GEL GENERATOR TECHNOLOGY VIABILITY FOR SMALL SCALE PRODUCTION - INDIAN EXPERIENCE

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1. INTRODUCTION

The radioisotope ^{99m}Tc is used in nearly 80% of all diagnostic imaging procedures in nuclear medicine and hence ensuring its uninterrupted availability is of prime importance to the nuclear medicine industry. Of the various options available for accessing ^{99m}Tc from its precursor ^{99}Mo through a generator system, the ^{99m}Tc generator using a bed of acidic alumina column for column chromatographic separation of ^{99m}Tc from ^{99}Mo remains the most popular procedure world over. The uninterrupted availability of high specific activity (n,f)^{99}Mo, an essential requirement for the alumina column generators and produced by few large scale commercial suppliers, needs to be ensured to avoid frequent disruption in ^{99m}Tc supplies. Alternate technologies that could use (n,γ)^{99}Mo to meet partial/complete domestic demands are worth exploring to reduce import dependency/foster self-sufficiency particularly in countries having the necessary infrastructure in place.

The Indian pursuit of gel generator technology for ^{99m}Tc was driven mainly by three considerations, namely, (i) reliable, well-established and ease of production of (n,γ)^{99}Mo in TBq quantities in the research reactors in Trombay/Mumbai, India, (ii) need for relatively low-cost alternate technology to replace the solvent (MEK) extraction generator system in use in India since 1970s and (iii) minimize dependency on weekly import of fission-produced ^{99}Mo raw material required for alumina column generator. The development of column type ^{99m}Tc generator based on conversion of (n,γ)^{99}Mo as zirconium molybdate-^{99}Mo (ZrM) gel matrix and subsequent separation of ^{99m}Tc by elution in normal saline was an important development in this direction [1-5], as this combines the advantages of using (n,γ)^{99}Mo and a column based separation technique. A considerable volume of work was carried out at the Board of Radiation and Isotope Technology (BRIT) both independently [6-11] and as a part of IAEA's CRP [4,9] for standardization of the process.

After successful completion of feasibility studies and small scale production and supply of gel generators to local hospitals, development of technology for regular production and supply was undertaken. A multidisciplinary core team comprising of chemists and engineers working in close collaboration enabled successful completion of the project. The technology development entailed four major aspects: (i) adaptation of chemical process to automation, (ii) design and erection of a production facility with adequate shielding, (iii) design/fabrication/installation of operation specific gadgets, and (iv) design of a compact, portable, easy to assemble and reusable generator assembly.

The production facility, having a capacity to produce up to 25 generators per batch in an 8 hour shift operation, has been operational since the past five years. We report here the salient aspects of technology development and operational experience of producing the gel generators thereby demonstrating the viability of the technology.

2. TECHNOLOGY DEVELOPMENT ASPECTS

2.1. ADAPTATION OF CHEMICAL PROCESS TO AUTOMATION

The preparation of the generator under suction without decapping the seal and thus providing the highest level of safety and avoiding spillage of contents involves various complex steps of precipitation, filtration, drying, cake fragmentation to granular form and drying to obtain free flowing granules for dispensing in individual columns. Performing all the above steps through remote operations inside a closed shielded plant facility posed a number of challenges.

The production process entails the various steps shown in Fig.1.

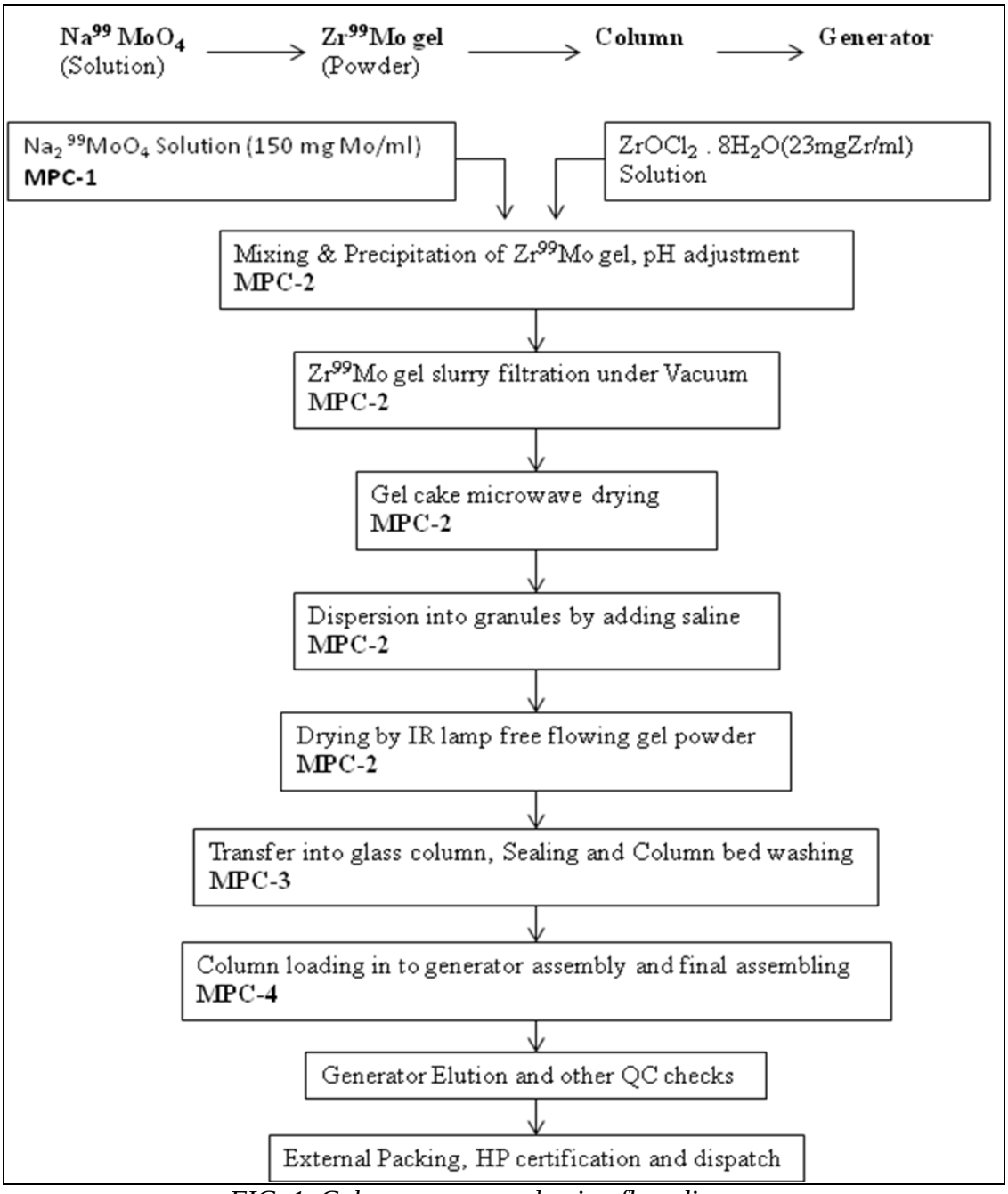

FIG. 1. Gel generator production flow diagram.

Two major issues addressed were process time reduction and process adaptation to automation in a shielded facility.

2.1.1 Process time reduction

The multi-step process has two critical rate determining steps: (1) filtration of the thick, viscous, gelatinous precipitate, which undergoes rapid sedimentation and forms an impervious barrier preventing further filtration, and (2) drying of ZrM cake (which contains about 85% water) in a controlled manner taking care to retain 'structural water' necessary to enable ^{99m}Tc elution from the matrix. A special Buchner type filter was designed and polypropylene filter cloth of specified porosity was used. Filtration was carried out using a vacuum pump and the filtered cake was recovered by inverting the filter and applying compressed air. For achieving reduction in drying time, a domestic microwave oven rendered amenable to remote operations was used and drying was carried out under controlled intensity [12]. The optimization of the microwave drying conditions and its adaptation to gel processing in a shielded facility was a major breakthrough paving the way for batch size enhancement [13].

2.1.2 Process adaptation to automation in shielded facility [14-16]

Special process apparatus were designed and fabricated to suit operational requirements for slurry filtration, collection of filtered cake and granule collection post drying. Solution/slurry transfers were affected using peristaltic pumps. For filtration, an oil-free, moisture–free diaphragm type vacuum pump was used. After filtration, the gel-cake was discharged into a collection vessel and dried in a domestic microwave oven rendered amenable for remote operations. The cake collection dish and granule receiver were moved from one station to another by pneumatically operated actuators**.** Special ducting was connected to the oven to exhaust the moisture laden air during drying of the gel cake [13]. The dried lumps were transferred into another vessel and rendered into granular form using a shower arrangement for spraying normal saline. The granules were converted into free flowing form by drying under an infra-red lamp.

2.2. DESIGN OF PRODUCTION FACILITY AND OPERATION SPECIFIC GADGETS

A 100mm lead-shielded production facility comprising 4 interconnected processing cells (MPC-1 to MPC-4) was designed and erected for carrying out the production operations (Fig. 2). Each cell was equipped with specially designed gadgets to suit operational requirements. In the first cell, the sodium molybdate-^{99}Mo solution containers were handled and the contents transferred to a pooling vessel under suction without opening the containers using a specially designed gadget.

FIG. 2. Generator production facility.

In the second cell (MPC-2), the entire process from precipitation of zirconium molybdate-^{99}Mo gel to converting it to free flowing granules is carried out (Fig. 1). This cell is equipped with process vessels such as a mixing vessel, specially designed filters, cake collection dish, granule receiver vessel, and gadgets like a microwave oven, an IR lamp (250W) for drying, a peristaltic pump for solution/slurry transfers and a pneumatic powered material handling system (Fig. 3, Fig. 4). The material handling system can move to different pre-programmed stations such as microwave drying station and IR drying station with three-dimensional controlled movement.

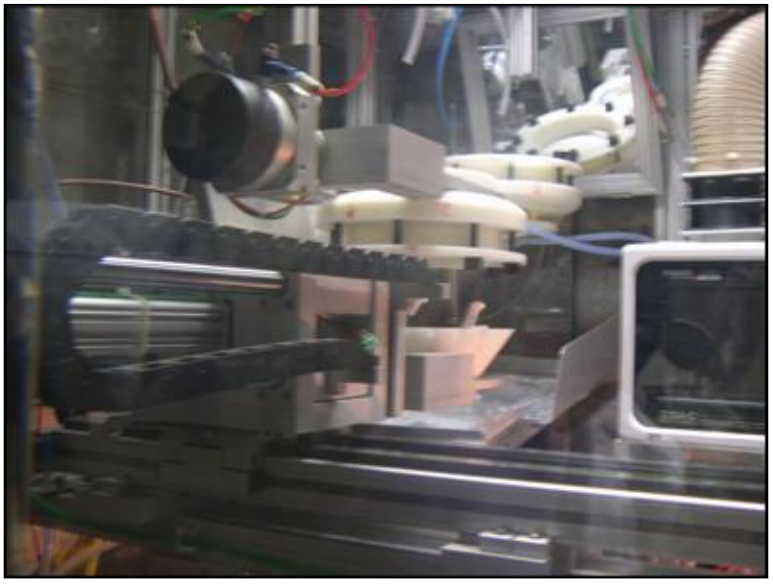

FIG. 3. Gel cake discharge from filter.

FIG. 4. Microwave drying.

For filtration, an oil-free, moisture–free diaphragm type vacuum pump is used. After filtration, the gelcake is discharged into a collection vessel and dried in a domestic microwave oven made amenable for remote operations. Special ducting is connected to the oven to exhaust the moisture laden air during drying of the gel cake [13]. The cake collection dish and granule receiver are moved from one station to another by the pneumatic powered material handling system. The dried lumps are transferred into another vessel and rendered into granular form using a shower arrangement for spraying saline. The granules are converted into free flowing form by drying under an IR lamp.

In the third cell (MPC-3), equipped with operation specific gadgets, the ZrM granules are dispensed into individual glass columns using a specially developed dispensing device in which a variable quantity of granules can be dispensed. The rubber closure and aluminium cap are inserted to seal the column using special pick and place devices and the columns crimped remotely using a crimper. The cell also has provisions for washing the column beds with saline under suction.

In the fourth cell (MPC-4), the activity containing glass columns are transferred into pre-assembled cold generator assembly, the top shielding plug is inserted in place and the generator is moved outside the MPC-4 to elution testing station through a conveyor system.

2.3. DESIGN OF GEL GENERATOR ASSEMBLY

The gel generator is a dual column system comprised of a primary column containing zirconium molybdate-^{99}Mo gel granules and a secondary acidic alumina purification column for adsorption of traces of any co-eluted ^{99}Mo. While designing the generator assembly, due consideration was given to the necessity to house dual columns with provision to disconnect the secondary alumina column if needed and render it compatible for applying suitable concentration procedures for availing pertechnetate of higher radioactive concentration. Other features, such as making the design amenable to recyclability, ease of dismantling and assembling, and incorporation of on-line sterile membrane filter, were borne in mind while developing the generator assembly.

The compact, portable generator assembly has an external casing of ABS plastic and internal components of lead and stainless steel (Fig. 5). The unique design of the ‘cold’

generator assembly has been well appreciated and an export order to Kazakhstan has been executed through IAEA.

FIG. 5. Geltech generator assembly.

3. FACILITY OPERATIONS AND PRODUCTION STATUS

Consequent to process technology and production facility development, formal review of the safety features was carried out by the regulatory authority, Atomic Energy Regulatory Board (AERB) and stage-wise clearance for ^{99}Mo activity handling was obtained progressively increasing from 74GBq (2Ci) to 370GBq (10Ci) and 1.1TBq (30Ci) per batch.

The production facility has been operational for the last 5 years, initially on a fortnightly and later on a weekly basis and over 200 batches of generators have been processed at the time of writing. 50g of Mo (75gMoO_3) are converted to 160-170g ZrM gel granules and used for preparing 15-25 generators in a single 8h working shift. The process yield is 75-80%. The typical specific activity of indigenous (n,γ)^{99}Mo used for processing is ~11GBq/g ^{99}Mo and generators of activity 9.3 GBq on calibration date are supplied. Generators of activity 15 GBq and 28 GBq were supplied occasionally by spiking (n,γ) produced ^{99}Mo with fission moly. Marketed under the name ‘Geltech’ generator, over 2500 generators have been supplied to nuclear medicine hospitals in India. The ^{99m}Tc elution efficiency when eluted with 10ml saline is ~75%. The pertechnetate eluted from the generators is compatible for preparing all Tc radiopharmaceuticals such as ^{99m}Tc-MDP, ^{99m}Tc-MIBI, ^{99m}Tc-EC, ^{99m}Tc-ECD, ^{99m}Tc-DTPA and good quality images have been obtained on use in patients.

3.1. LIQUID WASTE MANAGEMENT STRATEGY

~10L of liquid waste are generated per 50g Mo processed. The waste comprises of filtrate of gel precipitate, product granule fines washed down during the gel fragmentation stage, column bed washing and process vessel and tubing rinsings. The liquid waste is collected in glass bottles placed in the processing cells and transferred by gravity, through pneumatic drain valves, to a HDPE carboy kept in the bottom compartment of the processing

cells which are provided with 4 inch lead shielding on the front and rear side. A new carboy is used for each batch. After allowing for a decay period of ~6 months, aliquots from each batch are assayed to determine the radioactive concentration (Bq/ml), identify and quantify presence of long-lived radionuclide contaminants etc. Thereafter the carboys are transferred to Waste Management Division, BARC, for appropriate handling prior to disposal.

3.2. RECYCLING OF GEL GENERATOR ASSEMBLIES

The practicability of recycling and repeated use of non-consumable hardware components has been demonstrated to satisfaction. Generators are supplied to all hospitals on a returnable basis. The main radioactive gel glass column, needles, secondary alumina column etc are removed from generator assembly, stored and disposed of appropriately and non-consumable hardware parts of the generator are hygienized and reused.

Prior to processing day, each generator is assembled completely in a Laminar Flow Bench, and a dummy empty column and secondary alumina column are inserted in place. An elution check is carried out to ensure the integrity of all connections. The dummy column is replaced with the column containing radioactive gel powder in MPC-4 after the processing has been completed.

3.3. PROSPECTS OF POST-ELUTION CONCENTRATION OF PERTECHNETATE (PEC)

Post-elution concentration (PEC) of pertechnetate would help to enhance the prospects to utilize $(n,\gamma)^{99}Mo$ along with larger beds of ZrM columns. Our work has shown that the purification trap column of alumina contained in the ZrM system can be used for the dual purposes of purification and concentration [17,18]. Use of de-ionised water as primary eluent, after carefully applying pre-treatment procedures on ZrM granules, is compatible to trapping traces of ^{99}Mo and all the ^{99m}Tc eluted; subsequent elution of the alumina trap bed with a few ml of normal saline releases pure ^{99m}Tc in quantitative yields. The post elution concentration procedure standardized by us provides a nearly 3-fold increase in radioactive concentration of ^{99m}Tc. The duration of this concentration process is ~3 minutes. The critical requirement is to ensure absence of macroscopic anionic load in the primary eluate. The prospects of adopting such a scheme in a central radiopharmacy setting, to access pertechnetate of higher radioactive concentration especially for preparing ^{99m}Tc-MDP and ^{99m}Tc-MIBI appear promising. The Geltech generator design has been suitably modified for adopting the post elution concentration procedure [19] for the portable type generator also.

4. CONCLUSION

We have thus demonstrated the gel technology viability by maintaining an uninterrupted production and supply of ‘Geltech’ generators for the past five years. The generator activity is a function of the specific activity of ^{99}Mo used for processing and the quantity of ZrM granules filled in the column. In our present set up, this can be varied up to a maximum of 10g defined by the column capacity and the volume required for elution kept at 10ml. Thus for a batch processed using 15GBq/g ^{99}Mo, generators of maximum activity 15GBq calibrated for 2 days post production are feasible. The practicability of recycling of generator hardware has been demonstrated making it a cost-effective and environment friendly initiative. The procedure developed by us for concentration of pertechnetate post elution and its adaptation in the generator assembly has widened the scope of utility of gel generator, even when faced with lower specific activities of ^{99}Mo.

The important details available from the Indian experience, as well as the comprehensive technical know-how, will be of considerable value for other producers and countries planning to pursue the gel generator strategy. The gel technology option could thus serve as a good complement to ensuring the availability of ^{99m}Tc in countries with low to medium requirements and local reactor production capability for (n,γ)^{99}Mo, even as alumina column chromatographic generators based on the use of fission product ^{99}Mo continue to remain the main source of ^{99m}Tc for most of the large-scale production needs.

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REFERENCES

1. EVANS J.V., MOORE P.W., SHYING G. M. E., SODEAU J. M., "A new generator for technetium-99m", 3rd Congress of World Fed. of Nucl. Med. & Biol., Paris Vol. II, Ed. Raynaud C. p.1592, 1982.

2. EVANS J.V., MOORE P.W., SHYING M.E., SODEAU J.M. ET AL., "Zirconium molybdate gel as a generator for ^{99m}Tc-I: The concept and its evaluation", Appl. Radiat. Isot. 38, 19-23, 1987.

3. NARASIMHAN D.V.S., VANAJA P., MANI R.S., "Preparation of sterile closed system^{99m}Tc generator based on zirconium molybdate, J. Radioanal. Nucl. Chem. Letters 85, 163-172, 1984.

4. NARASIMHAN D. V. S., SARASWATHY P., SINGH L. N. PATEL R. R., SARKAR S. K., **"**Procedures for Production of ^{99m}Tc Generators based on ^{99}Mo conversion to Zirconium Molybdate, In 'Alternate Technologies for ^{99m}Tc Generators', IAEA-TECDOC-852, Vienna, 1995.

5. SARASWATHY, P., SARKAR, S.K., PATEL, R.R., ARORA, S.S., NARASIMHAN, D.V.S, "^{99m}Tc Gel generators based on zirconium molybdate-^{99}Mo: I: Process standardization for production Radiochimica Acta 83**,** 97-102, 1998.

6. SARASWATHY P, SARKAR, S.K., RAMAMOORTHY, N., ARJUN.G, PATEL, R.R.: ^{99m}Tc Gel generators based on zirconium molybdate-^{99}Mo: II: Evaluation of preparation and performance, Radiochimica Acta, 83, 103-108, 1998.

7. SARKAR S. K., SARASWATHY P., PATEL R.R., "Evaluation of Microwave drying method for bulk preparation of Zirconium Molybdate-^{99}Mo for gel generators" ,Proceedings of NUCAR-, DAE-BRNS, India, 270- 272, 1997.

8. SARASWATHY, P**.,** SARKAR, S.K., NARASIMHAN, D.V.S., PATEL, R.R RAMAMOORTHY,N, "Microwave oven drying of zirconium molybdate-^{99}Mo for use in ^{99m}Tc Gel generator" Applied Radiat & Isot., 50,277-281,1999.

9. SARASWATHY P., SARKAR S.K., PATEL R.R, ARORA S.S, ARJUN .G., NARASIMHAN D.V.S., RAMAMOORTHY, N., "Evaluation of preparation and performance of gel column ^{99m}Tc generators based on zirconium molybdate-^{99}Mo", *IAEA TECDOC,* 1029, 385-397,1998.

10. SARASWATHY, P., "Studies on the Separation, Characterization and Evaluation of technetium-99m: Applicability to ^{99}Mo-^{99m}Tc generator for medical use", PhD Thesis, University of Mumbai, India, 2002.

11. SARASWATHY P, S.K.SARKAR, ARJUN.G, NANDY S.K, RAMAMOORTHY N., "^{99m}Tc gel generators based on zirconium molybdate-^{99}Mo: III: Influence of preparatory conditions of zirconium molybdate-^{99}Mo gel on generator performance", Radiochimica Acta, 92, 259-264, 2004.
12. P.SARASWATHY, A.C. DEY, PRABHAKAR NASKAR, S.K. SARKAR, CHETAN KOTHALKAR ET.AL. "A multistage radiochemical process for medium-scale zirconium molybdate-^{99}Mo preparation for use in ^{99m}Tc column generators, Proceedings of NUCAR-2005, DAE-BRNS, India, 617-618,2005.
13. A.C.DEY, PRABHAKAR NASKAR ET.AL., "Microwave Drying of Zirconium Molybdate- ^{99}Mo Gel in a Shielded Tong Box: Evaluation With Respect To Radiation Safety Aspects" Proceedings of 27th National conference of Indian Association For Radiation Protection, Mumbai,130-132, 2005.
14. N. RAMAMOORTHY, "Production and availability of 99mTc generators and of 99Mo: Technology considerations and IAEA's contributions", Proceedings of NUCAR-2007, DAE-BRNS, India, 24-32,2007.
15. Saraswathy Padmanabhan, Chemical process related technology development for production of Zirconium Molybdate- ^{99}Mo based ^{99m}Tc gel generators: Indian experience", Proceedings of NUCAR-2007, DAE-BRNS, India, 45-48,2007.
16. P.SARASWATHY, A.C.DEY, S.K.SARKAR, C.KOTHALKAR, P.NASKAR, G.ARJUN, S.S.ARORA, A.K.KOHLI, V.MEERA, V.VENUGOPAL AND N.RAMAMOORTHY, ^{99m}Tc generators for clinical use based on Zirconium Molybdate-^{99}Mo gel and (n,γ) produced ^{99}Mo: Indian experience in the development and deployment of indigenous technology and processing facilities, Proceedings of the XXIX International Meeting on Reduced Enrichment for Research and Test Reactors, Prague, Czech Republic, September 23-27, 2007.
17. S.K.SARKAR, P.SARASWATHY, G.ARJUN, N.RAMAMOORTHY, "High radioactive concentration of ^{99m}Tc from zirconium molybdate-^{99}Mo gel generator using an acidic alumina column for purification- cum-concentration", Nucl. Med. Comm. 25, 609-614, 2004.
18. S.K.SARKAR, "Studies on the preparation and evaluation of novel delivery system for ^{99m}Tc based on ion-exchanger columns in tandem", PhD Thesis, University of Mumbai, India, 2004.
19. CHETAN KOTHALKAR, SARKAR S.K, "Adopting the simple concentration procedure of pertechnetate into Zirconium Molybdate-^{99}Mo gel generator," Proc of NUCAR-2007, DAE-BRNS, India, 567-568,2007.