Original Article

Indigenous technology development and standardization of the process for obtaining ready to use sterile sodium pertechnetate-Tc-99m solution from Geltech generator

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ABSTRACT

Purpose of the Study: The indigenous design and technology development for processing large scale zirconium molybdate-Mo-99 (ZrMo-99) Geltech generator was successfully commissioned in Board of Radiation and Isotope Technology (BRIT), India, in 2006. The generator production facility comprises of four shielded plant facilities equipped with tongs and special process gadgets amenable for remote operations for radiochemical processing of ZrMo-99 gel. **Results:** Over 2800 Geltech generators have been processed and supplied to user hospitals during the period 2006-2013. Geltech generator supplied by BRIT was initially not sterile. Simple elution of Tc-99m is performed by a sterile evacuated vial with sterile and pyrogen free 0.9% NaCl solution to obtain sodium (Tc-99m) pertechnetate solution. A special type online 0.22 μm membrane filter has been identified and adapted in Geltech generator. **Conclusions:** The online filtration of Tc-99m from Geltech generator; thus, provided sterile Tc-99m sodium pertechnetate solution. Generators assembled with modified filter assembly were supplied to local hospital in Mumbai Radiation Medicine Centre (RMC) and S.G.S. Medical College and KEM Hospital) and excellent performances were reported by users.

Keywords: Geltech generator, hydromillex SLST025DM 0.22 μm sterile membrane filter, sterile sodium pertechnetate-Tc-99m, technology development

INTRODUCTION

There are several methods for routine separation of Tc-99m from molybdenum-99 (Mo-99) for use in hospital radiopharmacy. The alumina column based chromatography generator system for Tc-99m is the most used generator system world-wide. High specific activity Mo-99 (>10^3 Ci/g of Mo) obtained from fission of U-235 is adsorbed on an acidic alumina column and Tc-99m is eluted with normal saline, which is considered as the "gold standard" generator for Tc-99m. Due to simplicity of operation, column chromatographic generators are the method of choice.[1]

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The essential requirement for alumina column chromatography generator is the high specific activity fission produced (n, f) Mo-99, which is expensive and not easily indigenously available in many developing countries. The reason for requirement of fission produced Mo-99 is that the acidic aluminum oxide has a limited adsorption capacity for molybdenum, 20 mg Mo/g of alumina, at pH, <4.5 and in turn dictates the column size and the final elution volumes and radioactive concentration of Tc-99m eluate. Because of this constraint, medium and low flux reactor produced (η, γ) Mo-99 (7.4-14.8 GBq [200-400 mCi] of Mo-99/g of Mo) easily accessible in developing countries cannot be used for alumina column chromatography generator. Production of 1 Ci Mo-99 by fission route produces about 100Ci of other gaseous and solid radioactive products,[2] which is a concern for the environment and costly waste management issue.

Although, it is possible to prepare generators with (η, γ) Mo-99, but generators made with such low specific activity Mo-99 require substantially larger columns which in turn, require increased

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volumes of eluent leading to low concentrations of Tc-99m and hence not suitable for radiopharmaceuticals formulations. An impressive number of studies have been reported for use of (η, γ) Mo-99 for separation of Tc-99m[3-5] for radiopharmaceutical use. Other alternative is to develop new adsorbent material for Mo of higher capacity for preparation of column generator using (η, γ) Mo-99. Japanese Scientists have reported success using an adsorbent, called polymeric zirconium compound (PZC). This is a new adsorbent material having higher adsorption capacity for Mo-99 (200 mg/g of PZC). Scientist in Bhabha Atomic Research Centre (BARC) has also reported about nano-zirconia, titania, and γ-alumina[6-8] adsorbent material for adsorption of molybdenum with higher adsorption capacities for preparing Mo-99/Tc-99m column generator.

Zirconium molybdate-Mo-99 (ZrMo-99) gel generator is a novel option, which combines both advantages of column generator and enables the utilization of indigenously produced low to medium specific activity (η, γ) Mo-99. The preparation of ZrMo-99 gel matrix involves several challenging radiochemical processing steps such as precipitation, filtration, drying, disintegration, washing and handling of ZrMo-99 gel powder.[9-19] The processing of large scale ZrMo-99 gel of reproducible quality is hence a challenging task for remote operation and automation, which have been overcome in Board of Radiation and Isotope Technology (BRIT).[12-16] The indigenous facility has four shielded plant (with 100 mm lead shielding) connected in series comprising of remotely operated gadgets for transferring sodium molybdate (Mo-99) solution for precipitation with $ZrOCl_2 \cdot 8H_2O$ solution in a reaction vessel, filtration of ZrMo-99 gel precipitate using specially fabricated Buchner funnel under vacuum, transferring and discharge of gel precipitate to a pneumatic-driven ZrMo-99 collection dish, keeping the dish in a microwave oven for drying gel, specially designed dispenser for dispensing particular volume of dry gel powder in glass column stationed in an indexer table, sealing of gel column and loading of gel columns into the pre-assembled generator housing etc. The indigenous facility for regular processing of Geltech generator has been successfully commissioned in BRIT, India in 2006[18] and successfully used until mid-2012.

Conversion of 50 g of Mo into 170-180 g ZrMo-99 gel powder in two cycles of 25 g/batch is found feasible in the present facility.[20] Market studies revealed that generators of activity minimum of 400-500 mCi (15-18.5) GBq Mo-99 on Monday would be required by most hospitals. The specific activity of indigenously produced (η, γ) Mo-99 was in the range of 7.4-14.8 GBq/g of Mo, there was a need to spike with (n, f) Mo-99 for preparing clinically useful generators of 15 GBq Mo-99 generator on Monday. In case of non-availability of (n, f) Mo-99, gel generators of 250 mCi (9.25 GBq) Mo-99 on Monday were prepared using (η, γ) Mo-99 alone containing larger quantity gel 9-10 g bed (3-4g Mo) to sustain regular supply of generator. The pH adjustment of gel and drying of gel cake are the most important for processing so as to get gel of desired quality. Depending upon the pH, both transitional metals form multiple polymeric species in aqueous solutions and produce quantitative precipitate of ZrMo-99 gel and subsequent drying give amorphous gel powder with varying water molecules, which facilitates free diffusion of Tc-99m from gel generator during elution. Performance evaluation of gel generators were carried out in terms of elution of Tc-99m, which were smooth, rapid and completed in about 2 min. Clear eluates of pH 5-6 were always observed. The consistent results of over 75% yield of Tc-99m, $<10^{-2}$% Mo-99 breakthrough, >95% Radiochemical Purity (RC) purity of pertechnetate, less than 10 ppm of Mo, Zr and Al in eluates could achieved. Compatibility of this Tc-99m for formulating even sensitive Tc-99m compounds such as Tc-L, L-ethyl cysteinate dimer, and Tc-methoxy isobutyl isonitrile indicated satisfactory quality of pertechnetate (Tc-99m). Good quality images were reported by various users.

Geltech generators of capacity 250-400 mCi (9.25-14.8 GBq) Tc-99m are being processed regularly and supplied by BRIT on a weekly basis to the different nuclear medicine centers across India.[19,20] It is a dual column system comprising of primary gel column and a secondary purification alumina column connected in tandem. Elution of Tc-99m is carried out by the users by passing 10 ml normal saline through the gel column and collecting Tc-99m in a sterile evacuated vial connected at the end of a secondary alumina column. The users were advised to sterile Tc-99m sodium pertechnetate eluted in 0.9% NaCl solution either by autoclaving at 121°C for 30 min at 15 psi or using 0.22 μm membrane filtration for labeling before patient administration. Many other commercial suppliers for Tc-99m alumina column chromatography generators such as Isorad, Amersham, CIS-Bio etc. are supplying generators with on-line 0.22 μm membrane filters for providing sterile sodium Tc-99m pertechnetate. Therefore, there was a definite need to avoid the extra step of sterilization of Tc-99m from gel generator. Our aim of the studies were to supply column type Geltech generator with modified generator assembly, so as to accommodate an on-line 0.22 μm membrane filter, for providing sterile sodium (Tc-99m) pertechnetate throughout the shelf-life of the generator for the users.[20] The specialty of the membrane is that it is composed of both hydrophilic and hydrophobic membrane housed in the same filter assembly permitting repeated passage of sterile saline and sterile air. Thus, a single filter can be used unchanged throughout the generator shelf-life. Large numbers of Tc-99m eluates (more than 100) were collected using this filter from 8 batches of Geltech generators. Sterility and pyrogenicity of sodium (Tc-99m) pertechnetate solution was found to meet with Indian pharmacopoeial (IP) requirement. The Geltech generator system with modified filtration assembly has been adopted in the present Geltech generator system, which can be used in due course in hospital radiopharmacy for obtaining sterile and apyrogenic sodium (Tc-99m) pertechnetate solution.

A total of 238 batches of Geltech generators have been processed (with a maximum of 24 generators per batch, containing up to 44 GBq (1.2 Ci) Mo-99 (on production day) in 5-6 g and sometimes 9-10 g ZrMo-99 gel powder and supplied to user hospitals including 14 field trial batches.

We report our results on processing of a large number of Geltech generator and sterility and apyrogenicity of sodium (Tc-99m) pertechnetate obtained from Geltech generator in this paper.

MATERIALS AND METHODS

All chemicals used were from commercial sources and mostly of GR/AR grade. Aluminum oxide active acidic, 100-200 mesh, of Brockman grade 1, for chromatographic analysis, from Prabhat Chemicals, Mumbai was used. (η, γ) Mo-99 was available as sodium molybdate in 3.5 M NaOH (150 mg of Mo/ml, concentration: 1.1-2.2 GBq/ml, specific activity: 7.4-15 GBq/g of Mo) from Radiochemical Section, Radiopharmaceuticals Division, BARC. The different types of glass columns, needles, rubber stopper used were procured locally. Filter sterile hydromillex (hydrophilic and hydrophobic filter) pore size 0.22 ηm, sterile, 25 mm dia, separately packed filter, Millipore Cat.: No. SLST025DM was procured from Pramukh Healthcare, Mumbai. Polypropylene barbed Luer adapter male luer with lock connector was procured from Cole Parmer. Kits for Tc-99m compounds were in-house produced. An ionization chamber (NPL, UK) pre-calibrated with Cs-137 and Atomlab dose calibrator were used for the assay of radioactivity.

Modification of the gel generator for assembling of on-line 0.22 μm membrane filter

In order to adopt an on-line 0.22 μm membrane filter the modification of Geltech generator has done in the following way. The ZrMo-99 gel column and the secondary purification alumina column are connected with a stainless steel U-needle. There are two needle adopters, one for 10 ml saline charge and another for collecting Tc-99m O_4^- in the 15 ml evacuated vial. The elution of the Tc-99m requires around 1-2 min through both the columns. A stainless steel adapter has been made to accommodate on-line 0.22 μm membrane filters with connecter at the alumina column end for collection of Tc-99m through the on-line 0.22 μm membrane filter.

Figure 1 shows the photograph of the Geltech generator with on-line 0.22 μm membrane filters.

Evaluation of performance of Tc-99m gel generator

The general procedure for preparing ZrMo-99 gel generators and their performance evaluation has been described earlier.[12-18] (η, γ) Mo-99 was converted into insoluble ZrMo-99 with mole ratio of reactant Mo: Zr was 1:1.25 and pH of the precipitate was adjusted to 4-5 with 4 N NaOH. The dried gel was disintegrated with normal saline, re-dried using IR lamp under suction to obtain free flowing gel granules. ZrMo-99 gel powder then transferred to a glass column (35 mm × 13 mm). The gel column containing 6-7 g (~2 g Mo) ZrMo-99 granules was sealed and assembled in the generator assembly.

The Geltech generator performance in terms smoothness of elution, pH and clarity of eluate, Tc-99m elution yield and Mo-99 breakthrough were ascertained. The quality of pertechnetate eluate was evaluated as per the IP specifications. The pharmaceutical purity aspects, sterility and apyrogenicity were checked by carrying out conventional sterility and apyrogenicity tests on decayed Tc-99m eluates.[21,22] Sterility and pyrogen tests performed for 5 generators and 27 Tc-99m eluates selected randomly from different batches of geltech generator.

RESULTS AND DISCUSSION

Geltech generator of capacity 250-400 mCi (9.25-14.8 GBq) Mo-99 activity are prepared and supplied to hospitals. The production data of Geltech generator since 2006 (April-March) is shown in Table 1 and the indigenous production facility is shown in Figure 2. Normal elution of Tc-99m from Geltech generator is performed by passing 10 ml of 0.9% normal saline through the primary ZrMo-99 gel column and collecting in a 15 ml sterile evacuated vial connecting at the Tc-99m collection end after secondary alumina column. Sterility of Tc-99m eluates is performed either by using sterile 0.22 μm membrane filter or autoclaving Tc-99m eluates. In the case of using the sterile 0.22 μm membrane hydrophilic filter (meant for single use) of Tc-99m eluates, there could be a loss of Tc-99m activity (~10%) due to

Figure 1: Gel generator with sterile filter assembly

Figure 2: Tc-99m Geltech generator production facility

the hold-up of Tc-99m solution in the filter medium. The same filter can't be used for subsequent filtration due to the formation of impervious air-film on the membrane filter. Whereas, in the case sterility obtained by autoclaving the product at 121°C for 30 min at 15 psi, there could be a loss of Tc-99m activity (10-11%) due to decay loss (it may take ~45-60 min for heating and then cooling of the product for use and 0.89% is the decay factor for Tc-99m for an hour).

The loss of Tc-99m activity due to decay and hold-up of activity in the membrane have been avoided by using on-line sterile 0.22 µm hydromillex membrane filter where both the hydrophilic and hydrophobic membrane filter are housed in the same polypropylene housing. The filter connected on-line can be used unchanged without affecting the quality of pertechnetate-Tc-99m and performance of the generator. Geltech generators which are evaluated under this investigation have modified generator assembly with on-line sterile 0.22 µm membrane filter. The elution efficiency for Tc-99m (average ~83%), Mo-99 break through (radionuclidic purity) and other quality features of eluted Tc-99m are summarized in Table 2. Colorimetric spot tests for Zr, Al, Mo were carried out as limit tests, which were less than 10 ppm. The radiochemical purity of Tc-99m O_4^- was >99% while that of the labeled formulation prepared using pertechnetate was >95%. Typical performance evaluation of Geltech generator for a period of 14 days with on-line 0.22 µm membrane filters is shown in Table 3.

There is almost negligible loss of volume of Tc-99m eluates in the elution process with sterile 0.22 µm membrane filter. The pH of all the eluates was in the range of 4.5-6. Sterility test results of 15 Geltech generators show the eluates are sterile and apyrogenic which is shown in Table 4. The sterility of Tc-99m eluates selected randomly were tested from eight different batches of geltech generators for a period of 10-21 days and found to meet IP requirement and shown in Table 5. The eluates of Geltech generators, which were evaluated post-expiry also showed that the eluates were also apyrogenic [Table 6].

Table 1: The production data of Geltech generator since 2006 (April-March)

Year	No. of batches prepared	Mo-99 activity handled Ci (GBq)	No. of gen supplied	Generator activity on calibration date mCi (GBq)
2006-2007	10	16.75 (620)	67	250 (9.25)
2007-2008	26	60.75 (2248)	243	250 (9.25)
2008-2009	27	89.18 (3300)	371	150-400 (5.55-14.8)
2009-2010	53	205.29 (7596)	638	150-400 (5.55-14.8)
2010-2011	49	190 (7030)	814	150-400 (5.55-14.8)
2011-2012	47	139.18 (5150)	564	150-400 (5.55-14.8)
2012-2013	12	26.5 (980.5)	114	150-400 (5.55-14.8)

Table 2: Performance evaluation of Geltech generators with online 0.22 µm membrane filter

Geltech gen. no.	Mo-99 act. on gen. mCi (GBq)	No. of elution	Tc-99 m eluted mCi (GBq)	^{99}Mo-99 break through	ST results	Remarks
Gen-7	250 (9.25)	10	223-9 (8.25-0.33)	Nd	Passed	–
Gen-19	400 (14.8)	9	278-24 (10.3-0.88)	2.2×10^{-3}	Passed	–
Gen-5	250 (9.25)	10	148-2 (5.5-0.07)	3.3×10^{-3}	Passed	–
Gen-20	400 (14.8)	10	304-26 (11.2-0.96)	Nd	Passed	–
Gen-5	250 (9.25)	12	103-6 (3.8-0.22)	Nd	Passed	Gen prepared on Friday
Gen-20	400 (14.8)	12	338-37 (12.5-1.37)	0.06	Passed	–
Gen-4	250 (9.25)	11	120-31 (4.44-1.15)	Nd	Passed	–
Gen-19	250 (9.25)	11	56-6 (2.07-0.22)	Nd	Passed	Gel bed with less powder

ST: Sterility test, Nd: Not detected

Table 3: Typical performance evaluation of Geltech generator with online 0.22 µm membrane filter

Mo-99 activity on column mCi (GBq)	Tc-99m growth period (h)	Tc-99m activity smCi (GBq)		Tc-99m practical yield (%)	Mo-99 break-through (%)
		Expected	Recovered		
300 (11.1)	96	289 (10.7)	223 (8.25)	77	6.7×10^{-3}
222 (8.5)	26	205 (7.6)	178 (6.4)	84	2.9×10^{-3}
140 (5.2)	46	135 (5.0)	114 (4.2)	84	4.4×10^{-3}
67 (2.5)	73	65 (2.4)	54 (1.99)	83	7.4×10^{-3}
51 (1.9)	24	46 (1.7)	39 (1.44)	85	1.2×10^{-2}
38 (1.4)	27	38 (1.4)	30 (1.11)	79	1.3×10^{-2}
30 (1.1)	22	26 (0.96)	22 (0.81)	84	1.3×10^{-2}
22 (0.8)	22	21 (0.77)	18 (0.66)	86	Nd

Nd: Not detected

Table 4: Sterility and pyrogen test data of sodium (Tc-99m) pertechnetate eluates from Geltech generator with 0.22 µm on-line membrane filter

Tc-99m eluates sl. no.	Product code	Gen. batch no./gen. no.	Sterility test	Pyrogen test
1-8	TCG-1	ZrM 118/G-4/E-1-E-8	Passed	Passed
9	TCG-1	ZrM 118/G-4/E-9 (PE)	Passed	Passed
10-11	TCG-1	ZrM 121/G-15/E-1-E-2	Passed	Passed
12	TCG-1	ZrM 121/G-15/E-6	Passed	Passed
13	TCG-1	ZrM 121/G-15/PE-1	Passed	Passed
14-15	TCG-1	ZrM 122/G-14/E-1-E-2	Passed	Passed
16	TCG-1	ZrM 122/G-14/E-6	Passed	Passed
17	TCG-1	ZrM 122/G-14/PE-1	Passed	Passed
18	TCG-1	ZrM 126/G-13/E-3	Passed	Passed
19	TCG-1	ZrM 126/G-13/E-5	Passed	Passed
20	TCG-1	ZrM 126/G-13/E-6	Passed	Passed
21	TCG-1	ZrM 126/G-13/PE-1	Passed	Passed
22-23	TCG-1	ZrM 127/G-17/E-1-E-2	Passed	Passed
24-26	TCG-1	ZrM 127/G-17/E-4-E-6	Passed	Passed
27	TCG-1	ZrM 127/G-17/E-7 (PE)	Passed	Passed

ZrM: Zirconium molybdate-Mo, TCG: Technetium column generator, PE: Post-expiry, E: Eluates, TCG-1 is 150 mCi (5.55 GBq) Geltech generator

Table 5: Sterility test results of Tc-99m eluates from Geltech generator with on-line 0.22 μm membrane filter

Geltech gen. batch no.	Gen. no.	No. of Tc-99m eluates tested	Period of elution and evaluation (days)	ST results
ZrM-77	G-19	11	13	Complies
ZrM-79	G-7	10	18	Complies
ZrM-80	G-19	09	14	Complies
ZrM-81	G-5	10	21	Complies
ZrM-82	G-20	10	14	Complies
ZrM-83	G-5	12	10	Complies
ZrM-84	G-20	12	13	Complies
ZrM-85	G-4	11	11	Complies
Total Gen.: 8		Total eluates tested: 85		

ZrM: Zirconium molybdate-Mo, ST: Sterility test

Table 6: Pyrogen test results of Tc-99m eluates from Geltech generator with on-line 0.22 μm membrane filter

Batch no.	Gen. no.	No. of Tc-99m eluates tested	Pyrogen test results (post-expiry)
ZrM-96	G-15	1/PE-2	Complies
ZrM-98	G-16	1/PE-2	Complies
ZrM-100	G-18	1/PE-2	Complies
ZrM-102	G-16	1/PE-2	Complies

ZrM: Zirconium molybdate–Mo

CONCLUSION

We have thus adopted a simple procedure for obtaining ready to use sterile and apyrogenic sodium (Tc-99m) pertechnetate from Geltech generator.

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