setting prior to use of the extracted Tc99m product. Compendial limits for Mo99 breakthrough are 0.15 kBq of Mo99/1 MBq of Tc99m at the time of use of the clinical preparation (USP, 2012). We performed tests where both the 100 mg/mL and 250 mg/mL molybdenum solutions were spiked with Tc99m-pertechnetate and the resulting solutions were extracted through three Dowex™-1 amounts (45, 125, and 250 mg).

We quantify the efficiency of Tc99m extraction through the column into the TBAB eluate and relate this as a ratio to the molybdenum amounts. As shown in Figure 2, efficiency of extraction of Tc99m is decreased in the presence of higher concentration of molybdenum, and with higher amounts of resin. The latter effect is most probably a result of greater residual adsorption and retention of the Tc99m on the expanded surface areas with the higher resin amounts. Also, the uniformly linear nature of the relationship indicates that the residual adsorption capacities of the resins are not saturated, even at the lowest 45 mg resin amount.

With respect to the impaired Tc99m extraction efficiency effect seen with increase in molybdenum concentration, we speculated that higher molybdenum amounts affect the capacity of TBAB to extract the Tc99m from the Dowex^{TM}-1 resin. We conducted further tests with a higher volume (10 mL) of TBAB and the results appear to support this, with significant and consistent improvement of the elution yields of Tc99m elution compared to the standard 5 mL (Table 2). When fractions of the elution aliquots were collected and separately assayed (Table 2 and Figure 3), it is seen that even though similar overall extraction efficiencies are obtained for resin amounts of 45 mg and 250 mg, there is a clear difference in the elution profile. The 45 mg has a higher initial Tc99m elution extraction and the profile flattens out sooner compared to the 250 mg molybdenum solution's elution profile.

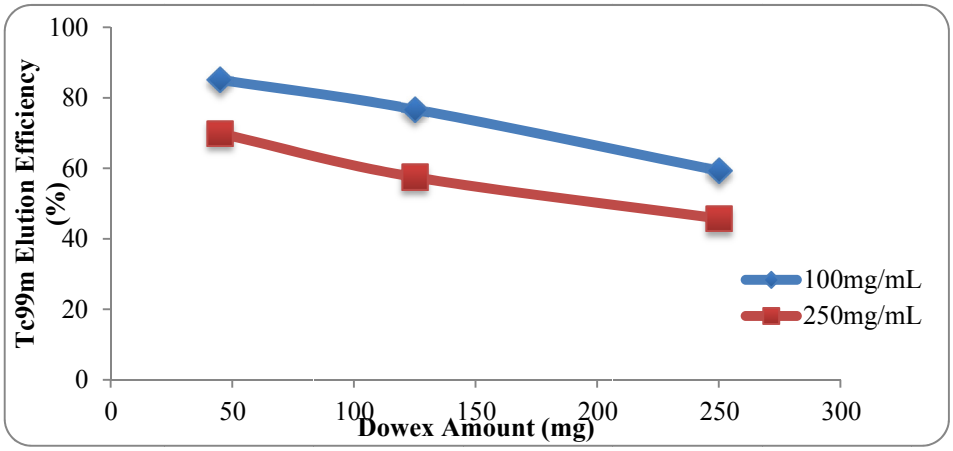

Figure 2. Tc99m recovery efficiency

Note. The percent of the Tc99m in sodium molybdate solution loaded onto the column that is eluted into the TBAB solvent, for three different Dowex^{TM}-1 amounts and two different molybdenum concentrations (n=3).

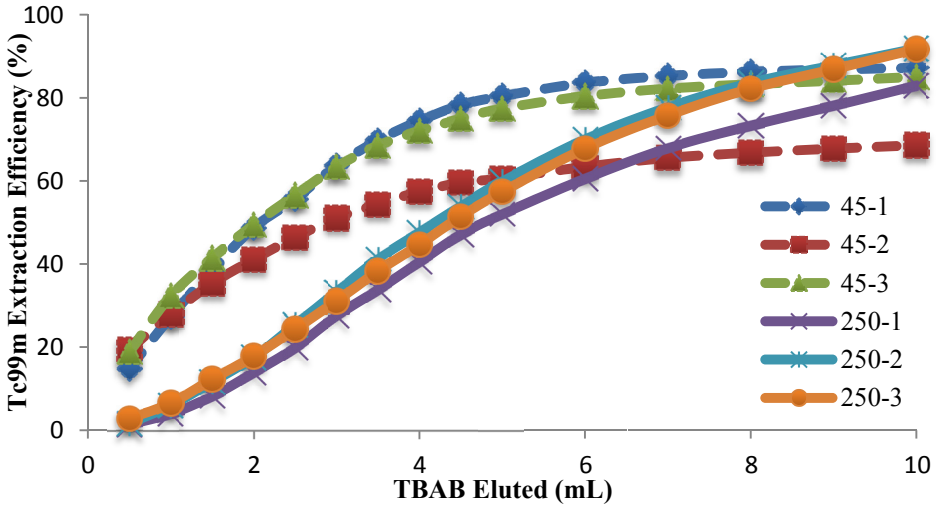

Figure 3. Elution profiles of Tc99m in TBAB eluate

Note. Volume-aliquot profile for 45 mg and 250 mg Dowex^{TM}-1 columns using 10 mL of TBAB solvent collected in 0.5 mL aliquots for the first 5 mL and 1 mL aliquots for the second 5 mL.

Table 2. Tc99m extraction efficiencies

Amount Dowex (mg)	Run #	% Extraction Efficiency -**5 mL**	% Extraction Efficiency -**10 mL**
45	1	80.41	87.20
	2	60.61	68.56
	3	77.42	85.02
250	1	52.00	82.94
	2	59.90	91.86
	3	57.36	91.73

Note. A comparison of Tc99m extraction efficiency following collection of 5 and 10 mL of TBAB used in elution of a 250 mg/mL molybdenum solution through 45 and 250 mg Dowex^{TM}-1columns, respectively.

The amounts of chemical molybdenum in the 15 TBAB aliquots collected in the Tc99m-spiked elution study were measured using ICP-OES assays (Table 3). A clear difference is observed in the elution profiles for the two resin amounts, with the full amount of molybdenum eluted in the first 0.5 mL for the 45 mg Dowex^{TM}-1 column while for the 250 mg Dowex^{TM}-1 column, more TBAB solvent was required for full elution. It is notable, nevertheless that even for 250 mg resin, all the molybdenum was eluted within the standard 5 mL of TBAB volume. Chemical and radionuclidic molybdenum impurities in the final eluted Tc99m therefore appear to be concentrated in early aliquots, while the desired Tc99m product elutes at a more delayed profile. This elution differential allows for and could, if necessary, be exploited in difficult separations to optimize higher ratios of Tc99m to molybdenum in elutions, by discarding a small early fraction in the elution that would proportionately carry the highest impurity concentration.

Table 3. Molybdenum concentrations in TBAB eluate

Dowex Amount	**45 mg**	**250 mg**
TBAB Eluted (mL)	Avg. Molybdenum Concentration (ppm)	Avg. Molybdenum Concentration (ppm)
0.5	10.44	5.532
1.0	0	0.234
1.5	0	0.011
2.0	0	0.128
2.5	0	0.027
3.0	0	0
3.5	0	0
4.0	0	0
4.5	0	0.032
5.0 to 10.0 in 1 mL aliquots	0	0

Note. Molybdenum concentrations of 15 TBAB aliquots collected after passing 10mL of TBAB through two different amounts of Dowex^{TM}-1 resin columns, to extract the components of a Tc99m-spiked 250mg/mL molybdenum solution passed through the column (n=2, 0.5mL aliquots for first 5mL and 1.0 aliquots for second 5mL).

The molybdenum extraction results in Table 3 are consistent with the Tc99m extraction profiles in Table 2 with respect to higher amounts of Dowex^{TM}-1 resin leading to a poorer elution profile of the solute during TBAB extraction of the column. The 250 mg Dowex^{TM}-1 column requires more TBAB to run through the column before all the molybdenum is removed. As far as satisfying molybdenum breakthrough requirements, the higher amounts of TBAB used do not create issues by increasing molybdenum breakthrough into the final product as overall molybdenum in the 15 aliquots for the 10 mL TBAB solvent volume are similar to the values obtained when only using 5 mL of TBAB. We would therefore prefer to adopt the higher amount of TBAB to elute the Dowex^{TM}-1 column.

4. Conclusion

These experimental results show that high initial molybdenum recoveries and low molybdenum impurity elutions in the final TBAB solvent are obtained at the different concentrations tested of the parent sodium molybdate solution. The amounts of Dowex^{TM}-1 used in the columns has no significant effect for amounts up to 175 mg but a significant change is noticed when Dowex^{TM}-1 amounts reach 250 mg. These results indicate that the concentration of molybdenum in the sodium molybdate load solution is not as critical as the amount of Dowex^{TM}-1 resin used in the column. It is recommended that amounts of Dowex^{TM}-1 resin be kept at or lower than 175 mg for similar sets of separation parameters.

Acknowledgments

Katarina Popovic for invaluable assistance in the preparation of the manuscript for publication.

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