

Chapter 5

Radioisotope production for health applications

English version of:

Capítulo 5

Producción de radioisótopos para aplicaciones en la salud

Published originally in the book:

**Contribuciones del Instituto Nacional de Investigaciones Nucleares al
Avance de la Ciencia y la Tecnología en México
Edición Conmemorativa 2010**

Translation: Fabiola Monroy Guzmán

Radioisotope production for health applications

Fabiola Monroy-Guzmán¹
Jose Alanís Morales²

¹Radiation Protection Department
²Radioactive Materials Department

fabiola.monroy@inin.gob.mx

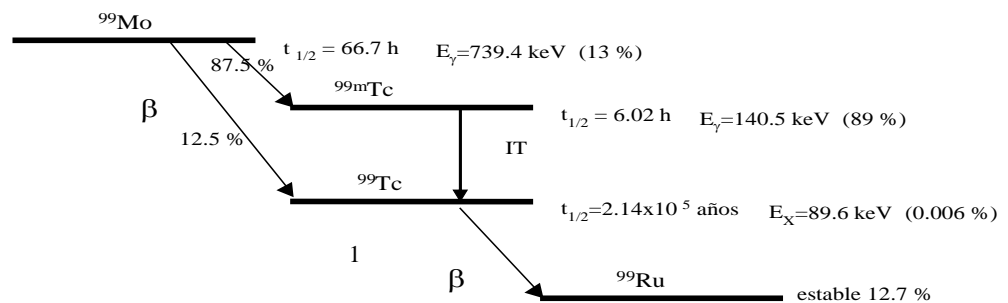
1. Introduction

In the Department of Radioactive Materials of the National Institute of Nuclear Research, processes for radioisotope production of interest in medicine, research, industry and agriculture have been studied and developed. In particular five new processes have been developed over the past 10 years by the Radioactive Materials Research Laboratory Group (RMRL) to produce: $^{99}\text{Mo} / \text{Tc}^{99m}$ and $^{188}\text{W} / ^{188}\text{Re}$ generators, the radiolanthanides: ^{151}Pm , ^{147}Pm , ^{161}Tb , ^{166}Ho and ^{177}Lu , and ^{131}I and ^{32}P . All of these radioisotopes are artificial and can be produced in either nuclear reactors or particle accelerators.

Radioisotope generators of particular interest, such as $^{99}\text{Mo} / ^{99m}\text{Tc}$ and $^{188}\text{W} / ^{188}\text{Re}$ are presented in this chapter, because they allow continuous production of an artificial radioisotope, in this case ^{99m}Tc and ^{188}Re without the need for a nuclear reactor or a particle accelerator. They are perfectly shielded compact systems that are safe to handle such that, once the radioactive material has decayed, no radiological risk exists either for the environment or the population. These systems are therefore very useful in places where there are no nuclear reactors or no continuous supply of the radioisotope, due to its decay, its cost or logistical problems in their supply, as is the case with many hospitals and research centers or industry of our country. These generators base their operation in the continuous production of a radioisotope (daughter), for example ^{99m}Tc , by the radioactive decay of its parent, in this case ^{99}Mo , which has a half-life greater than that of

its daughter (see Figure 1).

Figure 1
Radioactive decay of ^{99m}Tc and ^{99}Mo



The generator system allows separation of two radioisotopes, applying chromatographic techniques, so that the father radioisotope becomes the generator while the daughter radioisotope is isolated for its immediate implementation. This cycle is repeated until the father radioisotope decays completely.

The radiolanthanides ^{131}I and ^{32}P production are due to radioactive decay of a parent, but the separation of father and daughter is carried out in a single stage given that the system is not capable of continuously producing the daughter radioisotope. Thus, the main goal for developing generators and generally radioisotope production is to find the most appropriate methodologies to separate and purify radioisotopes in a fast and secure manner.

2. $^{99}Mo/^{99m}Tc$ Generators based on ^{99}Mo gels-zirconium, titanium and magnesium molybdates.

^{99m}Tc is a widely used radioisotope in nuclear medicine, since approximately 53 radiopharmaceuticals can be prepared from it, and it is approved for use in humans, which is 65% of all nuclear medicine studies practiced worldwide and 80% in Mexico. ^{99m}Tc is used in the production and development of radiopharmaceuticals for diagnosis in bone diseases (tumors, osteomyelitis, etc.), system (cholestasis, jaundice, cholecystitis, etc.), brain (detection of mental disorders, vascular lesions, etc.) heart (study of at least 14 cardiac functions) kidney (renal perfusion studies), lung (pulmonary strokes, emphysema, asthma, etc.), and for diagnosis of hidden infectious processes [1].

The radionuclide ^{99m}Tc is an important tracer in nuclear medicine due to its physico-chemical and nuclear properties, which are principally the emission of a 140 keV photon, technically suitable for detection by gammametry and its half-life of only 6.02 hours allows low doses irradiation studies for patients [1,2]. The ^{99m}Tc ($t_{1/2} = 6.02$ h) is the daughter of ^{99}Mo ($t_{1/2} = 66.7$ h) and decays spontaneously emitting negative beta radiation (β^-), giving rise to two nuclear isomers Tc (see Figure 1).

^{99m}Tc is commercially produced from $^{99}Mo/^{99m}Tc$ generators, using a chromatographic column loaded with alumina, where ^{99}Mo , fission product of ^{235}U , is eluted with the $^{99}TcO_4^-$ is through a saline solution (see Figure 2), thus providing a highly purified sample in a simple to operate system. However, ^{99}Mo production from ^{235}U fission requires complex radiochemical

separations, generating significant quantities of medium activity radioactive waste. In addition, alumina adsorbs only 0.2% of ^{99}Mo , a situation which forces a high specific activity of ^{99}Mo ($\sim 10^3$ TBq/g) to be employed, which can only be obtained through ^{235}U fission [2].

In Mexico, the only nuclear reactor available for such applications is located in ININ (TRIGA-Mark III reactor). However its technical characteristics are limited to producing ^{99}Mo from ^{235}U , hence the need to import ^{99}Mo from Canada for use in $^{99}\text{Mo}/^{99m}\text{Tc}$ generators (GETEC). They cover about 60% of national demand and even exported to some Latin American countries and the U.S. Given the technical and economic importance of ^{99m}Tc , alternative generators of low and medium activity prepared from ^{99}Mo produced via the nuclear reaction $^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}$, have been proposed as an option for daily use in nuclear medicine centers, offering the opportunity to produce $^{99}\text{Mo}/^{99m}\text{Tc}$ generators in countries with limited nuclear infrastructure, as is the case of Mexico. Generators constructed on the basis that molybdenum gels act as radioactive arrays within a chromatographic column have been particularly promising. This type of generator is based on the preparation of ^{99}Mo -molybdates gels from ^{99}Mo produced from the nuclear reaction: $^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}$, allowing more than 30% weight of ^{99}Mo to be incorporated on the gel and the use of low specific activity (^{99}Mo per unit concentration) (mass or volume) (50-500 G Bq/g), while maintaining quality and purity consistent with commercial generators [2,3].

The Radioactive Materials Research Laboratory (RMRL) Group has studied and developed methodologies for preparing $^{99}\text{Mo}/^{99m}\text{Tc}$ gel-based generators from ^{99}Mo -zirconium, titanium and magnesium molybdates in order to commercially establish a viable production methodology. Characteristics of this type of generator primarily depends upon the factors or conditions governing gel preparation, such as pH, molar ratio between reagents, concentrations, drying temperature, etc. These parameters have been carefully studied to reproduce the characteristics of these gels and to define optimum operation conditions for the generator [4-9].

2.1 Synthesis of ^{99}Mo -zirconium, titanium and magnesium molybdate gels

In general, the synthesis of zirconium, titanium and magnesium molybdates gels consist of reacting a solution of ^{99}Mo -molybdates with a solution of zirconium, titanium and magnesium [4-9]. The mixture is agitated perfectly, dried, titrated and finally added to the chromatographic column.

2.1.1 Gels to ^{99}Mo - zirconium molybdates base

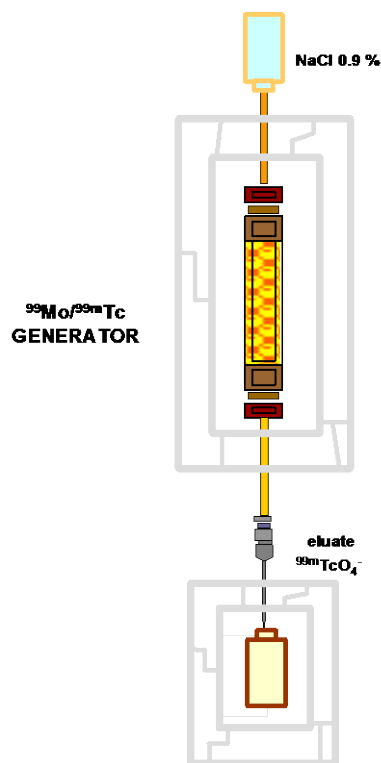
To determine the optimum conditions for gel preparation of ^{99}Mo -zirconium molybdates used as $^{99}\text{Mo}/^{99m}\text{Tc}$ generator arrays, gels were synthesized by varying parameters such as the molar ratio zirconium: molybdenum, pH of the ^{99}Mo -molybdates and gel concentration as well as preparation time of zirconium solution.

Figure 2: $^{99}\text{Mo}/^{99m}\text{Tc}$ generator

Subsequently the gels were added to chromatographic columns to form $^{99}\text{Mo}/^{99m}\text{Tc}$ generator (see Figure 2) and eluted every 24 hours with 6 mL of NaCl to 0.9%. The ^{99m}Tc eluates were then analyzed to determine the following parameters: (1) elution performance (percentage of $^{99m}\text{TcO}_4^-$ recovered from the chromatographic column) through a NaI detector, (2), ion radiochemical purity $^{99m}\text{TcO}_4^-$ (percentage of the chemical species $^{99m}\text{TcO}_4^-$ on the eluate) through ascending paper chromatography, (3) radionuclide purity (presence of ^{99}Mo in $^{99m}\text{TcO}_4^-$ eluates) with the help of a gamma spectrometry system, (4) pH by means of test strips, (5) evidence of sterility in soya and sodium thioglycolate, (6) pyrogen tests with strains of *Limulus amoebocites* (LAL) and (7) eluate appearance by visual appreciation [4.7].

The characteristics of ^{99m}Tc eluates from our generators were compared with values set by the pharmacopoeia for human use in order to establish the most adequate methodology for preparing ^{99}Mo -zirconium molybdates gels based generators, as follows: ^{99}Mo purity less than 0.15 μCi of $^{99}\text{Mo}/\text{mCi}$ of ^{99m}Tc , radiochemical purity greater than 95% ($^{99m}\text{TcO}_4^-$), pH between 4.5-7.5, pyrogen-free, sterile, containing less than 10 ppm aluminum and must be a clear liquid [10].

A methodology for synthesis of ^{99}Mo - zirconium molybdate gel was established from these studies which allowed design and construction of the " Synthesis Device For $^{99}\text{Mo}/^{99m}\text{Tc}$ Gels Generators " (DISIGEG) (see Figure 3), an indispensable tool for upgrading our methodology of $^{99}\text{Mo}/^{99m}\text{Tc}$ gel-based generators of ^{99}Mo -zirconium molybdates to a prototype, prior to the



commercial production of these generators. DISIGEG construction was carried out jointly between the RMRL Group and the Automation Department of ININ, led by Eng. Tonatiuh Rivero Gutiérrez, technicians Paulino Rojas Nava and Carlos Vázquez Maldonado, and staff of General workshops: Sabino Hernández Cortés and Francisco Jiménez Barreiro [11-13].

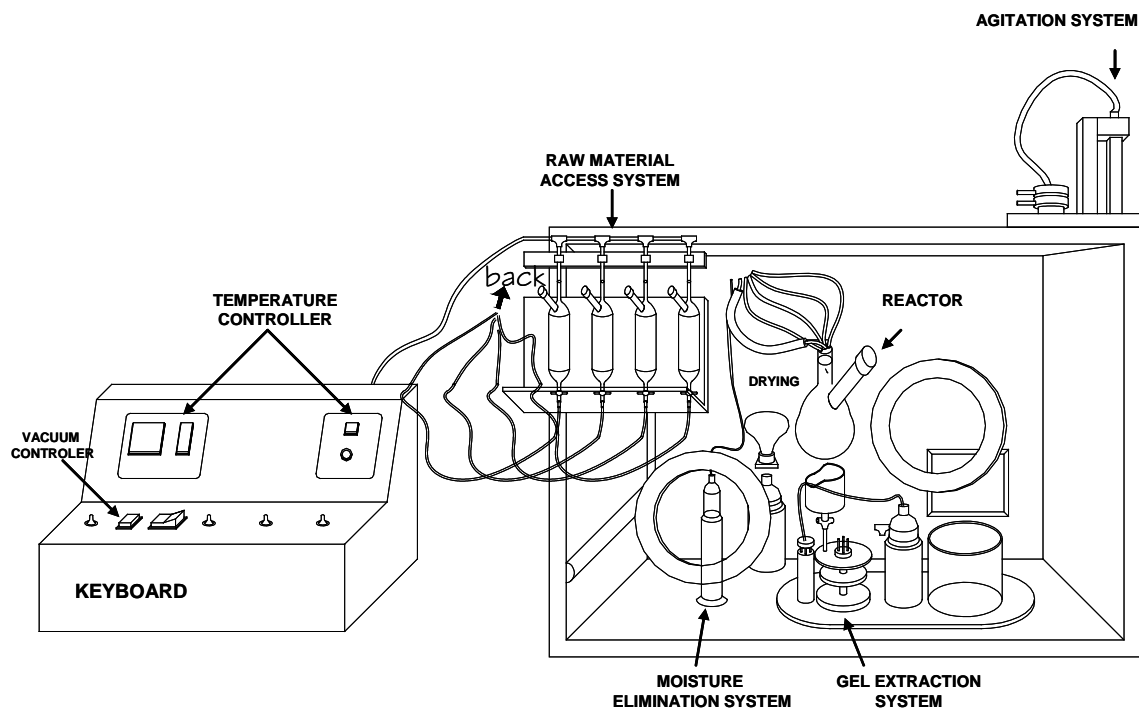


Figure 3: Synthesis Device For $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ Gels Generators (DISIGEG)

The DISIGEG consists basically of a synthesis reactor, mounted in a cell, along with five systems: (1) reagents supply, (2) product agitation, (3) gel drying, (4) humidity elimination and (5) gel extraction. The systems are regulated via an external control console with its operation based on pneumatic and electronic operations.

Finally, in the DISIGEG synthesis method of ^{99}Mo - zirconium molybdates proposed in our prior work, defining gel drying conditions (temperature, time and drying air flow) and establishing a final protocol for $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator preparation based on ^{99}Mo -zirconium molybdate gels was optimized [12,13]. Approximately 150 tests were performed to establish the final protocol, shown in Figure 4. The proposed methodology uses 0.1 mol/L zirconile chloride solutions, prepared a day before the synthesis, ^{99}Mo -sodium molybdates at pH 4.5, maintaining a molar ratio of 1: 1 Zr:Mo between both solutions, drying the gels at 80 ° C for 5 hours to 90 mm of air

flow. This methodology produces generators, which can be used for medical purposes, with the following characteristics: Elution yields exceeding 69.95%, whose ^{99m}Tc eluates have: average radionuclide purity 99.9924% (^{99}Mo in the eluates, around 0.0076%), radiochemical purity above 96%, pH of 6, aluminium present at less than 10 ppm, transparent appearance, pyrogen free and sterile [12,13].

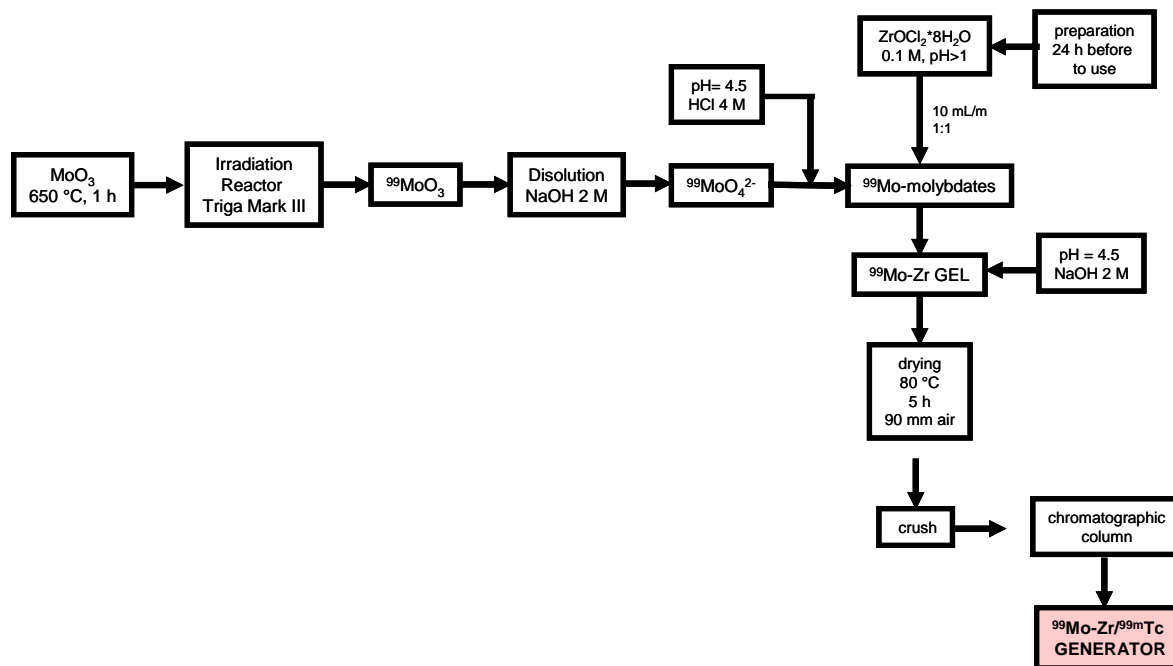


Figure 4: Preparation protocol for $^{99}\text{Mo}/^{99m}\text{Tc}$ generator based on ^{99}Mo -zirconium molybdates

During $^{99}\text{Mo}/^{99m}\text{Tc}$ generator preparation, various synthesized zirconium molybdate gels were characterized to explain the behavior of these generators due to their physico-chemical properties. Zirconium molybdate gels were analyzed through neutron activation analysis to determine Mo and Zr content by infrared spectroscopy, electron microscopy scanning, thermogravimetry, surface area and x-ray diffraction. According to these studies, generator characteristics are closely related to the structure of zirconium molybdate gels. It has been proposed that the mechanism of $^{99m}\text{TcO}_4^-$ ion elution is based on its dissemination by the array and the gel is made up of an ensemble of octahedral units of isopolymolybdates, packaged around tetrahedra containing zirconium. The settlement and formation of these ensembles is modified by zirconium and molybdenum species precursor during gel formation and their drying conditions (water content), which may promote the formation of rigid or flexible structures that

impede or facilitate the passage of $^{99m}\text{TcO}_4^-$ ion respectively [4,7]. In general, zirconium gel molybdates are amorphous, having average weight 30% molybdenum and zirconium and 15% water with a porous volume of about $0.08 \text{ cm}^3/\text{g}$ [3,4,7,14,15].

2.1.2 Gels with ^{99}Mo - titanium and magnesium molybdate base

Generator preparation based on ^{99}Mo -molybdates zirconium gels, on the basis of $^{99}\text{MoO}_3$, involves using DISIGEG to properly manipulate the radioactive material, and consumes at least 5 hours processing time. To prevent these disadvantages, RMRL Group carried out studies focused on preparing these generators, by first synthesizing zirconium molybdate gels and then irradiating them. However, this methodology causes decreased efficiency of the generator and activation of the zirconium gel content, mostly producing the radioisotope ^{93}Zr ($t_{1/2} 1.5 \times 10^6$ years), ^{95}Zr ($t_{1/2} 64$ (d)) and ^{97}Zr ($t_{1/2} 16.9\text{h}$) [16]. Hence, easy to produce generators were developed with high elution efficiencies in finding new alternatives for production of $^{99}\text{Mo}/^{99m}\text{Tc}$ generators. These were $^{99}\text{Mo}/^{99m}\text{Tc}$ - titanium and magnesium molybdate based, which were irradiated after its synthesis given the short half-life of the unique radioisotope produced by titanium and magnesium respectively: ^{51}Ti ($t_{1/2} 5.79\text{min}$) and ^{27}Mg ($t_{1/2} = 9.46 \text{ m}$). Basically titanium and magnesium synthesis are still a methodology similar to the one described for the zirconium molybdates: ammonium molybdate solutions, prepared from non-radioactive MoO_3 dissolved in NH_4OH solutions of Ti (III), Ti (IV) or Mg (II) were added, and once formed, the pH is adjusted for the respective molybdates using NH_4OH solutions. They are then dried, titrated, wash and irradiated in TRIGA Mark III reactor from ININ and $^{99}\text{Mo}/^{99m}\text{Tc}$ generators prepared based on ^{99}Mo - titanium or magnesium molybdates. Nearly 90 titanium and magnesium molybdates gels were synthesized, varying parameters such as pH gels, molar ratio Ti:Mo or Mg:Mo, drying temperature, addition sequence of reagents and concentration and type of Ti solutions (TiCl_4 or TiCl_3) or Mg (MgSO_4 , $\text{Mg}(\text{NO}_3)_2$, MgCl_2). Generators based on ^{99}Mo - titanium and magnesium molybdates were eluted every 24 hours with NaCl to 0.9%, ^{99m}Tc eluate characteristics were evaluated (elution efficiency, radionuclide, radiochemical, and chemical purities) and compared with the values set by pharmacopoeia. Inactive and irradiated titanium and magnesium molybdates were also characterized by XDR, scanning electron microscopy, thermogravimetry, infrared spectrometry and neutron activation to determine irradiation effect of these molybdates on physico-chemical properties [5, 6, 8, 9].

According to our results, titanium molybdates, as well as their counterparts in zirconium, are formed from alkaline hydrolysis of titanium solutions in the presence of molybdates and are amorphous materials with cation exchange properties. The titanium molybdates are formed by titanium pentagonal faces joined to molybdenum octahedral, whose cavities allow $^{99m}\text{TcO}_4^-$ ion diffusion through the material. Packaging and distribution of titanium and molybdenum structures, and hence cavity size and $^{99}\text{Mo}/^{99m}\text{Tc}$ generator properties, directly dependent upon the conditions governing gel preparation. For example, the presence of salt occluded in gels during its dehydration, as well as washing after drying, improved $^{99m}\text{TcO}_4^-$ ion diffusion, elution efficiency and general characteristics of the generators.

This work showed that the irradiation of titanium molybdate gels does not significantly affect the characteristics of the $^{99}\text{Mo}/^{99m}\text{Tc}$ generators, because amorphous materials are less disturbed by its irradiation-induced defects. Thus, these studies show the feasibility of producing $^{99}\text{Mo}/^{99m}\text{Tc}$ generators based on ^{99}Mo -titanium molybdates, by first synthesizing titanium molybdate gels and then radiating them; reducing preparation time of the generators and eliminating the use of special facilities. Generators prepared from the irradiation of gels synthesized under the conditions shown in Figure 5, comply with the values set by the Pharmacopoeia, and can therefore be used for medical purposes: radionuclide purity is around 99.9999%, elution efficiency of 95%, purity radiochemical of 95%, and ^{99m}Tc eluates with 6.5 pH [6].

In the case of the magnesium molybdates, preparation conditions also influence their physico-chemical properties and generators. In particular, the type of magnesium salt (MgCl_2 , $\text{Mg}(\text{NO}_3)_2$, MgSO_4) used in the synthesis of these molybdates, combined with molybdate pH and initial molar ratio Mg:Mo, favours or inhibits magnesium molybdate formation (MgMoO_4 , MgMO_2OH_7), magnesium salts (NH_4MgCl_3 , $\text{Mg}_2(\text{OH})_3\text{Cl}_4$), polymolybdate ($\text{NH}_4\text{Mo}_3\text{O}_{10}$, Mo_4O_{11} , Mo_7O_{24} , Mo_9O_{26} , $\text{Mo}_{14}\text{O}_{42}$) or molybdenum oxides (MoO_3). These compounds, unlike generators based on ^{99}Mo -zirconium and titanium molybdates, are crystal clear, and changed its colour upon irradiation, in general more intense and in some cases turning to blue hues, the characteristic color of molybdenum oxides (MoO_3). In general, $^{99}\text{Mo}/^{99m}\text{Tc}$ generators prepared with arrays where magnesium molybdates dominate and/or insoluble polymolybdates presented the best properties. However, the presence of ^{99}Mo in ^{99m}Tc eluates is common (radionuclide purity), in proportions ranging from 1 to 100 times the value recommended by

Pharmacopoeia (0.015%). In addition, only a third of these generators, commonly prepared based on magnesium nitrates, have more than 70% efficiencies. Meanwhile generators synthesized with magnesium chlorides and sulfates respectively, have the lowest ^{99}Mo percentages in eluates and larger radiochemical purities. According to our results, $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators based on magnesium molybdates synthesized from $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ 0.5 mol/L solutions and ammonia molybdates of pH = 4.5, molar ratios of Mg:Mo 1:2 and washed prior to irradiation, comply with the characteristics set out in the national pharmacopoeia: radiochemical purity greater than 90%, ^{99}Mo percentage less than 0.015% on the eluates, eluates pH from 5.9 to 6.4, elution volume around 3 mL and less than 10 ppm magnesium content. However, $^{99\text{m}}\text{Tc}$ elution efficiency in this generator is only 20%, a value impractical for commercial use at the hospital level [8.9].

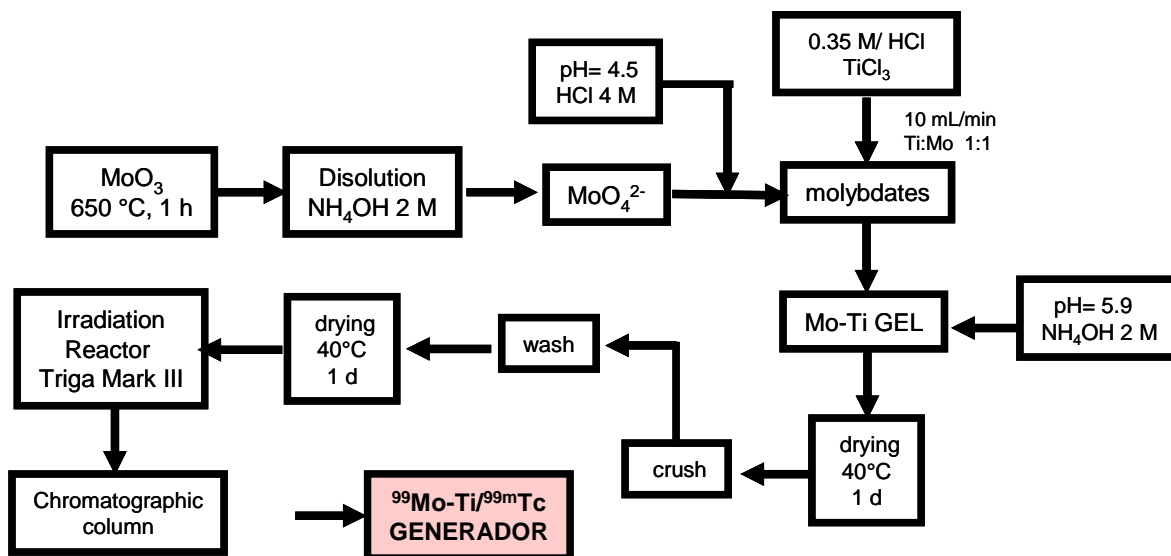


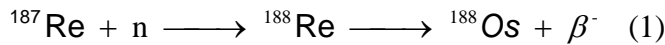
Figure 5: $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators based on ^{99}Mo - titanium molybdates

3. $^{188}\text{W}/^{188}\text{Re}$ Generators for use in radiotherapy

The appropriate nuclear characteristics of ^{188}Re makes it useful for various types of cancer radiotherapy: it emits high energy particles β^- (2.12 MeV) and 155 KeV gamma Ray, has a half-life of 16.9 (h) and a chemical behavior similar to technetium [17]. Radiopharmaceuticals of ^{188}Re - HEDP, ^{188}Re - EDTMP and ^{188}Re - ABP are clinically applied in Europe, United States and China, to patients suffering from bone pains of metastatic origin; ^{188}Re - Lipiodol or ^{188}Re -(HDD)

- lipiodol to people with inoperable liver cancer, ^{188}Re -MAG₃ as renal excretory agent, ^{188}Re -DTAP) in the early prevention of stenosis that can be produced by an angioplasty, of ^{188}Re -Sn radiosinovectomia colloids, microspheres and colloids labeled with ^{188}Re for treatment of diseases such as rheumatoid arthritis, peritoneal effusion and various solid tumors, among other diseases [18]. These radiopharmaceuticals production firstly demand, ^{188}Re free carrier availability (that do not contain stable Re) and with high specific activities (a high radioactive concentration of ^{188}Re per unit of mass or volume).

^{188}Re can occur by two processes: (1) from irradiating ^{187}Re with thermal neutrons in a nuclear reactor causing it to decay whilst emitting negative beta particles β^- and generating ^{188}Os , which is a stable element (see reaction 1). No carrier free ^{188}Re is obtained in this process.



and (2) from $^{188}\text{W}/^{188}\text{Re}$ generators allowing continuous ^{188}Re acquisition without need for a nuclear reactor or particle accelerator in hospitals and research centers. Thus, the $^{188}\text{W}/^{188}\text{Re}$ generator is a viable option for continuous ^{188}Re . These generators base their operation on ^{188}W decay, which has a half-life of 69.4 d, generating ^{188}Re , which in turn decays by emitting β^- and

closing the radioactive chain to form ^{188}Os (see Figure 6).

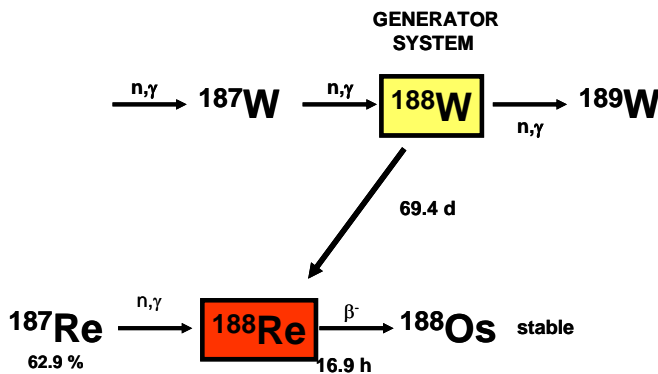


Figure 6: $^{188}\text{W}/^{188}\text{Re}$ generator system

This type of generators are commonly formed as in the case of commercial $^{99}\text{Mo}/^{99m}\text{Tc}$ generators, by a chromatographic column loaded with an array, usually based on inorganic compounds, where ^{188}W is absorbed and $^{188}\text{ReO}_4^-$ eluted by means of an appropriate solution. Once eluted $^{188}\text{ReO}_4^-$, ^{188}W retained on chromatographic column begins to decline to again generate ^{188}Re , which can again be separated by column elution [17]. The production of high specific activities ^{188}W ($> 195 \text{ GBq/g}$), necessary to prepare generators with arrays of low

adsorption capacity (W retained by array weight mg), it is only possible in nuclear reactors with greater than 10^{15} neutron fluence / cm^2sec given that a nuclear reaction of double neutron capture is required to produce ^{188}W (see Figure 6). In the world only two nuclear reactors have these capabilities: ORNL reactor (Oak Ridge National Laboratory) in the U.S. and RIAR (Research Institute of Atomic assessment) in Russia, and only the laboratories of ORNL and POLATOM in Poland buys ^{188}W from RIAR, commercially produced $^{188}\text{W}/^{188}\text{Re}$ alumina-based generators [19]. ^{188}Re can be produced on a daily basis by this average or every third day for the maximum ^{188}Re activity to be extracted from the generator. This ^{188}Re production cycle has a useful life of about 6 months, what makes this type of system appropriate in places where there is no possibility for nuclear reactors or a continuous supply of the radioisotope.

The development of $^{188}\text{W}/^{188}\text{Re}$ generators has driven clinical applications of radiopharmaceuticals labelled with ^{188}Re and stimulated research activities focused on the developing new ^{188}Re labelled radiopharmaceuticals that are more specific for each type of tumor [18]. Given these conditions, and the importance of health systems in Mexico to have ^{188}Re available, RMRL research group focused its efforts on developing methodologies for $^{188}\text{W}/^{188}\text{Re}$ generator preparation based on chromatographic columns similar to those previously described for $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators. Three different chromatographic arrays were evaluated: (1) alumina, (2) hydroxyapatite and (3) arrays based on ^{188}W - titanium and zirconium tungstenates [20-23]. The objective of these studies was to define the array and the most suitable environment, to permanently maintain ^{188}W in the array, while ^{188}Re can be quantitative and periodically removed, so a $^{188}\text{W}/^{188}\text{Re}$ generator can be prepared for clinical use with the following: ^{188}Re elution efficiency of more than 70%, radionuclide purity higher than 99.985%, that is, a presence of ^{188}W less than 0.015% in the eluates, radiochemical purity greater than 90%, pH of eluates between 4.5 and 7.5 and elution volumes around 6 mL [10].

3.1. Generating $^{188}\text{W}/^{188}\text{Re}$ alumina and hydroxyapatite

The conditions governing $^{188}\text{W}/^{188}\text{Re}$ generator preparation with alumina and hydroxyapatite base were identified in two stages, the first where the adsorption behaviour of tungsten and rhenium in alumina and hydroxyapatite under various experimental conditions is studied: eluent type and pH, mass and size of adsorbent particle, and adsorbent-eluent contact time; applying the radiotracer technique under static conditions. In the second stage, $^{188}\text{W}/^{188}\text{Re}$ generators were

prepared under conditions similar to first phase, and its properties evaluated: ^{188}Re percentage recovered from the column (elution efficiency), ^{188}W percentage in ^{188}Re eluates (radionuclide purity), percentage of $^{188}\text{ReO}_4^-$ chemical species in the eluates (radiochemical purity), eluate pH, elution volume and aluminum or phosphate mass in the eluates for alumina-based generators and hydroxyapatite respectively [20-22]. The generators were eluted during 6 months every third day.

3.1.1. $^{188}\text{W} / ^{188}\text{Re}$ generators based on alumina

According to adsorption studies, it is feasible to prepare $^{188}\text{W} / ^{188}\text{Re}$ generators in alumina, eluting $^{188}\text{ReO}_4^-$ with 0.9% NaCl solutions to pH's lower than 5.6 or with HCl solutions less than 0.1 mol/L. Under these circumstances, alumina is able to retain 0.337 meq/g W, adsorbing only 3% rhenium and 99.9% tungsten; i.e. alumina presents a great affinity for ^{188}W and zero ^{188}Re retention. Based on these results $^{188}\text{W} / ^{188}\text{Re}$ alumina-based generators were prepared, which were eluted with 0.9% NaCl (pH = 5.7) and HCl 0.01 mol/L; and whose eluates were evaluated for 6 months. The generator that presented the best features, compliance with the values set by the pharmacopoeia and was therefore likely to be prepared for distribution in Mexico, the eluted with 0.9%NaCl solutions, containing 10 mg alumina W/g; under these conditions the following were obtained on average: elution efficiencies of 83% ^{188}Re , $4.5 \times 10^{-4}\%$ ^{188}W in the eluates (radionuclide purity), 92% radiochemical purity (percentage of the $^{188}\text{ReO}_4^-$ species in the medium), a elution volume of 8.3 mL with less than 10 ppm aluminum content and 5.5 pH. It is important to mention that all of the generators evaluated provided a reduction in generator efficiency with the number of elutions, due to the reduction of Re (VII) to Re (IV), the latter weakly held in alumina due the fact that its affinity for hydroxyl groups is greater than that of Re (VII) or possibly by ReO_2 precipitation caused by its concentration increase on alumina [20].

The strong affinity of alumina to tungsten in these generators can be explained by the acid-base properties that both alumina and tungsten ions possess. On one hand, alumina is an ion donor

with amphoteric properties, i.e. can exchange anions or cations (see Fig 7).

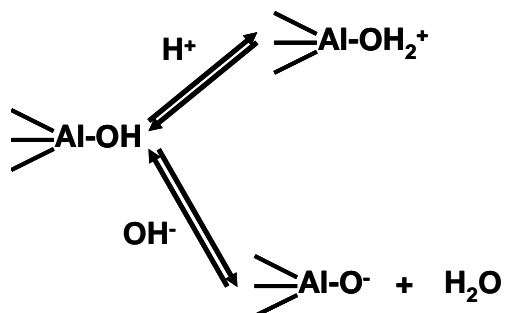


Figure 7: Ion exchange in alumina

Anion exchange is favored by acidic conditions, such that it gives cations to alkaline pH. In the case of the tungsten ions, WO_4^{2-} are present in basic medium, as long as pH acids polymerize if WO_4^{2-} concentrations are greater than 5×10^{-5} mol/L, paratungstenates and metatungstenate, as shown in Figure 8. The tungstenate solutions used in our studies varied from 0.08 to 0.2 mol/L. Thus, the strong affinity of alumina to polytungstenates anions is favored in acid, because it acts as a heat exchanger of anions to these conditions. Conversely, rhenium is not favored by alumina because it presents a greater affinity for the ions of the medium instead of the chloride ions $^{188}\text{ReO}_4^-$ [20].

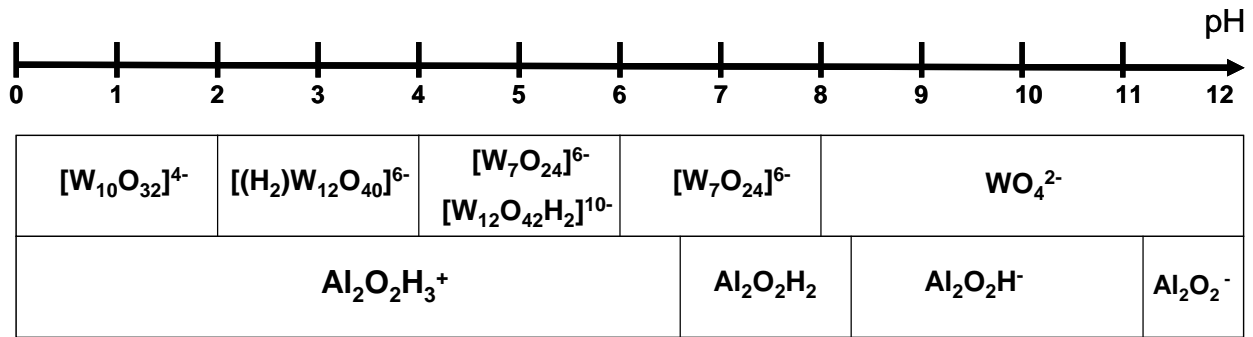


Figure 8. Diagram showing distribution of tungsten and aluminum species depending on the pH

3.1.2. $^{188}\text{W} / ^{188}\text{Re}$ generators based on hydroxyapatite

In order to improve the characteristics of alumina-based generators, the use of the hydroxyapatite as a array of the $^{188}\text{W} / ^{188}\text{Re}$ generators and $^{99}\text{Mo} / ^{99m}\text{Tc}$ was evaluated, given its excellent properties of anion exchange and promising use in fission retention of nuclear waste products. Adsorption studies showed that it is not feasible to use hydroxyapatite as a array of $^{99}\text{Mo} / ^{99m}\text{Tc}$ generators, when they are eluted with saline solutions, because Mo (VI) or Tc (VII) are retained by hydroxyapatite under these conditions. However, if the eluent is CaCl_2 , its use as a generator is feasible, but not for medical applications, and is therefore not possible to directly manage a ^{99m}Tc patient in this medium [21-23].

In the case of $^{188}\text{W} / ^{188}\text{Re}$ generators, our results showed that W (VI) adsorption depends on the pH of the medium, and is strongly retained in the hidroxyapatita only with 0.9% NaCl solutions

and pH's between 6.5 and 7, while Re (VII) adsorption is practically non-existent between pH of 6 and 12. These results were prepared by hydroxyapatite-base $^{188}\text{W}/^{188}\text{Re}$ generators, eluting with ^{188}Re with saline solutions of pH between 5.5 and 7. These generators generally presented more than 90% radiochemical purity, eluates pH of 6.5 and elution efficiencies between 65 and 71%, values which satisfy Pharmacopoeia limits. However in all cases, ^{188}Re eluates presented ^{188}W percentages to be more than 0.03% and phosphate ion concentrations of more than 1000 ppm, thus making it impossible to use these generators for clinical applications [21,22]. Phosphate release during generator elution is probably due to ion exchange in the hydroxyapatite for anions in the medium, in this case chloride ions [24]. Phosphate presence provides evidence for hydroxyapatite dissolution by saline solutions and explains the ^{188}W leak. In order to reduce phosphate release, tests were performed in the generators using calcium phosphate solutions as eluents; however, the phosphate ions were invariably present in ^{188}Re eluates.

3.1.3 $^{188}\text{W}/^{188}\text{Re}$ generators based on ^{188}W -tungstenates

Even though alumina is proven to be a suitable array to prepare $^{188}\text{W}/^{188}\text{Re}$ generators, its poor adsorption capacity has led to the search for alternative arrays to use ^{188}W with low specific activity, which can be produced in reactors with Neutron flux of less than 10^{15} n/cm²sec, leaving the possibility of its generation open to other laboratories. Based on the RMRL Group experience with $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ -based generators gels of zirconium and titanium molybdates [4,6,7] and considering the chemical similarity that Mo and W presents, and Tc and Re, $^{188}\text{W}/^{188}\text{Re}$ generators were prepared with ^{188}W -zirconium and titanium tungstenate base, in developing an alternative array for these generators. The gels were synthesized using the sol-gel methodology based on zirconium and titanium alkoxides and ^{188}W -sodium tungstenate solutions at different pH's, a device built especially for it, with the help of the technical personnel Paulino Rojas Nava and Departmental automation engineer Tonatiuh Rivero Gutiérrez, and whose working principle is based on the DISIGEG, described in section 1.1.1 [22].

The sol-gel methodology reduces synthesis time by almost 50% with respect to the precipitation method for $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators, which requires 6 to 7 hours, also reducing energy consumption. The use of ^{188}W -sodium tungstenate solutions, pH of highly acidic or very basic, in gel synthesis, decreases generator efficiency and increases ^{188}W presence in ^{188}Re eluates. It is therefore advisable to work with ^{188}W -sodium tungstenate solutions with pH between 4.5 and 7.

Generators that presented the best features were those prepared with ^{188}W - zirconium tungstenate gels. However, in all cases the eluate radionuclide purity was below 99.9%. Therefore, it is advisable to continue these studies to improve generator radionuclide purity.

Iron, calcium and manganese tungstenates were also proposed as an alternative for preparing $^{188}\text{W}/^{188}\text{Re}$ generators, considering that these minerals are poorly soluble in aqueous medium and in the presence of Cl^- ions (2×10^{-4} mol/L). This was determined in the salt solubility, using a radiometric methodology. Ca, Mn and Fe tungstenates were first prepared under various conditions, and then irradiated with thermal neutrons and its solubility in 0.9% saline solution was determined from ^{187}W activities. These results show that manganese and calcium tungstenates ($S < 0.05$ mg/mL), are good alternatives for $^{188}\text{W}/^{188}\text{Re}$ generator arrays [25]. However, it is necessary continue with the second phase of these studies, i.e. the preparation of the $^{188}\text{W}/^{188}\text{Re}$ generators, to assess ^{188}Re eluate quality in connection with the limits recommended by the Pharmacopoeia.

4. Production of Radiolanthanides

Lutetium-177, holmium-166, promethium-149 or Terbium-161 attached to molecules of type: EDTMP, DTAP, DOTA or Biotin, have demonstrated their enormous potential in metabolic radiotherapy (treatment with radiopharmaceuticals specifically designed for the tumor, to provide a dose of selective radiation to destroy malignant cells without harming healthy tissue), in particular for treatments against rheumatoid arthritis, ovarian cancer, bone marrow ablation, multiple myeloma, bone cancer or as *in vivo* generators [26]. The feasibility for using these agents crucially depends upon the cost and availability of the radioisotope. Unfortunately in Mexico, these radioisotopes are not commercially available, therefore the RMRL group proposed developing a methodology to produce the following radiolanthanides: promethium-149 (^{149}Pm) or 151 (^{151}Pm), Terbium-161 (^{161}Tb), holmium-166 (^{166}Ho) and Lutetium-177 (^{177}Lu) so that it can be distributed in hospitals or for research as required locally.

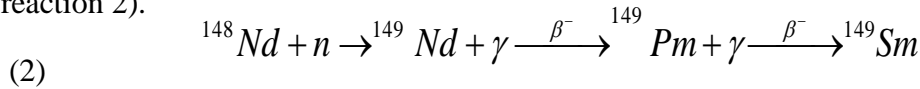
Radioactive lanthanides ^{149}Pm or ^{151}Pm , ^{161}Tb , ^{166}Ho and ^{177}Lu possess favourable nuclear characteristics for use in metabolic radiotherapy: β^- particle emission > 0.6 MeV, γ ray emission < 0.3 MeV, with half-lives from 1 to 6 days and they have chemical properties that allow easy insertion in appropriate molecules (see table 1). However, without the availability of these radioisotopes with high specific activities (Bq/g) and carrier free is essential, because a low mass

administration is required to minimize possible pharmaceutical effects of the radiopharmaceutical and/or minimize receptor saturation. This is an important aspect often compulsory for potential clinical use of the radiopharmaceutical agent labelled with these radioisotopes.

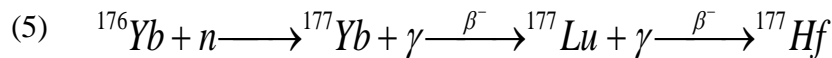
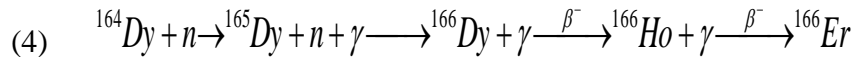
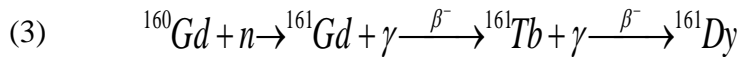
Table 1. Nuclear properties of radiolanthanides

RADIOISOTOPE	HALF LIFE	β- Maximum (MeV)	γ ray emission (keV)
¹⁴⁹Pm	2.2 (d)	1.07	285.9
¹⁵¹Pm	28.4 (h)	1.18	256
¹⁶¹Tb	6.9 (d)	2.56	74.6
¹⁶⁶Ho	26.7 h	1.85	80.5
¹⁷⁷Lu	6.7 (d)	0.49	208.3

The production of carrier-free radioisotopes with high specific activities should take place through indirect methods. For example, to obtain ¹⁴⁹Pm, it is necessary to radiate ¹⁴⁸Nd (stable isotope) with thermal neutrons, to generate ¹⁴⁹Nd, radioisotope with a half-life of 1.73 h, which decays by emission of β- particles to form ¹⁴⁹Pm and this in turn will produce a β- particle to form ¹⁴⁹Sm, stable isotope. (See reaction 2).



Once formed, ¹⁴⁹Pm should be separated from the father neodymium (^{Nd¹⁴⁸} and ¹⁴⁹Nd). This same principle continues to produce ¹⁶¹Tb, ¹⁶⁶Ho and ¹⁷⁷Lu, as shown in reactions 3, 4 and 5.



Two major difficulties are encountered to quantitatively isolate *Nd/Pm*, *Gd/Tb*, *Dy/Ho* and *Yb/Lu*, pairs: on the one hand, their chemical properties are virtually identical and on the other, the difference in mass between parents and daughter elements involved in the process. Levels are macroscopic, in the order of mg, in the case of the elements (Nd, Gd, Dy and Yb) parents and atoms or ng in daughter radioisotopes: ^{161}Tb , ^{166}Ho , ^{149}Pm and ^{177}Lu .

With the aim of establishing the most technically and economically appropriate methodology, for producing radiolanthanides ^{149}Pm , ^{161}Tb , ^{166}Ho and ^{177}Lu with a radionuclide purity greater than 99.99%, the feasibility of separating the following pairs was investigated: *Nd/Pm*; *Gd/Tb*, *Dy/Ho* and *Yb/Lu*, using two techniques: (1) chromatography by ion-exchange, using hydroxyapatite arrays and fluorite in various media [27,28] and (2) chromatography extraction, using the Ln SPS Eichrom resin as eluent to nitric acid [29,30]. Once established, the separation methodology of these pairs is designed and a special device is constructed that would allow the separation process to be easy, fast and safe [31].

4.1 Separation of lanthanides by ion exchange

Studies of hydroxyapatite affinity and fluorite by *Nd/Pm*, *Gd/Tb*, *Dy/Ho* and *Yb/Lu* lanthanides, were done by the radiotracer technique in static conditions, in five complex media: potassium thiocyanate, disodium tartrate, sodium citrate, EDTA and aluminona (ammonium aurintricarboxylate), at various concentrations and pH in order to determine the feasibility of its use as a means of lanthanide separation. The affinity was determined by the distribution coefficient K_d . According to our results, it was not possible to separate the *Nd/Pm*, *Gd/Tb*, *Dy/Ho* and *Yb/Lu* pairs with hydroxyapatite, the K_d values of the pairs are virtually identical, whereas in the fluorite, the lanthanides are not retained under any studied conditions [27,28].

4.2 Separation of lanthanides by extractive chromatography

The affinity of SPS Ln resin towards Nd, Pm, Gd, Tb, Dy, Ho, Yb and Lu was also studied by extractive chromatography. In order to achieve this, median distribution coefficients (K_d) were determined by the dynamic method, using radioactive tracers and nitric acid of different concentrations as eluent. The extractant agent of resin Ln SPS Eichrom of Darien is the acid di(2-ethylhexil_ortophosphoric) (HEDHP) supported on a polymer. The results showed that (1) the K_d values of those elements, increase with reduction of HNO_3 concentration, (2) the daughter

elements (Pm, Tb, Ho, and Lu) have greater affinity for the stationary phase than the father elements (Nd, Gd, Dy and Yb) and (3) Kd decrease by increasing atomic number, with a similar concentration of nitric acid, which is why the elution order goes from Nd to Lu [29,30]. From the Kd data, intervals of suitable HNO₃ concentration were chosen for pair separation of *Nd/Pm*, *Gd/Tb*, *Dy/Ho* and *Yb/Lu*, imposing Kd maximum values of 200 mL/g, to reduce volumes and separation times. Separation tests of all pairs were done to finally select the best conditions, considering maximum efficiency and lowest eluate cost. In general, the parent elements are first eluted of the chromatographic column, and then the daughter elements, with specific solutions of HNO₃. The best conditions for pair separation of ¹⁵⁹Gd /¹⁶¹Tb, ¹⁵⁷Dy /¹⁶⁶Ho, ¹⁴⁷Nd /¹⁵¹Pm and ¹⁶⁹Yb /¹⁷⁷Lu, are listed in table 2.

Table 2. Separation conditions of ¹⁴⁹Nd /¹⁴⁹Pm, ¹⁶¹Gd /¹⁶¹Tb, ¹⁶⁶Dy /¹⁶⁶Ho and ¹⁷⁷Yb /¹⁷⁷Lu pairs [29,30].

Pair	Father		Efficiency separation	Daughter	
	Radioisotope	[HNO ₃] mol/L	father/ daughter (%)	Radioisotope	[HNO ₃] mol/L
¹⁴⁹ Nd / ¹⁴⁹ Pm	¹⁴⁹ Nd	0.18	89	¹⁴⁹ Pm	1.5
¹⁶¹ Gd / ¹⁶¹ Tb	¹⁶¹ Gd	0.8	100	¹⁶¹ Tb	3
¹⁶⁶ Dy / ¹⁶⁶ Ho	¹⁶⁶ Dy	1.5	99	¹⁶⁶ Ho	3
¹⁷⁷ Yb / ¹⁷⁷ Lu	¹⁷⁷ Yb	3.4	65.1	¹⁷⁷ Lu	9

The separated radioisotopes: ¹⁵¹Pm, ¹⁶¹Tb, ¹⁶⁶Ho and ¹⁷⁷Lu have a radionuclide purity greater than 99.99%. The high concentrations of nitric acid used, prevent direct usage for radiopharmaceutical synthesis. For this reason, it was necessary to change the medium and concentration of these solutions, by adding drops of NaOH to pH higher than 9's, to ensure lanthanide precipitation in the form of hydroxides (Ln (OH)₃ Ln = Pm, Tb, Ho, or Lu). The precipitate was then deposited in a filter column, which was rinsed with a HCl solution 0.1 mol/L to dissolve the hydroxides and convert them to chlorides (LnCl₃) as a final product.

4.3 Radiolanthanides Separation Device (RSD)

The methodology for obtaining radiolanthanides ^{151}Pm , ^{161}Tb , ^{166}Ho and ^{177}Lu , established from studies of LnSPS resin affinity for the lanthanides, formed the basis for designing and building the Radiolanthanides Separation Device (RSD) that allows easy, safe and routine pair separation of $^{149}\text{Nd} / ^{149}\text{Pm}$, $^{161}\text{Gd} / ^{161}\text{Tb}$, $^{166}\text{Dy} / ^{166}\text{Ho}$ and $^{177}\text{Yb} / ^{177}\text{Lu}$, to produce radioisotopes ^{149}Pm , ^{161}Tb , ^{166}Ho and ^{177}Lu .

The RSD was designed and built by the RMRL Group, the technician Francisco Jiménez Barreiro from General Workshops and the Automation Department of ININ. So, separation methodology of ^{151}Pm , ^{161}Tb , ^{166}Ho and ^{177}Lu was divided into seven fundamental stages: (1) irradiation of Nd, Gd, Dy and Yb nitrate, in TRIGA Mark III reactor from ININ with thermal neutrons to form the 4 radiolanthanide pairs: $^{149}\text{Nd} / ^{149}\text{Pm}$, $^{161}\text{Gd} / ^{161}\text{Tb}$, $^{165}\text{Dy} / ^{165}\text{Ho}$ and $^{177}\text{Yb} / ^{177}\text{Lu}$ (2) dissolution of radioactive salt, (3) setting of radioactive solution, containing the pair to be separated, in a chromatographic column filled with Ln SPS resin, (4) radioisotope recovery father through elution of column with HNO_3 , (5) daughter recovery by elution with HNO_3 radioisotope, (6) radioisotope daughter precipitate, (7) precipitate redissolution and obtaining the final product [31].

The RSD is placed in an acrylic cell, shielded with two lead walls of 10 cm thickness, and is comprised of four main systems: (1) reagent entry system, (2) radiated vial opening (3) separation system integrated with a separation column and a recovery column mounted in a central carousel and (4) extraction and air system (see Figure 9).



Figure 9: Radiolanthanides Separation Device (RSD) interior and exterior view.

RSD allows separating the $^{149}\text{Nd}/^{149}\text{Pm}$, $^{161}\text{Gd}/^{161}\text{Tb}$, $^{165}\text{Dy}/^{165}\text{Ho}$ and $^{177}\text{Yb}/^{177}\text{Lu}$ pairs with the following efficiencies: 84, 100, 99 and 67%, to produce radioisotopes: ^{149}Pm , ^{161}Tb , ^{166}Ho and ^{177}Lu with radionuclide purity of greater than 99.99%, in a time of 2 to 5 hours, depending on the pair to be separated.

4.4 Preparation of extractive resins in RMRL [32]

Commercially Eichrom Technologies Inc. produces the extracted Ln SPS Eichrom resin prepared from di (2-ethylhexil) orthophosphoric acid (HDEHP) and used for lanthanide and actinide separation with great success. The popularity of the HDEHP is due to the advantageous separation factors for rare earth using infused hydrophobic (kieselguhr) or silica gel as support for extraction by chromatography [33]. However, the disadvantage of this extract is the cost (50 g: \$ 730). For this reason our group proposed to develop a methodology for preparation of extractive resins based on HDEHP, to separate the pairs $^{149}\text{Nd}/^{149}\text{Pm}$, $^{161}\text{Gd}/^{161}\text{Tb}$, $^{165}\text{Dy}/^{165}\text{Ho}$ and $^{177}\text{Yb}/^{177}\text{Lu}$ and generate a technology for preparing these resins. Prepared resins with six supports: kieselguhr DG, alumina, red tezontle, chiluca, quarry and fluorite; using two types of treatment of silanization of the supports: dimetildiclorosilano/heptane solution 1: 30 and by contact with DMCS (dimethyldichlorosilane) vapor in vacuum, and changing the ratio of the HDEHP extract in acetone (1: 4, 1: 8, 1: 15, 1: 20, 1: 30 and 1: 40). The $^{161}\text{Gd}/^{161}\text{Tb}$ pair was selected to test the efficiency of these resins, identifying two main parameters: Gd-Tb separation efficiency and ^{161}Tb radionuclide purity, which express the viability of separating both elements and ^{161}Tb purity. 0.8 mol/L HCl is used as eluent to recover Gd and 3 mol/L to extract ^{161}Tb .

Physical and chemical changes in different stages of preparation of the mineral-extracting resins were determined by various means: X-Ray Diffraction (XRD), to determine the crystalline phases of the sample; Scanning Electron Microscopy (SEM), for the morphology of the materials used; Infrared Spectroscopy (IR), for the molecular structure; and surface area measurement. The characterization of the media used (kieselguhr, alumina, quarry, chiluca, tezontle and fluorite) showed that the first two are the best options to develop this type of resin; given that the Alumina showed a surface area greater than 190 m²/g, allowing the majority of the extract to be retained.

According to our results, using DMCS vapor is the best procedure for the silanization of the media, with best HDEHP/acetone concentration of 1: 20 and the best support is kieselguhr. The extractive resin prepared under these conditions allows the *Gd/Tb* pair to be separated with an

efficiency of 90.7% while obtaining ^{161}Tb with a purity of 99.86%, improving even the Ln SPS resin performance for which 85.9% efficiencies are obtained with purities of 99.5%. On the other hand, the preparation of 1 g of extractive resin with the proposed methodology has a cost of \$7.6 USD as the commercial resin Ln SPS Eichrom is \$14.6 USD/g [32].

5. Collection of ^{131}I by distillation from TeO_2

There is a constant development of radiopharmaceuticals of iodine, as well as in obtaining labelled biomolecules in nuclear medicine. Radiopharmaceuticals of iodine include proteins, biomolecules of low molecular weight and monoclonal antibodies. The iodine radioisotopes used in the preparation of radiopharmaceuticals in nuclear medicine are: ^{123}I , ^{125}I and ^{131}I . This is used for clinical diagnostics for the following reasons: a) its half-life is 8.05 days, allowing radiopharmaceuticals to be prepared in commercial proportions, b) obtaining it is easy, through TeO_2 irradiation with low production cost and c) gamma energy 364 keV, enough to penetrate deep into human body tissue and to obtain gammagraphic images. At present, ^{131}I is produced from: a) products of uranium fission and b) from tellurium and tellurium oxide (TeO_2) irradiation using dry distillation methods. In dry distillation, the target (TeO_2), is placed inside a quartz capsule and once inside an electric oven; the oven temperature is increased, ^{131}I is released from TeO_2 in the form of gas which is suctioned through a vacuum system and captured in a receiver containing NaOH, where it becomes Na^{131}I .

When the separation of the ^{131}I is carried out under conditions of uniform temperature throughout the entire oven, where it does not have a distillation control system connected to the electrical system and the distillation system, there is a high probability that pollution accidents occur. Exposure rates within the processing cell are high and therefore put the operator at risk. With the aim of eliminating these drawbacks, the RMRL Group developed distillation equipment for ^{131}I . This equipment consists of three systems interconnected with each other: the control system for target distillation, the electrical system and the distillation system. This equipment guarantees low levels of ^{131}I contamination, high yield in obtaining the end product, ease of handling and precise control of the distillation parameters of ^{131}I [34-36].

5.1 Obtaining of ^{131}I by dry distillation from TeO_2

Due to the demand that exists in Mexico to develop applicable radiopharmaceuticals production techniques in nuclear medicine, the National Nuclear Research Institute decided to develop a process for obtaining ^{131}I by the dry method from TeO_2 .

The process of obtaining ^{131}I , begins with the synthesis of TeO_2 as a raw material, from the oxidation of elemental tellurium with HNO_3 , in the presence of air. Subsequently the TeO_2 passes to the synthesis process in the form of ingots allowing its encapsulation with aluminium, to be irradiated under optimal parameters in the nuclear reactor. The irradiated TeO_2 , goes to the cooling stage and then to the dry distillation of ^{131}I . The processing equipment consists principally of three parts: a) the distillation system, made from pyrex glass, quartz, where ^{131}I is separated from radioactive parents: ^{131}Te and $^{131\text{m}}\text{Te}$, b) distillation system control and (c) the electronic system for the furnace ventilation system and vacuum system [34].

The kinetics of TeO_2 synthesis reaction was studied as well as conditions which favored more effective ^{131}I capture and optimal cooling time. Irradiation parameters were optimized in the nuclear reactor such as irradiation time and TeO_2 mass, to obtain maximum ^{131}I output, at the lowest cost. Additionally, temperature and pressure conditions during distillation were studied [34-38].

The most important equipment aspects include the design of each component, resulting in the effectiveness of routine ^{131}I production (industrial), whose final product can reach a radiochemical and radionuclide purity of over 99%, thus achieving a more pure and economic product with fewer risks, from the perspective of radiation safety and above all, preventing its importation and allowing Mexico to become self-sufficient in ^{131}I production provided that Mexico must have a nuclear reactor with power ≥ 10 MW; currently the TRIGA reactor Mark III has a potential nominal maximum of 1 MW [39].

6. Extraction of phosphorus-32 from sulfur-32

Research studies from the original material (sulphur-32), its purification and irradiation in the reactor, production process at the prototype level and finally, industrial design and construction were carried out for phosphorus-32 (^{32}P) production.

The ^{32}P method was selected based on previously established studies of physical and chemical sulfur and nuclear reaction properties were studied to produce ^{32}P in the nuclear reactor TRIGA Mark III.

Once sulfur is irradiated, it must be separated from ^{32}P using various tests, then a prototype and finally production equipment must be developed mainly composing of: to) reagent injection system, vacuum and gas extraction system b) the electrical system and c) the mechanical system. With this equipment (see figures 10 and 11), a maximum of 30 g of sulphur mass, can be processed independently from other parameters involved during reactor irradiation. The resulting ^{32}P occurs in the form of $\text{H}_3^{32}\text{PO}_4$ solution and can be used in medicine, industry and agriculture [40-41].

7. Perspectives

Applications of radioisotopes in medicine, industry and research depend on the specific needs of each area and the availability of these radioisotopes for use. It is therefore of vital importance for our institution to depend upon radioisotope production programs covering both present and future needs of radioisotopes users in Mexico. This involves a multidisciplinary work between administrators and scientists or technologists. The RMRL Group will have as objectives, to identify the needs of the domestic market and develop the required radioisotope production methodologies. It is also desirable that the ININ has a catalogue of new radioisotopes that promotes the need for its use and enhance its applications, as is the case of $^{188}\text{W}/^{188}\text{Re}$ generators and radiolanthanides, whose production methodologies are already finished products requiring institutional impetus for their exploitation and utilization. The same applies to the processes of ^{131}I , ^{32}P and $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators that after having required arduous input into its development, scaling to a commercial stage still has not been materialized. In addition, it is essential that ININ has a nuclear reactor or a particle accelerator that has the capacity to produce radioisotopes in a commercial manner; currently only samarium-153 is locally produced and the rest of radioisotopes (^{99}Mo , ^{131}I , ^{125}I , ^{202}Tl) are purchased abroad. For example, a cyclotron would develop methodologies for radioisotope production of ultrashort and short half-life of special interest in nuclear medicine.

Acknowledgments

The authors thank CONACYT and IAEA, for funding the projects: (1) "Research and Development of $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ - gel Based Generator for Medical Applications" CONACYT J33049, ("2) Production of Radioactive Radiolanthanides for Radiotherapy" CONACYT/health 2004-C01-001", (3) Development of Radionuclide Generator Technologies for Therapeutic Radionuclides" IAEA/CRP No. 12879/R0, as well as the Mexico-United States Foundation for Science (WSCF) and the Mexican Academy of Sciences (AMC) and Dr. Russ Knapp of ORNL. We express our appreciation to all staff of Radioactive Materials Department for their support in the development of these projects: Germán Desales, Edilberto Garza, Baldomero Delgado, Jose Luis Reyes, Marco Antonio López, Paz González, Beatriz Rivera, Sergio Pérez, Rafael de la Rosa, Consuelo Lavalle, Triga Mark III reactor team in ININ: Wesceslao Nava, Braulio Ortega, Margarito Alva, Robert Raya and Edgar Herrera, as well as fellows who participated in these projects: Aída Contreras, Laura V. Diaz, Ociel Cortes, S. Thania Jiménez, León Gallico, Heriberto Díaz, C. Itzel Aguilar, F. Genoveva García, Edgar James, Z. Iris Lopez, Celia C. De la Cruz, Ana L. Vera, Cesar Rosales, Issiel Ortega and Ana Lilia Mata. We also appreciate the support of the Chemistry Department and chemist Leticia Carapias.

References

1. Eckelman WC, Coursay BM. Special issue on technetium-99m. *Int. J. Appl. Radiation Isotopes*, **10**, 33, 1982.
2. Evans JV, Moore PW, Shying ME, Sodeau JM. *Appl. Radiat. Isot.* **38(1)**, 19-23, 1987.
3. Monroy-Guzmán F, Arriola Santamaría H, Ortega Álvarez I, Cortés Romero O, Díaz Archundia LV. Determination of Mo, W and Zr in molybdates and tungstates of zirconium and titanium. *J. Radioanal. Nucl. Chem., Articles*. **271(3)**, 523-532, 2007.
4. Monroy-Guzmán F, Díaz Archundia LV, Contreras Ramírez A. Effect of Zr:mo ratio on $^{99\text{m}}\text{Tc}$ generator performance based on zirconium molybdate gels. *App. Radiat. Isot.* **59(1)**, 27-34, 2003.
5. Monroy-Guzmán F, Cortés Romero O, Longoria L, Martínez Castillo T. Titanium molybdate gel as $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator matrix. *Synth. Appl. Isot. Lab. Comp.*, **8**, 321-324, 2004.
6. Monroy-Guzmán F, Cortes Romero O, Díaz Velázquez H. Titanium molybdate gels as matrix of $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators. *J. Nucl. Radiochem. Sci.* **8(1)**, 11-19, 2007.

7. Monroy-Guzmán F, Díaz Archundia LV, Hernández Cortés S. $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators performances prepared from zirconium molybdate gels *J. Braz. Chem. Soc.* **19(3)**, 380-388, 2008.
8. Jiménez Martínez TS, Monroy Guzmán F. Efecto de las condiciones de síntesis de compuestos Mg-Mo en las características de los generadores $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$. XVI Congreso de la SNM, Oaxaca, 10-13 julio 2005, SNM, 1-11, 2005.
9. Jiménez Martínez TS, Monroy Guzmán F. Compuestos de Mg-Mo como generadores de $^{99\text{m}}\text{Tc}$. XL Congreso Mexicano de Química, Morelia Michoacán, 24-28 septiembre 2005, SQM, 1-10, 2005. www.quimicanuclear.org.
10. Farmacopea de los Estados Unidos Mexicanos (FEUM) Vol. 1, 8ª ed. Secretaría de Salud, México, 2004.
11. Monroy-Guzman F, Barron Santos ES, Hernandez S. Synthesis installation of zirconium ^{99}Mo -molybdate gels to $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator. *Synth. Appl. Isot. Lab. Comp.*, **8**, 325-329, 2004.
12. López Malpica IZ, Monroy-Guzman F. Optimización del proceso de síntesis de geles zirconio ^{99}Mo -molibdatos. XVII Congreso de la SNM and First American IRPA Congress Acapulco, Guerrero, 4-8 septiembre 2006, SNM, 1-8, 2006.
13. López Malpica IZ, Rivero Gutiérrez T, Rojas Nava P, Monroy Guzmán F. Prototipo para la producción de generadores $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ a base de geles. XLI Congreso Mexicano de Química, México D.F., 24-28 septiembre 2006, SQM, 1-10, 2006. www.quimicanuclear.org.
14. Contreras Ramírez A, Monroy Guzmán F, Díaz Archundia LV. Síntesis y caracterización de molibdatos de zirconio de generadores $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$. XXV Congreso Latinoamericano de Química, Cancún Quintana Roo, 22-26 septiembre 2002, SQM, 1-5, 2002. www.quimicanuclear.org.
15. Quiterio Chan A, Monroy Guzmán F. Cristalización de geles de molibdatos de zirconio matrices de los generadores $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$. XXXIX Congreso Mexicano de Química, Mérida Yucatán, 3-7 septiembre 2004, SQM, 1-10, 2004. www.quimicanuclear.org.
16. Contreras Ramírez A, Monroy Guzmán F, Díaz Archundia LV. Síntesis e irradiación de geles de zirconio molibdatos utilizados como matrices de generadores $^{99}\text{Mo}-^{99\text{m}}\text{Tc}$. XIII Congreso la Sociedad Nuclear Mexicana, Ixtapa Zihuatanejo, Gro., 10-13 de noviembre 2002, SNM, 1-8, 2002.

17. Knapp FF, Callahan AP, Beets AL, Mirzadeh S, Hsieh BT. Processing of reactor produced ^{188}W for fabrication of clinical scale alumina-based $^{188}\text{W}/^{188}\text{Re}$ generators. *Appl. Rad. Isot.* **45(12)**, 1123-1128, 1994.
18. Jeong JM, Chung JK. Therapy with ^{188}Re -Labeled Radiopharmaceuticals: An overview of promising results from initial clinical trials. *Cancer Biother & Radiopharm.* **18(5)**, 707-717, 2003.
19. *Therapeutic radionuclide generators: $^{90}\text{Sr}/^{90}\text{Y}$ and $^{188}\text{W}/^{188}\text{Re}$ generators.* Technical Reports Series No. 470, Vienna, IAEA 2009.
20. Monroy Guzman F, Hernandez Paz M, Galico Cohen L, Rosales CJ, Badillo Almaraz V. Tungsten and rhenium sorption study on alumina to prepare $^{188}\text{W}/^{188}\text{Re}$ generators. *Sep. Sci. Tech.* **44(5)**, 1120-1143, 2009.
21. Monroy-Guzmán F, Badillo Almaraz VE, Flores de la Torre JA, Cosgrove J, Knapp FF. Hydroxyapatite-based $\text{Mo}/^{99\text{m}}\text{Tc}$ and $^{188}\text{W}/^{188}\text{Re}$ generator systems. *Trends in Radiopharmaceuticals* Vol. 1, Viena, IAEA, 333-347, 2007. <http://www-pub.iaea.org>
22. Monroy-Guzmán F, Badillo Almaraz VE, Rivero Gutiérrez T, Gállico Cohen L, Cosgrove J, Knapp FF, Rojas Nava P, Rosales CJ. Development of inorganic adsorbents as matrices of generators for therapeutic radionuclides. *Therapeutic radionuclide generators: $^{90}\text{Sr}/^{90}\text{Y}$ and $^{188}\text{W}/^{188}\text{Re}$ generator.* Technical Reports Series No. 470, Vienna, IAEA, 161-173, 2009. <http://www-pub.iaea.org>
23. Aguilar Dorado IC, Monroy Guzmán F, Badillo Almaraz VE. Estudio de la viabilidad de la hidroxiapatita como matriz del generador $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$. International Joint Meeting LAS/ANS-SNM-SMSR, Cancún Quintana Roo, 11-14 de julio 2004, SNM, 1-7, 2004.
24. Vázquez Guerrero S, Badillo Almaraz V E, Monroy Guzmán F. Influencia del electrolito en la fijación de ^{99}Mo en hidroxiapatita como matriz del generador $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$. XVI Congreso de la SNM, Oaxaca, Oaxaca, 10-13 julio 2005, SNM, 1-6, 2005.
25. Monroy Guzmán F, Rosales Torres CJ. Determinación de solubilidad de tungstenatos de Ca, Mn y Fe mediante técnicas radiométricas. XLII Congreso Mexicano de Química, Guadalajara Jalisco, 22-26 septiembre 2007, SQM, 1-13, 2007. www.quimicanuclear.org.
26. Cutler CS, Smith CJ, Ehrhardt GJ, Tyler TT, Jurisson SS, Deutsch E. Current and potential therapeutic uses of lanthanide radioisotopes. *Cancer Biotherapy Radiopharm* **15**, 531-545, 2000.

27. García Montes de Oca FG, Monroy-Guzmán F. Adsorción de lantánidos en hidroxapatita en medio tiocianato de potasio. XVII Congreso de la SNM, Acapulco, Guerrero, 4-8 septiembre 2006, SNM, 1-11, 2006.
28. Genoveva García Montes de Oca F, Monroy Guzmán F. Adsorción de Nd, Pm, Gd, Tb, Dy, Ho, Yb y Lu en hidroxapatita en medio tartrato de sodio. XLI Congreso Mexicano de Química, México D.F., 24-28 septiembre 2006, SQM, 1-8, 2006. www.quimicanuclear.org.
29. Jaime Salinas E, Monroy Guzmán F. Separación de Nd y Pm, Gd y Tb mediante cromatografía de extracción. XLI Congreso Mexicano de Química, México D.F., 24-28 septiembre 2006, SQM, 1-9, 2006. www.quimicanuclear.org.
30. Monroy-Guzmán F, Jaime Salinas E. Preparación de Ho-166 y Lu-177 para radioterapia. XLII Congreso Mexicano de Química, Guadalajara Jalisco, 22-26 septiembre 2007, SQM, 1-13, 2007. www.quimicanuclear.org.
31. Vera Treviño AL, Jiménez Barreiro F, Monroy-Guzmán F, Vázquez Maldonado JC. Dispositivo de Separación de Radiolantánidos (DISER). XIX Congreso de la SNM, Mérida Yucatán, 6 al 9 de julio 2008, SNM, 322-330, 2008.
32. De la Cruz Barba CC, Monroy-Guzmán F. Preparación de resinas extractivas para producción de Terbio-161. XX Congreso Anual de la SNM, Puerto Vallarta, 6-9 de julio 2009, SNM, 255-264, 2009.
33. Horwitz EP, Bloomquist CAA, Delphin WH. Radiochemical separations liquid-liquid chromatography using PSM Support. *J. Chrom.Sci.*, **15**, 41-46, 1977.
34. Alanis J. Estudio de investigación y optimización de los parámetros del proceso de obtención de Iodo-131 del ININ. Tesis Doctoral, Facultad de Química, UNAM, México, 2000.
35. Alanis J, Navarrete M. Industrial production of I-131 by neutron irradiation and melting of sintered TeO₂. Applications of Accelerators in Research and Industry. Sixteenth International Conference, Denton Texas, 853-856, 2001.
36. Alanis J, Navarrete M. Optimal conditions to obtain purity sintered TeO₂ useful as a thermal neutron target for the I-131 industrial production particulate. *Science and Technology*, **18**(1), 1-18, 2000.
37. Segovia A, Alanis J, Garduño M. Automating tasks on hot cell using small microcontrollers. *WESEAS Transac. Sist.* **4**, 149-154, 2005.

38. Alanis J, Segovia A, Navarrete M. Safety conditions for irradiation, transporting and meeting of sintered TeO_2 during the ^{131}I industrial production. *Health Physics.*, **87(2)**, 34-36, 2004.
39. Mazón Ramírez, R. El reactor nuclear TRIGA Mark III. *Actividad Científica y Tecnológica en el Instituto Nacional de Investigaciones Nucleares*, México, Innovación Editorial Lagares de México, 397-409, 2008. www.inin.mx
40. Alanis J, Navarrete M. Phosphorus-32 production by sulfur irradiation in a partially moderated neutron flux by $^{32}\text{S}(\text{n,p})^{32}\text{P}$ reaction. *Mediamond International Proceedings.* **1**, 83-88, 2005.
41. Alanis J, Navarrete M. Industrial production and purification of ^{32}P by sulfur irradiation with partially moderated neutron fluxes and target melting. *J. Radioanal. Nucl. Chem.* **273(3)**, 659-662, 2007.

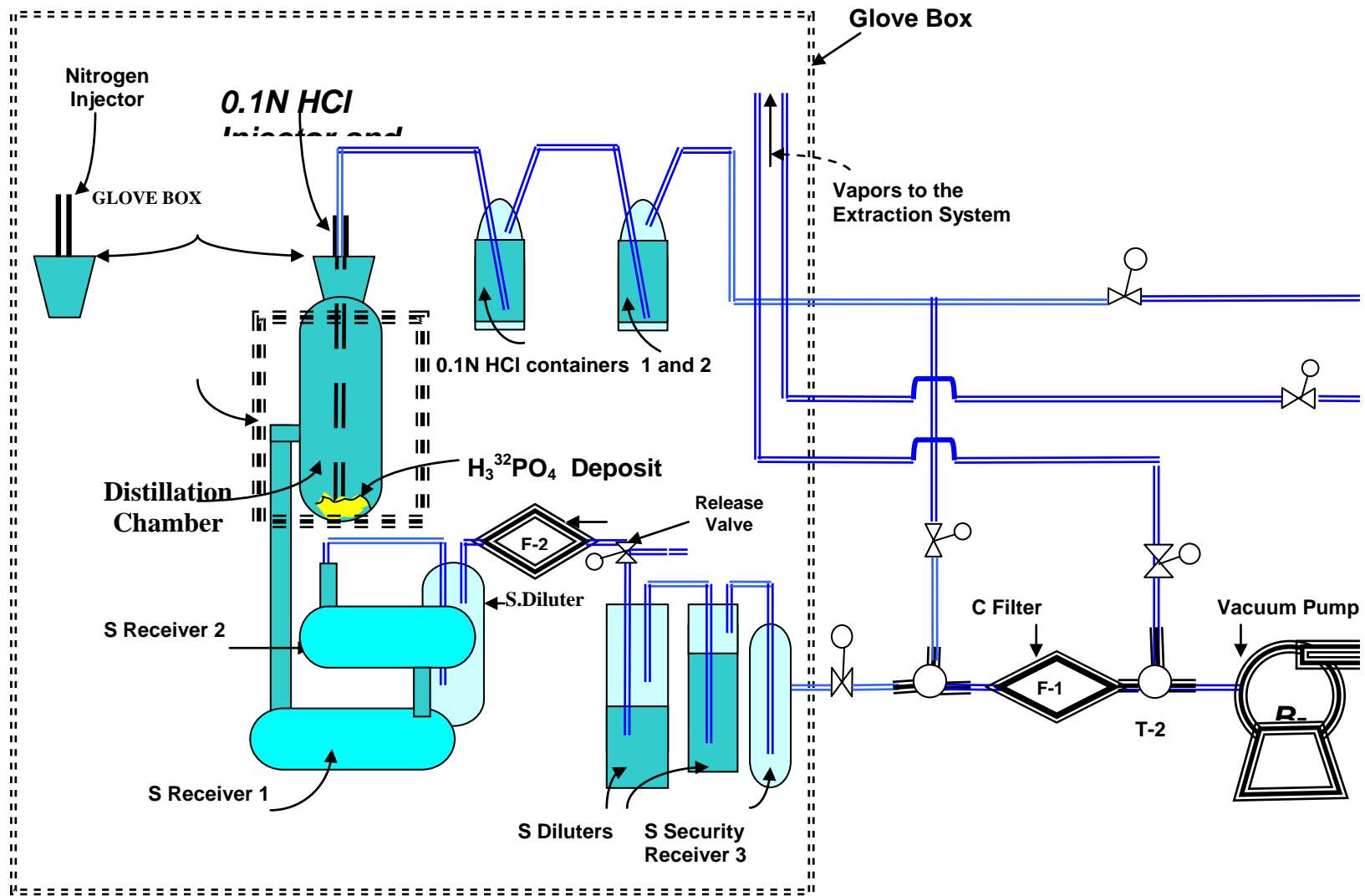


Figure 10. Phosphorus-32 production process.

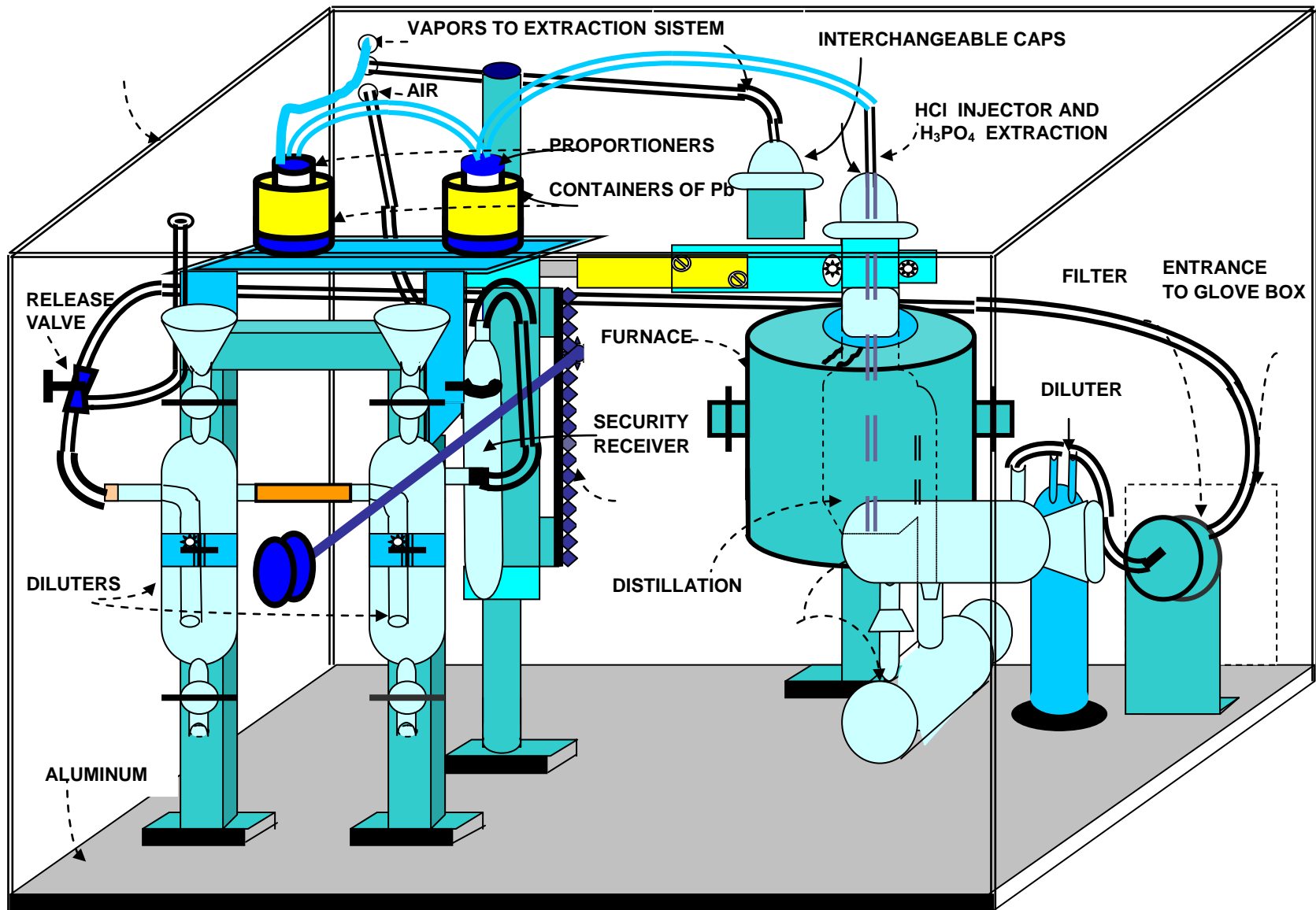


Figure 11. Processing of phosphorus-32 (^{32}P) from sulfur-32.