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Removal of Tc from Neutron-Capture ^{99}Mo using Eichrom's ABEC Resin

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ABSTRACT

NorthStar Medical Radioisotopes is pursuing a neutron capture [^{98}Mo(n,γ)^{99}Mo] route for ^{99}Mo production at the University of Missouri Research Reactor (MURR). Argonne is assisting NorthStar in the development of some aspects of the operation. Once the molybdenum targets are removed from the reactor, they will undergo dissolution. The output of the dissolution results in ~1500 mL of a 200 g/L Mo, 9.3 M K^+, 5 M OH^-, 0.1 M NO_3^- solution containing ~400 Ci of ^{99}Mo, as well as a few byproducts (compared to fission) including Tc. This solution is pumped from a shielded cask through a chromatography column containing ABEC to remove Tc present from the target irradiation. This polishing step will allow radiopharmacies to use the first aliquot of Tc they elute from their generators. Currently, radiopharmacies discard the first aliquot from the generator, as it contains unacceptable levels of ^{99g}Tc. Various ABEC cartridge sizes and flow rates through these cartridges have been investigated, and a method for processing the 1500 mL of 5 M OH^- solution has been investigated.

1. Introduction

More than 80% of nuclear medicine diagnostic tests or approximately 70,000 medical imaging procedures throughout the world daily use metastable technetium-99 (^{99m}Tc), [1]. In 2009, it was reported that Canada's Chalk River research reactor and the Netherlands' High Flux reactor produce approximately 85% of Europe's and North America's ^{99}Mo supply [2]. It was recently announced that the Chalk River reactor will cease ^{99}Mo production after 2016, creating a worldwide shortage of ^{99}Mo unless reliable, alternative production

methods are developed. ^{99m}Tc cannot be stockpiled because its parent isotope is molybdenum-99 (^{99}Mo), which has a 66-hour half-life [3]. One possible production method is based on the [^{98}Mo(n,γ)^{99}Mo] reaction pathway.

The typical reaction pathway for the production of ^{99}Mo is neutron-induced fission of high-enriched uranium (HEU; ≥20% ^{235}U) in a nuclear reactor. After irradiation of the HEU target, the ^{99}Mo is isolated from the uranium and other fission products, purified, and loaded onto a generator for delivery to radiopharmacies. The radiopharmacies then use the generator to separate the decay product or daughter, ^{99m}Tc, from the ^{99}Mo. The ^{99m}Tc has a 6-hour half-life and can be administered to patients on-site [4]. The production of ^{99}Mo with HEU is a nuclear proliferation concern, because HEU can be weaponized. It is far more desirable to produce ^{99}Mo from either non-uranium-based sources, such as Mo irradiation, or using low enriched uranium (LEU ≤ 20% ^{235}U) [4]. The major downside of ^{99}Mo production using non-HEU is that much more target material is needed, regardless of whether the reaction pathway uses Mo or non-HEU uranium, in order to synthesize an equal amount of Mo as with HEU. Production using non-HEU methods, whether with a reactor or an accelerator, are greatly preferred because nuclear proliferation concerns are greatly reduced [5].

The reaction [^{98}Mo(n,γ)^{99}Mo] is of interest, as it uses no uranium targets and presents no proliferation concern. After irradiation in the University of Missouri Research Reactor (MURR) the Mo target undergoes dissolution that results in the reaction products being in a final solution of 200 g/L Mo, 9.3 M K^+, 5 M OH^-, 0.1 M NO_3^- and a volume of 1500 mL. Upon receipt of the dissolution solution, it is desired to remove the Tc that has built up during irradiation from the solution so that it can be aliquoted and delivered to the radiopharmacies for immediate use. Eichrom Technologies, LLC has developed ABEC, an extraction chromatographic resin specific for Tc which is being used to purify the final dissolution solution.

Eichrom's ABEC resin consists of polyethylene glycols (PEGs) physisorbed onto an inert support. Eichrom has previously characterized the behavior of the pertechnetate ion (TcO_4^-) on ABEC resin in both batch and low flow rate (<4 mL/min) column studies [6-9]. Due to restrictions for commercial production-scale, flow rates of >10 mL/min are necessary. In addition to this requirement, it is also necessary that all 1500 mL of solution are processed with the same ABEC cartridge. A successful process is defined as all post-ABEC cartridge aliquots (29 mL) containing < 30 % of the possible Tc per pre-ABEC cartridge (the stock solution) aliquot (29 mL). The possible Tc per aliquot is defined as the total amount of Tc in 1500 mL divided by 1500 mL multiplied by the aliquot volume (29 mL). The performance of 10 cc ABEC cartridges at a flow rate of 10 mL/min has been investigated in support of a Federal Drug Administration (FDA) Process Analytical Technology (PAT) study.

A FDA PAT study provides a framework for the implementation of innovative processes to be introduced into the pharmaceutical industry. The PAT study designed with NorthStar Medical Radioisotopes (NMR) requires 10 columns of 3 lots of ABEC resin to be tested using the same process as would be used in the full scale production operations. The results of the FDA PAT study, to date, are presented below.

2. Experimental

10 cc ABEC cartridges were slurry- packed at NMR's Madison, WI facility. American Chemical Society (ACS) reagent-grade potassium hydroxide pellets, potassium nitrate. American Chemical Society (ACS) reagent-grade molybdenum trioxide available from Acros Organics was used. Ultima Gold XR liquid scintillation cocktail was obtained from Perkin Elmer. The ^{99}Tc was originally in the ammonium pertechnetate chemical form and was obtained from Oak Ridge National Laboratory.

A stock solution of ~200 g/L Mo, 9.3 M K^+, 5 M OH^-, 0.1 M NO_3^- was made using 18 MΩ deionized water and filtered through a 0.22 μm polyethersulfone (PES) filter available through Fisher Scientific. After the filtration, ~170 μg of ^{99}Tc was added to 1500 mL of the stock solution. An aliquot of this sample is taken for Liquid Scintillation Counting (LSC) as a baseline for the starting solution. It is expected that 170 μg of total Tc is the upper limit of Tc at the End of Irradiation (EoI) of a natural molybdenum target.

The column was then attached to a dispensing unit developed by NMR. The dispensing unit uses pressure to push eluents through the ABEC column. The column was conditioned with ~10 bed volumes of 5 M KOH. After conditioning, an aliquot of 29 mL of the stock solution, containing ^{99}Tc, was passed through the ABEC cartridge and a sample collected for LSC. The sample passed through ABEC was then compared to the sample of the initial solution, to determine how much Tc was captured by the ABEC resin. A successful experiment is defined by two requirements: 1) greater than 70% of the Tc must be captured by the ABEC (this is based upon how much Tc would be present in a 29 mL aliquot of the initial solution); 2) the volume dispensed must be consistent with ≤0.1 mL deviation. The dispensed volumes were determined gravimetrically based on the density of the initial solution.

3. Results and Discussion

3.1 ^{99}Tc capture on ABEC

The first criterion for a column to be successful is that greater than 70 % of the Tc present in each aliquot must be captured by the ABEC resin. In order to assess this, a total of twenty 10 cc ABEC cartridges have been tested. Of the 20 columns tested 14 have passed the criterion listed above. Figure 1 shows the breakthrough curves for the first 8 ABEC cartridges that passed the criteria. Based on Figure 1 and the failure of 6 other columns, the columns do not perform consistently. It is believed that this is

due to an inconsistent cleaning of the ABEC resin prior to packing, and inconsistent packing of the 10 cc cartridges. A study on lot versus column failure and performance consistency versus lot is currently underway.

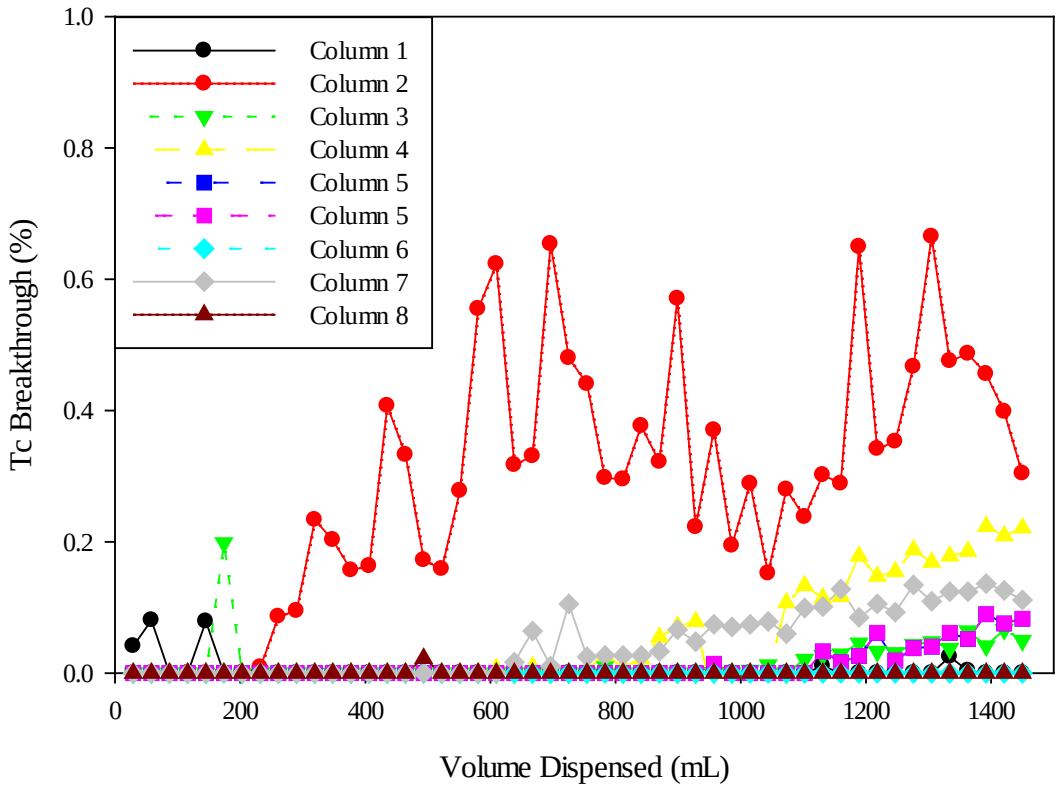

Figure 1. The breakthrough curve for ^{99}Tc on the first 8 successful 10 cc ABEC cartridges packed by NMR. This indicates that even the successful columns perform inconsistently, indicating the need to evaluate the cleaning and/or packing process for the ABEC resin.

3.2 Dispensing Consistency

The second criterion for a column to be successful is that the volume dispensed between samples must be ≤ 0.1 mL. In order to assess this, a total of twenty 10 cc ABEC cartridges (same cartridges as above) have been tested. Of the 20 columns tested 15 have passed the criterion listed above. Figure 2 shows the first 10 columns tested. It can be seen that in the first 10 columns tested that 4 failed to meet the volumetric dispensing requirements. It was determined that this is most likely due to the solution etching the glass bore of the syringe, which caused the syringe to leak and thus inaccurately dispense the desired volume. This problem is currently being addressed by improving the syringe design and possibly changing the syringe material from borosilicate glass to something more suitable.

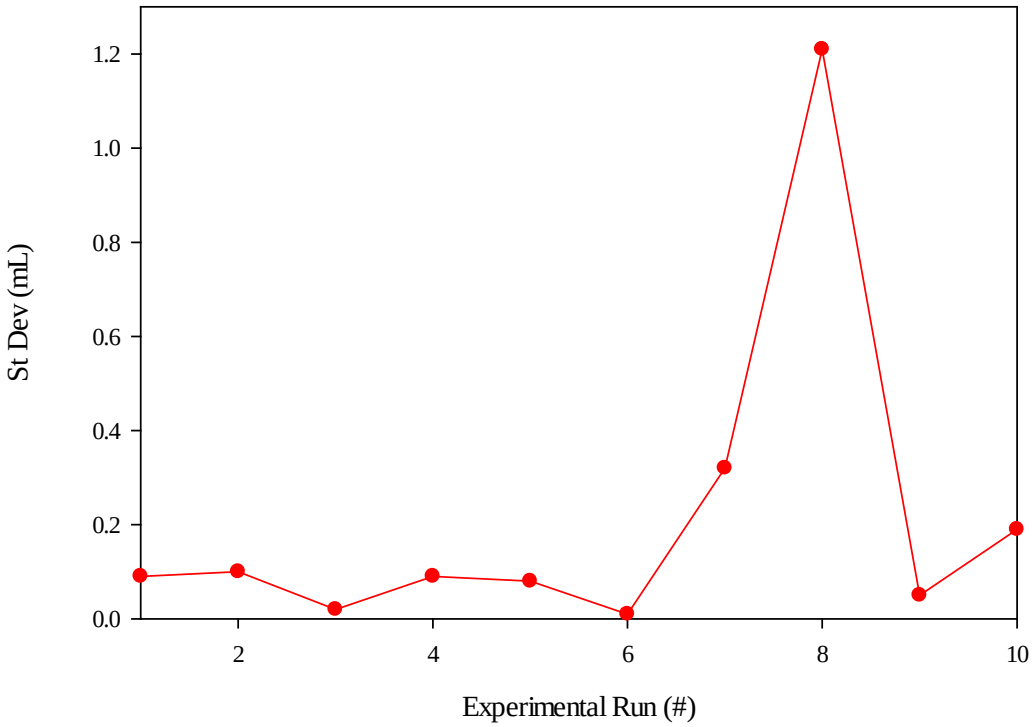

Figure 2. A standard deviation of <0.1 mL is necessary and this clearly shows that this was exceeded in several cases. This result is due to syringe pump failure.

4. Conclusions

A study of twenty 10 cc ABEC slurry-packed cartridges has been conducted with respect to two criteria; 1) greater than 70% of the Tc must be captured by the ABEC (this is based upon how much Tc would be present in a 29 mL aliq uot of the initial solution); 2) the volume dispensed must be consistent with ≤0.1 mL deviation. With respect to criterion 1, 14 of 20 ABEC cartridges were successful. It is believed that the failure of these cartridges is due to inconsistent cleaning and/or packing procedures for the ABEC resin. A study is currently being conducted to determine if 1 of the 3 lots of ABEC resin is out of specification. If this is the case this may explain the poor performance of some columns. In addition, a new packing procedure is being developed to address any packing issues, as post-separation analysis of the ABEC cartridges has indicated a bed collapse. With respect to criterion 2, 15 of 20 ABEC cartridges were successful. It is believed that this is due to the solution, which is highly corrosive (pH estimated to be 15-16), etching the borosilicate syringe barrel. Currently, a new syringe design is being developed. Due to the changes in packing procedure, possible failure of a single lot of resin and the changes in syringe design, a new FDA PAT study will need to be conducted.

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