$^{99}Mo/^{99m}Tc$ GENERATOR AND RADIOPHARMACEUTICALS PRODUCTIONS AT ÇEKMECE NUCLEAR RESEARCH AND TRAINING CENTER

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ABSTRACT

Molybdenum-99 is produced in large quantities as the parent radioisotope of ^{99m}Tc, which has been used in nuclear medicine. The rapid growth of nuclear medical diagnosis with ^{99m}Tc is due to completion of a system supplying radiopharmaceuticals labelled with a short lived radioisotope like ^{99m}Tc, and the development of nuclear medical instruments like an Anger Camera and a single photon emission tomography (SPECT or ECT). The Radioisotope and Radiopharmaceutical Department (RIF) at Çekmece Nuclear Research and Training Center (ÇNAEM) has been active in production of ^{99m}Tc and kits to be labelled to form radiopharmaceuticals. In generator produced eluates, the purity and chemical parameters must conform to special requirements. The requirements of European Pharmacopoeia for sodium pertechnetate ^{99m}Tc injection are fulfilled when it is prepared in our department. Assurance of radiopharmaceutical quality control, which involve test of biolog

ical purity and pyrogenity and sterility, is also performed.

INTRODUCTION

A radiopharmaceutical is a radioactive compound used for the diagnosis and therapeutic treatment of human diseases. In nuclear medicine nearly 95% of the radiopharmaceuticals are used for diagnostic purposes, while the rest are used for therapeutic treatment. Since they are administered to humans, they should be sterile and pyrogen-free and they should undergo all quality control measurements required for a conventional drug. A radiopharmaceutical may be radioactive element such as ^{99m}Tc and ^{131}I or labelled compound such as ^{131}I– iodinated proteins and ^{99m}Tc-labelled compounds. Therefore the most commonly used term is "radiopharmaceuticals

A radiopharmaceutical has two components, a radionuclide and a pharmaceutical. The radiopharmaceutical should be easily produced, inexpensive and readily available in any nuclear medicine facility. Radionuclides are produced in a cyclotron or a reactor. These facilities are available in only a few institutions and only long lived radionuclides can be supplied to distant user. The short-lived radionuclides can not be transported to the distant places because of their rapid decay. Recently, the use of short-lived radionuclides has grown considerably. This is because larger doses of those radionuclides can be administered to the patient with only

minimal radiation dose and excellent image quality. Nearly 80% of all radiopharmaceuticals used in nuclear medicine are ^{99m}Tc labelled compounds. The reason for such a pre-eminent position of ^{99m}Tc in clinical used is its extremely favourable physical and radiation characteristics with γ-energy of 140 keV and short half life of 6 h. This increasing appreciation of the short-lived radionuclides has let to the development of radionuclide generators that serve as convenient sources of the short-lived radionuclides. The importance of radionuclides generators lies in the fact that they are easily transportable and serve as sources of short-lived radionuclides in hospitals far from the any cyclotron any reactor facility. Furthermore, ^{99m}Tc is readily available in a sterile, pyrogen-free and carrier-free state from ^{99}Mo/ ^{99m}Tc generators.

Since nuclear pharmacy has become an essential central element of the nuclear medicine laboratory production of DTPA(dimethylen three amine penta aceticacid for kidney scanning), MDP (methylene di phosphanate for skeleton scanning), PYP (pyrophosphate for skeleten and hearth scanning) radiopharmaceuticals in Radioisotope and Radiopharmaceutical Department at Çekmece Nuclear Research and Training Center have served great benefit for the user in Turkey.

Since 1994 we have produced generators which transported with saline solution and radiopharmaceuticals depending on the demand of users.

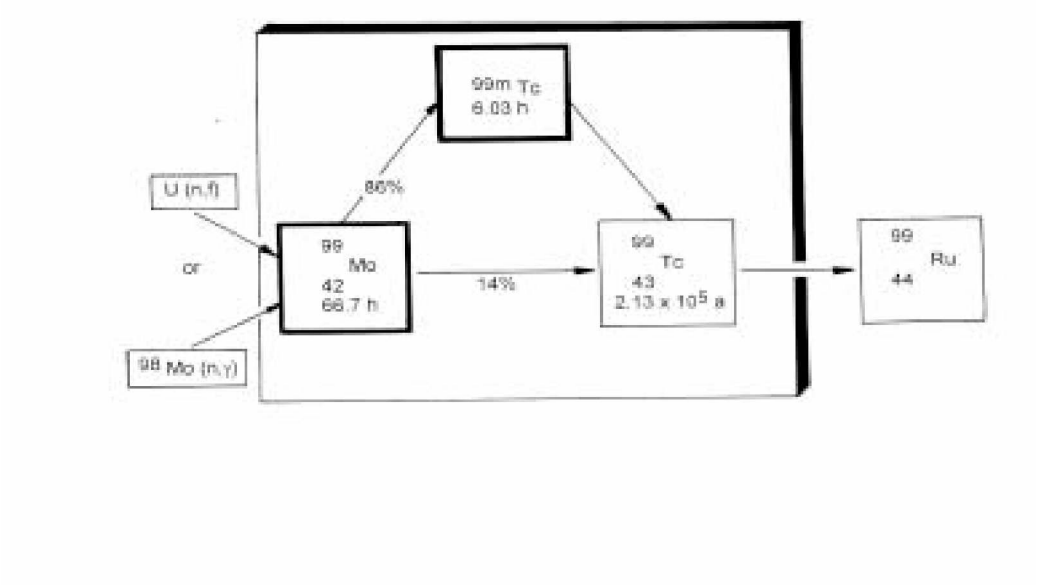
In this presentation, preparation of generators and pharmaceuticals, their quality control and dispensing are briefly discussed. Quality procedures including standard operating procedures (SOP), record forms are all line with Good Manufacturing Practice (GMP) standards.

MATERIAL AND METHOD

PRODUCTION OF GENERATOR

^{99}Mo/^{99m}Tc generator produced at ÇNAEM is used in nuclear medicine. Generators provide an elution with sterile and pyrogen free solution of pertecnetate.

It fulfils the requirements for Tc-injection set in monograms of European Pharmacopoeia. This solution can be used as oral and intravenous administration or as a starting material for aseptic preparation of various Tc-labelled radiopharmaceuticals.



A generator is constructed on the principal of the decay-growth relationship between a long-lived parent radionuclide and its short-lived daughter radionuclide. The chemical property of the daughter nuclide must be distinctly different from that of the parent nuclide so that the former can be readily separated. In a generator, basically a long-lived parent nuclide is allowed to decay to its short-lived daughter radionuclide and later is separated chemically. ^{99m}Tc is most used radionuclide in nuclear medicine because of favarouble 6 h physical half-life and the absence of β^- radiations permit the administration of millicurie amounts of ^{99m}Tc radioactivity without a significant radiation dose to the patient. In addition, the monochromatic 140 keV photons are readily collimated to give image of superior spatial resolution. Generator of most important way to supply ^{99m}Tc due to the problem of transporting of isotope with a half life only 6 h. This system is normaly used for a week in the hospital but will give lower yield of pertecnetate when it is eluated each day.

UNIT OF MANUFACTURES

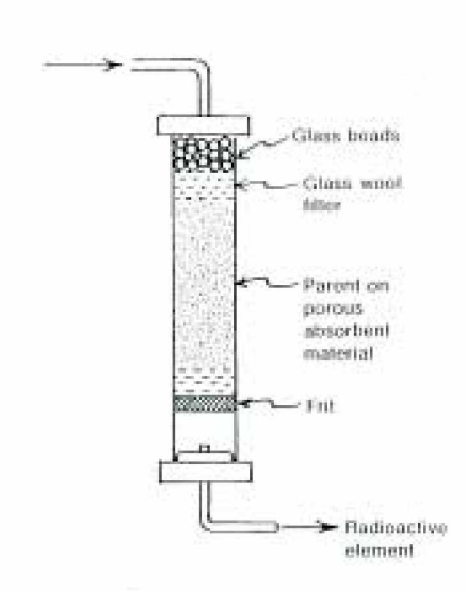
Specially designed units for manufacture of generator are called hot cells. They are made as sealed cells of plexi-glass, which are surrounded of 10-cm lead shield.

All manipulation of the production equipment is done using remote handling tongs fitted in the walls of the cell. Hot cells are situated in clean laboratory room where all the air entering the room is HEPA filtered. The cells have reduced pressure towards the surrounded laboratory to protect the personnel against the possible leakage of radioactive gases or small radioactive particles.

PREPARATION OF GENERATORS

The glass column is filled with aluminium oxide and placed in position in the production equipment.

Carrier is added to the alkaline solution of fission produced ^{99}Mo and pH adjusted to 3 to 7. The radioactive concentration of the ^{99}Mo is measured and its calculated volume is dispersed to the columns by the peristalting pump. So, ^{99}Mo is fixed to the aluminium oxide.



Through radioactive decay ^{99m}Tc is performed and it will be present as pertechnetate, which will not bind aluminium oxide. And therefore can be separated by using 20-ml saline solution. The columns are closed by rubber stopper and aluminium seals and sterilised by autoclaving.

MOUNTING THE INTERNAL PART OF THE GENERATORS

Specially designed stainless steel needles are connected to the column for passage of saline solution. Sterile filtered air is introduced to the system to get high yields of ^{99m}Tc and to ensure the sterility of whole system. Generator is eluted by using 20 ml sterilised evacuated vials and saline solution in 3 different vials.

The generator is placed in a stationery laboratory shield which gives additional protection when it is sent to the hospital. The generators are produced on Fridays and are all calibrated with regard to the activity on the following Monday. The hospital staff may then theoretically calculate how much activity that will be available each day of the week. As the fission produced ^{99}Mo contains very low amount of radioactive impurities fixed to the aluminium oxide, generators are returned to the manufacturer after used. In this way the hospitals avoids handling and storage of small amount of long lived radioactive waste product.

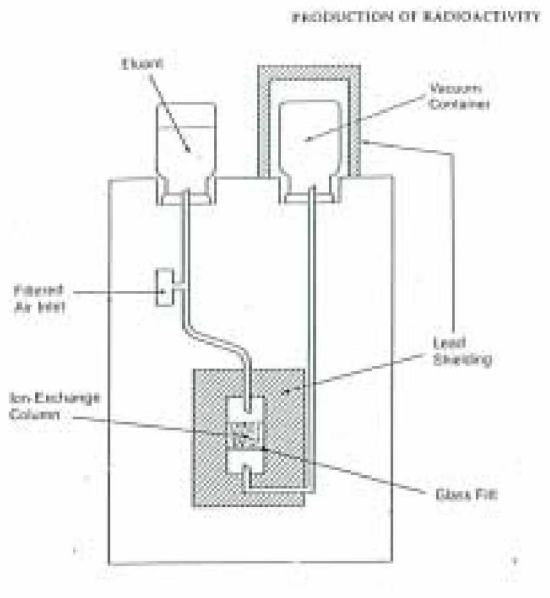
METHODS OF RADIOLABELLING AND PREPARING RADIOPHARMACEUTICALS

Radiopharmaceutical is a drug It is not only used for therapeutically purposes, more then 95% of the radiopharmaceuticals are used as diagnostic agents. They have two components. Radioactive atom, which gives off radiation necessary for detection and nonradioactive components which, provides the radiopharmaceuticals with the ability to localise the radioactivity in the target organ or tissue. ^{99m}Tc eluated directly from the ^{99}Mo/^{99m}Tc generator as sodium pertechnetate which can be used for several nuclear medicine procedures, including brain and thyroid imaging, organ blood flow imaging, and labelling of red blood cells. Its usefulness can be extended by complexing (or radiolabelling) this radionuclide on the variety of tissue-spesific compounds, thus forming several useful radiopharmaceuticals.

Generator produced ^{99m}Tc contains $NaTcO_4$ in the chemically nonreactive +7 oxidation state and will not label compounds by simple addition. Radiopharmaceutical preparation requires ^{99m}Tc reduction to a chemically reactive species, generally to +4 oxidation state, in order for labelling to occur. Reduction of $^{+7}TcO_4$ is done by stannous chloride in acidic medium according to this chemical reaction $2Tc^{7+}O_4+16H^{+}+3Sn^{2+}\rightarrow 2\ ^{99m}Tc^{4+}+3Sn^{4+}+8H_2O$

The reduced ^{99m}Tc species are highly reactive and combine with wide variety of chelating compounds. Reduced Tc + Chelating agent ↔ ^{99m}Tc- chelate (IV)

(MDP,PYP,DTPA) (Radiopharmaceutical)



^{99m}Tc radiopharmaceuticals utilise reduced states of ^{99m}Tc for labelling and are prepared using " KITS". These products are produced in our departments as sterile, pyrogenic vials that contain a reducing agent, the compound to be labelled and additional substances that facilitate the labelling reaction or enhance the stability of the formed ^{99m}Tc complex. The solution is

lyophilized (freeze-dried) and the vial flushed and filled with sterile nitrogen. The lyophilization renders the dried material in the vial readily soluble in aqueus solution and also aid in labelling by chelation. The preparation is carried out using sterile materials and under strict acceptic conditions in a laminar flowhood under positive pressure. When the TcO_4 solution is added to lyophilized chelating compounds in the kit vial ^{99m}Tc is reduced by Sn^{2+} in the Sn- chelat. This step is performed in the hospital.

QUALITY CONTROL

Quality control is part of the quality assurance programme at CNAEM. Quality assurance includes;

1. Establishment of relevant batches documentation system.
2. Establishment of documentation for the production procedures including implementation of Good Manufacturing Practice (GMP) procedures.
3. Quality control procedures.

Basically the quality control involves several specific tests and measurements that ensure the purity, product identity, biologic safety and efficacy of radiopharmaceuticals. The ultimate responsibility for quality assurance of radiopharmaceuticals lies with the radiopharmacist and the well-trained personnel in charge of the radioisotope production.

In every operation several general rules are followed with regard to the maintenance of quality assurance of radiopharmaceuticals. All preparations are handled aseptically. Each radiopharmaceutical whether a commercial or in-house preparation are subjected to several quality control tests.

The test programmes for the quality of the starting materials and the finished products are based on the monographs from the European Pharmacopoeia. The final quality control procedures are carried out on a product before release. These tests fall into two categories;

Physicochemical Tests	**Biological Tests**
pH and ionic strength	Sterility
Radionuclide purity	Pyrogenity
Radiochemical purity	Toxicity
Chemical purity	

CONTROL TESTS ON THE RADIOISOTOPES $^{99}Mo/^{99m}Tc$ GENERATOR

^{99m}Tc eluates for the control of the;

- Elution yield of each generator
- Radionuclidic purity (^{99}Mo) on each generator
- pH in the eluate (highest activity generator)

- Aluminium content in the eluate
- Radiochemical purity

The tests performed on production date before release of the product are;

Elution yield: ^{99}Mo and ^{99m}Tc activity are measured by dose calibrator for each column

$^{99}Mo/^{99m}$ Tc/ ratio is determined as a yield.

Radionuclidic purity: The ratio ^{99}Mo is measured in the eluate of every single generator. A gamma spectrum is obtained on a Canberra multi channel analyzer.

^{99}Mo breakthrough less than 0.1%

Radiochemical purity: is determined by paper chromatography. Min. 99.0% of the

^{99m} Tc activity as pertechnetate($^{99m}TcO_4^-$)

The test performed after the products has been release are;

Aluminium content (3 eluates): The analysis is performed about a week after the elution for the reason of radiation protection. The aluminium content is determined by spectrophotometer must be 5ppm/ml.

pH (3 eluates): The analysis is performed about a week after the elution for reason of radiation protections measured with combined glass electrode. 5.0 - 7.0

Determination of $^{89/90}Sr$: This is done by a chemical separation at least one week after the elution followed by a beta detection by a GM tube at least 3 weeks after the separation.

$^{89/90}Sr$ content in eluate less than ^{89}Sr 0.00006%

^{90}Sr 0.00006%

Tests performed of elusion accessories / stock solution before release is:

Sodium chloride 0.9%

Tests for pyrogen **:** A limulus test is performed with positive product

Pyrogen < 175 Eu / 20 ml

pH: 5.5 - 7.5

Osmotic pressure: 270 - 300 mOsm.

Sterility: Sterile

Evacuated vials:

Test for pyrogens (5 vials):

Pyrogen < 175 Eu / 20 ml

pH: 6.0 - 8.0

CONTROL TESTS ON THE RADIOPHARMACEUTICALS MDP, PYP, DTPA

Identity of MDP, PYP, DTPA : Colorimetric method

pH : Measured by pH meter.

Radiochemical purity: Chromatographic Methods

Sterility tests: Sterile

Apirogenicity: LAL test.

Sn : Titration methods

CONCLUSION

We have a great potential to supply to $^{99}Mo/^{99m}Tc$ generator to nuclear medicine laboratories. and hospitals. Distribution cover Turkey from west to East and from North to South. About 1800-2000 generator are produced (Israel origin) annually. When we compare with our compatitor 60 % of requirenement of the generators are transported by Monrol Nuclear Product INC facilities after producing prossess of Mo^{99} in our department, 30 % of them are given to the laboratories in Istanbul, 46 % of them are given to universities of government hospitals.

It is possible to reduce the cost of production by increasing the number of production. The market share of the local products will increase depending on the availability and the price compared to the imported ones. This co-ordination and coproduction will give the opportunity to establish new markets in D--8 countries and other countries.

We have allready transported of 100 boxes of MDP,PYP, DTPA kits annualy.We are wishing to increase the amount of our production to considerable extends.

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