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An automated module for the separation and purification of cyclotron-produced $^{99m}TcO_4^-$

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Abstract

Introduction: The shortage of reactor-produced molybdenum-99 (^{99}Mo, $t_{½}$=66 h) has renewed interest in alternative production methods of its daughter isotope, technetium-99m (^{99m}Tc, $t_{½}$=6.02 h). While adsorption chromatography serves as a mechanism for selective elution of sodium pertechnetate from technetium generators, this method of purification is not sufficient for many alternative production methods. Several ion-separation/solid phase extraction chromatography methods are known, yet none have been demonstrated on cyclotron-produced $[^{99m}Tc]TcO_4^-$. Herein we describe the design, manufacture and optimization of a remotely operated module for the purification of sodium pertechnetate from a bulk solution of molybdate.

Methods: The automated purification module was designed to separate $[^{99m}Tc]TcO_4^-$ using either Dowex 1x8 or an Aqueous Biphasic Extraction Chromatography (ABEC) resin. ^{100}Mo composite targets were irradiated with 18.5 MeV protons for 10 μA·h using an ASCI TR19 cyclotron. Once purified, the radiopharmaceutical quality of $^{99m}TcO_4^-$ isolated from each process (Dowex and/or ABEC) was established by assaying for molybdate breakthrough, alumina levels and, in the case of the Dowex approach, residual organics.

Results: The separation processes are efficient (75% for Dowex, 90% for ABEC) and complete in less than 30 min. Overall, up to 2.1 GBq of ^{99m}Tc was produced using the $^{100}Mo(p,2n)^{99m}Tc$ transformation, processed using the separation module and subjected to a detailed chemical and radionuclidic analysis. Due to its expense and limited availability, $^{100}MoO_4^{2-}$ was recovered in >90% yield using a precipitation/filtration/lyophilization approach.

Conclusions: $Na[^{99m}Tc]TcO_4$ was produced using a medical cyclotron, recovered using an automated purification module and found to exceed all established quality control parameters.

Keywords: Aqueous Biphasic Extraction Chromatography; Automation; Medical radionuclides; Technetium-99m; Pertechnetate

1. Introduction

Recent issues with the supply of reactor-produced ^{99}Mo, the parent isotope of ^{99m}Tc, have spurred the development of alternative production methods [1,2]. ^{99m}Tc is typically obtained from a $^{99}Mo/^{99m}Tc$ generator, which contains high specific activity ^{99}Mo embedded onto a small alumina column [3]. Daily extraction of $[^{99m}Tc]TcO_4^-$ is accomplished by exploiting the mobility differences between the $^{99}MoO_4^{2-}$ and $^{99m}TcO_4^-$ ions on alumina in isotonic saline. Selective chromatography defines the radionuclide generator concept and also largely defines the expectations of the nuclear medicine community when dealing with ^{99m}Tc-based radiopharmaceuticals. For this reason, any alternative production method of ^{99m}Tc must not only maintain acceptable US Pharmacopeia (USP) standards for chemical,

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radiochemical and radionuclidic purity, but must also enable access to ^{99m}Tc without requiring substantial infrastructure changes within the healthcare community.

Several alternative production methods for ^{99}Mo and ^{99m}Tc are already known, but all remain underdeveloped due to the historical acceptance of the ^{235}U(n,F)^{99}Mo approach [4]. Neutron-based methods include the irradiation of low enriched uranium (LEU) or irradiation of enriched ^{98}Mo targets to produce low specific activity ^{99}Mo via the ^{98}Mo(n,γ)^{99}Mo transformation [5–8]. Both approaches have downstream implications in either waste management or generator packing. Despite this, a few countries have transitioned their ^{99}Mo-producing infrastructure to use LEU or enriched ^{98}Mo coupled to the use of gel-generator technology [9,10]. Accelerator-based production (both proton and electron–photon) of both ^{99}Mo, via ^{238}U(γ, F)^{99}Mo and ^{100}Mo(γ,n)^{99}Mo, and ^{99m}Tc directly is also being explored [11–13]. Proton irradiation of enriched ^{100}Mo [i.e., ^{100}Mo(p,2n)^{99m}Tc] was identified almost 40 years ago as a particularly promising route to ^{99m}Tc, and its production parameters have since been investigated using a wide range of cyclotrons [14–20]. However, this route has only recently been demonstrated to produce large quantities of ^{99m}Tc. Currently, direct production is the focus of several groups seeking to establish a process for commercial-scale distribution of curie quantities of [^{99m}Tc]TcO_4^- [21,22].

The existing ^{99}Mo/^{99m}Tc production infrastructure is aging, making it likely that future supply will diverge through any number of the aforementioned production alternatives. All will require a demonstrated pharmaceutical equivalence of [^{99m}Tc]TcO_4^- to that obtained from a ^{99}Mo/^{99m}Tc generator. To this end, a versatile purification module capable of isolating pertechnetate has been developed and used to isolate and evaluate cyclotron-produced ^{99m}Tc. The assembly of the module, optimization of two ion separation processes using Dowex and Aqueous Biphasic Extraction Chromatography (ABEC) resins, and evaluation of the pertechnetate obtained at the end of the process are reported here [23,24].

2. Materials and methods

2.1. Module assembly

Components of the module are all regular stock items available from commercial sources. Valves used for fluid transfer were Burkett two- and three-way PEEK solenoid valves, and gas transfer control valves were Parker two-way Teflon solenoid valves (Peerless Engineering Sale Ltd., Burnaby, Canada). All fluid and gas transfer tubing and accessories were purchased from Upchurch (Idex Health & Science, North York, Canada). Either 1/16″ or 1/8″ PEEK tubing was used for fluid transfer and vacuum lines, with Teflon tubing being used for all gas transfer lines. All connectors were PEEK or Delrin 1/4-28 flangeless fittings. A conventional gas regulator was used to control gas pressure delivered to the module. Ion separation columns were constructed by suspending the required amount of resin in water followed by injection into an empty 1-ml syringe barrel fitted with polyethylene frits (20 micron Sigma-Aldrich, Oakville, Canada) at either end to hold the resin in place. A solid phase extraction (SPE) adaptor was used to connect the syringe barrel to a conventional Luer fitting. All glass fittings and reservoirs were purchased from Ace Glass (LaSalle Scientific Inc., Guelph, Canada), along with the required adapters to 1/4-28 fittings. The mini-vacuum pump was purchased from Parker Precision Fluidics (Hargraves Technology Corp., Mooresville, NC, USA) and was connected in-line with a liquid trap (from Ace Glass) to prevent accidental contamination of the pump. The module housing was manufactured from 1/8″ aluminum with a Delrin front fascia to which all components were attached. The radiation detectors were based around an S8559 photodiode Cs-I scintillator optimized for 140 keV. All electronic components were controlled remotely using Lookout software via a control interface box connected via Ethernet cable.

2.2. Ion separation process

All chemicals were purchased from Sigma-Aldrich (Oakville, Canada) and used as received unless otherwise stated, including Dowex 1x8 resin (100–200 mesh). ABEC-2000 resin (100–200 mesh) was a kind gift of Eichrom Technologies (Lisle, IL, USA). Sep-Pak classic (Waters, Mississauga, Canada) acidic alumina columns (1.85 g) and Bio-Rad (Mississauga, Canada) AG MP-50 resins were purchased directly from the supplier. ^{99m}Tc used in the optimization of the ion separation process was obtained from standard elution of an expired generator kindly supplied by Lantheus Medical Imaging (Vancouver, Canada).

2.3. Experimental

2.3.1. Module assembly

Pressurized helium was used to push the molybdate/-pertechnetate solution through the SPE column (i.e., either Dowex 1x8 or ABEC-2000), which immobilizes the pertechnetate and allows the molybdate to flow through into a suitable reservoir (waste 1). A radiation detector mounted behind the SPE column permits real-time monitoring of the immobilization and elution of pertechnetate. The SPE column was washed (effluent also to waste 1) before elution, which transfers the pertechnetate onto the alumina column. If the ABEC resin is being used, a small in-line cation-exchange (SCX, BioRad MP-50, Mississauga, Canada) cartridge is required to neutralize any residual base from the ABEC column and ensure that the pertechnetate is retained by the alumina. The effluent from this column is fed into a second waste reservoir (waste 2). Once the pertechnetate is immobilized onto the alumina column, it is washed with water (effluent to waste 2) before elution with saline into a vial contained within a