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Editorial

Radioisotope and radiation technology programme of the Departmental of Atomic Energy plays a pivotal role in the societal applications of nuclear Science and Technology India. Radioisotope production is the first step toward harnessing the benefits of the radiation emanating from useful radioisotopes for improvement of quality of life. I am confident that the present bulletin, guest edited by Dr. Sudipta Chakraborty, an experienced radiochemist in the field of radioisotope production, will provide in depth coverage of various aspects related to the production of radioisotopes. I hope this thematic bulletin will help young radiochemists to understand all the practical issues related to radioisotope production.

I thank Dr. Sudipta Chakraborty for agreeing to be the Guest Editor of this bulletin and the efforts he has put in bringing it out

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From President's Desk

Dear Members

Wish you a scientifically exciting and academically satisfying new year 2017.

I am glad that the much delayed IANCAS thematic Bulletin is about to be published. There are two major common links among the members of IANCAS, namely IANCAS website and IANCAS thematic Bulletins besides continuous interaction fora like workshops, seminars and conferences.

Continuous efforts by managing committee members and a few enthusiastic experts have resulted in the update of IANCAS Website. For sure, enough scope exists to improve further. In the current e-age, it is a matter of time that our thematic bulletins will ***only*** *be made available online so as to enhance ease of access to the information to members as well as non-members, and to reduce the cost of printing and posting. I earnestly appeal to all the members of IANCAS to update their email ids, inform fellow members about the need to provide email ids and let the scientific and academic community know about our website.*

One of the major non-power applications of nuclear energy programme or nuclear industry is applications of radioisotopes and radiations in a variety of fields like health care, industry, agriculture, hydrology, life sciences, pollution control and research & development. It is worth recollecting the efforts of pioneers, particularly Georg de Hevesy who was first to identify the ability of radioactivity (radioisotopes) to trace the path of a reaction and applying the same. He recollected,how it all began,in an IAEA conference held in 1964 in Salzburg, Austria. Hevesy joined Rutherford in University of Manchester's Institute of Physicsin 1911. One day, Rutherford gave a challenging chemical separation problem to Hevesy by saying "My boy, if you are worth your salt, you separate Radium D from all that nuisance lead." Hevesy accepted the assignment and later recalled, "being a young man, I was an optimist and felt sure that I should succeed in my task". Radium D could not be separated from the stable lead, as is known later that Radium D is an isotope of lead(^{210}Pb). In his own words, "To make the best of this depressing situation, I thought to avail myself of the fact that radium D is inseparable from lead and to label small amounts of lead by addition of radium D of known activity," a great intuition but based on logical deduction. The concepts of radioactive indicator and radio tracer were born with his subsequent works. It is well documented that later he applied radiotracers in many studies including life sciences.

Important criteria of choosing a radioisotope for an intended application are half life, type and energy of radiations emitted, ease of availability, cost of production etc. A large number of isotopes are identified for a variety of applications. Most important step in this direction is production of rdaioisotopes and their processing to suite an application. Cardinal principle of radioisotope production is to disturb the neutron to proton ratio of a stable isotope by inducing nuclear reactions using either neutrons or charged particles. Theme of the current IANCAS Bulletin is "Radioisotope Production" and a glance at the contents gives an impression that all aspects of radioisotope production have beendiligently covered by experts.It is hoped that praise worthy efforts of contributors, Guest Editor and Editor resulted in a good reference material on production of radioisotopes.

I would like to share with members that a request was received from Director, IOP, Bhubaneswar to form Eastern Chapter of IANCAS with IOP as the center. Over the last few years, IOP has been in forefront in extending its cooperation to IANCAS activities in Eastern region, particularly in Odhisha. In the forthcoming AGM during NUCAR 2017, the proposal will be discussed. On personal behalf I welcome the idea and appreciate the efforts of IOP.

All the members are urged to use the website for interacting with EC and other members.

A V R Reddy

From the Secretary's Desk

Dear All Life Members,

Wish you a happy, healthy and prosperous New Year 2017.

Publication of thematic bulletins is one of the most important activities of IANCAS apart from conducting workshops in various academic institutes on Nuclear Sciences in general and "Radiochemistry and Applications of Radioisotopes" in particular. IANCAS bulletins are very popular among the members of DAE as well as academic institutes. I am very happy that the current bulletin on the topic "Production of Radioisotopes" having six articles is being brought out by IANCAS. Radioisotope production is a very important work carried out by many researchers and Engineers of the Department towards achieving societal benefits of nuclear energy program. Radioisotopes find applications in the areas of food, agriculture, industry, health care and research. Through neutron activation route, radioisotopes like ^{99}Mo, ^{60}Co, ^{131}I, ^{198}Au, ^{82}Br, ^{65}Zn and ^{32}P are being produced mainly by Dhruva research reactor and ^{89}Sr by FBTR. Whereas carrier free radioisotopes like ^{18}F, ^{201}Tl and ^{67}Ga are being produced by Cyclotron at VECC. On behalf of IANCAS, I thank all contributors for their excellent articles on the subject of interest. I thank Dr. Sudipta Chakraborty, RPhD, BARC for accepting our request to be the Guest Editor and also contributing an article. We thank Dr. A Dash, Head, RPhD & Editor, IANCAS for his valuable guidance & support in bringing out this Bulletin. We are in the process of bringing out two more bulletins soon in this FY 2016-17.

I take this opportunity to inform you that with support from many resource persons and senior scientists from BARC and other units of DAE, IANCAS has successfully conducted a total of 94 national workshops and many one-day workshops. To cater to many requests from various institutes, IANCAS has started Two-Day workshops from 2015 onwards.

IANCAS thanks BRNS, DAE for the financial support for printing of IANCAS bulletins. IANCAS thanks Director, BARC, Chairman, BRNS and Chairman, AEC for their support and encouragement.

R. Acharya

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Production of Radioisotopes

Guest Editor

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FOCUS

Dr. B. S. Tomar
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Radioisotope production as well as application is one of the most important programs of Department of Atomic Energy (DAE), India. Radioisotopes find a variety of applications in diverse fields such as human healthcare, industry, agriculture, food preservation, environmental studies, water resource management and chemical research. A major breakthrough in nuclear science was achieved in 1934, when Frederic Joliet and Irene Curie demonstrated the production of first artificial radioisotope ^{30}P, by bombardment of alpha particles on ^{27}Al target. This was closely followed by another path breaking discovery by George De Hevesy, who had shown the utility of artificially produced radioisotope ^{32}P as a radiotracer. The invention of cyclotron and setting up of nuclear reactor opened the floodgate for production of radioisotopes. Till today, over 2500 radioisotopes have been produced artificially. Several of these artificially produced radioisotopes have been extensively used in improving the quality of human life by utilizing radiation emitted by them.

In India, utilization of radioisotopes plays a pivotal role in the improvement of quality of life of people and also in sustained economic growth. Radioisotope application is the most prominent peaceful application of atomic energy and is actively promulgated by the DAE. Sustained availability of radioisotope in appropriate radiochemical formulation and at an affordable cost is basic requisite in the successful utilization of radioisotope and radiation technology for societal benefits. In this respect, an advanced technology for production and radiochemical separation of desired radioisotopes in nuclear reactors and particle accelerators is of great utility. India is one of the major producers of a wide variety of radioisotopes like ^{60}Co, ^{137}Cs, ^{99}Mo, ^{131}I, ^{177}Lu, ^{82}Br, ^{198}Au, ^{32}P, ^{65}Zn and ^{18}F.

I am extremely glad that Indian Association of Nuclear Chemists and Allied Scientists (IANCAS) is bringing out this thematic bulletin consisting of six articles on various aspects, namely, production of radioisotopes using nuclear reactors, cyclotrons and radioisotope generator systems. The articles of the bulletin will give a glimpse on the advanced research and technology development in India in the field of radioisotope production. I thank all the authors of articles, Dr. A. Dash, Editor of IANCAs Bulletin and specially, Dr. Sudipta Chakraborty, RPhD, BARC (Guest Editor) for sparing their valuable time in bringing out this important thematic Bulletin.

Guest Editorial

Dr. Sudipta Chakraborty

Since the inception of the Department Atomic Energy (DAE), founded by Dr. H. J. Bhabha, radioisotope programme has played a pivotal role in the peaceful utilization of nuclear science and technology for the benefit of the people of India. India had an early entry in the field of radioisotope production amongst the then developing nations thanks to the commissioning of APSARA in 1956, the first research reactor in Asia. Radioisotope production had a modest beginning in India with the successful radiochemical isolation of ^{32}P from neutron irradiated elemental sulfur in the temporary isotope laboratory at Cadell Road in central Bombay. With the commissioning of CIRUS research reactor at Trombay in 1960, India embarked on the production of a number of major radioisotopes (^{60}Co, ^{99}Mo, ^{131}I, ^{192}Ir, ^{198}Au, ^{203}Hg etc.) for medical and industrial applications. Matching with these reactor facilities, increasingly sophisticated laboratories were set up for large-scale handling and radiochemical processing of radioisotopes. Starting with the Cadell Road Laboratories initially, production facilities were transferred in the mid-sixties to the intermediate laboratories in the South Site at Trombay. At the same time, detailed planning of more advanced facilities for large scale production was taken up, and finally radioisotope production facility at Radiological Laboratories were commissioned in the early seventies. Large-scale production and utilization of these radioisotopes became an important activity of DAE in the late eighties with the availability higher thermal neutron flux after the successful commissioning of 100 MW_{th} DHRUVA research reactor. At present, more than 10 KCi quantities of as many as 48 different radioisotopes are annually produced in Dhruva and deployed to various parts of our country for their utility in human healthcare, agriculture, industry and research. Apart from this, large quantity of ^{60}Co in produced in some of the power reactors operated by Nuclear Power Corporation of India Limited (NPCIL). Another important milestone was met in the year 2004 when the first medical cyclotron of the country became functional at Radiation Medicine Cenetre (RMC), Mumbai. Since then, large quantity of ^{18}F-labeled fluoro deoxy glucose ($[^{18}F]FDG$) and a few other ^{18}F-labeled agents are being produced for clinical positron emission tomography (PET) imaging.

Taking note of the important contribution of radioisotope programme of DAE in the societal application of nuclear science and technology in India, the Indian Association of Nuclear Chemists and Allied Sciences (IANCAS) has brought out this thematic bulletin on various aspects related to the production of radioisotopes covering the recent progress in this filed in India. There are six articles in this bulletin giving a vivid account of the scientific and technical aspects as well as the inherent intricacies involved in the production of various radioisotopes utilizing research reactor, fast breeder test reactor, cyclotron and radioisotope generator.

It has been an honour for me to be the Guest Editor of the Bulletin. I got immense pleasure in interacting with the authors of the articles. I take this opportunity to convey my sincere gratitude to each of them for their valuable contribution which turns this endeavor of IANCAS into a reality. I express my sincere thanks to Dr. Ashutosh Dash, Editor, IANCAS and Dr. Raghunath Acharya, Secretary, IANCAS for their continuous support and guidance.

Radioisotope Production in Research Reactors at Trombay

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Abstract

The programme of radioisotope production in India was initiated with the commissioning of the Apsara in August 1956 and production of the radioisotopes on industrial scale commenced with the commissioning of 40 MW research reactor Cirus in 1960. The quality and quantity of radioisotope production considerably improved with the operation of 100 MW research reactor Dhruva in the year 1985. The important isotopes produced in the research reactors include ^{131}I, ^{125}I, ^{60}Co, ^{99}Mo, ^{32}P, ^{192}Ir etc. The isotopes have been used extensively in various areas such as medicine, agriculture, forensic science, neutron activation analysis, radiography, etc. This paper highlights the utilization of various facilities available in the research reactors and the future plans for the production of radioisotopes.

Introduction

Apsara a swimming pool type reactor used highly enriched uranium as fuel in the form of U-Al alloy and demineralised water as coolant, moderator, reflector and shielding material. The programme of radio-isotope production in India started with the commissioning Apsara in August 1956. The procedures for safe handling of irradiated samples were evolved and streamlined with emphasis on strengthening safety culture. The reactor was well utilized and various radio-isotopes were produced in the facilities provided in the reactor. The facility helped in evolution of handling and reactor safety procedures. The reactor was used extensively for more than 50 years and after serving its intended purpose it was decommissioned in June 2008.

With commissioning of Cirus in 1960, a new era began for the industrial scale isotope program in India. A wide range of isotopes are produced in Cirus and a large number of isotopes are supplied to the users all over India and even abroad. The irradiation facilities available in the reactor are tray rods, self serves and J-rod annulus. The maximum thermal neutron fluxes available in these irradiation locations are 6.7 $x10^{13}$, 1.4 $x10^{13}$ and 1.0 $x10^{13}$ n/cm^2/sec, respectively. Cirus was permanently shut down on 31st December, 2010.

To meet the requirement of high specific activity of radio-isotopes, Dhruva, a 100 MW thermal research reactor wherein the thermal flux is about 2.5 times higher was commissioned in 1985. The reactor uses natural uranium metal as fuel, heavy water as moderator, coolant and reflector. The experience gained while operating Cirus reactor was well utilized in design and development of new irradiation facilities for isotope production in Dhruva reactor. The irradiation facilities available in the reactor are tray rods, Pneumatic carrier facility, adjuster rod, self serves, etc. The maximum thermal neutron fluxes available in these irradiation locations are 1.8 $x^{*}10^{14}$, 9.0 $x10^{13}$, 2.0 $x10^{14}$ and 1.5 $x10^{13}$ n/cm^2/sec, respectively. Normally solid samples are irradiated in these facilities. However to meet the special requirements of certain isotopes, a xenon tray rod facility was created to irradiate gaseous samples in Dhruva reactor.

At present, research reactor DHRUVA [1] provides majority of the research reactor based facilities to cater to the varied research needs of the vast pool of researchers in DAE and various other academic institutions of the country. It also caters to the requirement of radio-isotopes for use in medicine, agriculture and industry. Apsara and CIRUS have already been shut down and Dhruva would be about 40 years old by the year 2025, thus necessitating construction of a new research reactor so as to be available by the year 2025.

With an aim of achieving higher neutron flux to produce radioisotopes of higher specific activity similar to Cirus reactor, the 2 MW upgraded Apsara reactor is designed. The core is surrounded by BeO reflector elements. The BeO reflector elements are provided to achieve adequate excess core reactivity and to maximize the irradiation volume for isotope production and material testing. The core is loaded with dispersion type uranium (LEU)-silicide (U_3Si_2-Al) fuel in the form of plates.

To provide uninterrupted services of radioisotope supply of higher specific activity, material irradiation and facilities for condensed matter research, construction of 30 MW High Flux Research Reactor (HFRR) is planned at Vizag, keeping in view the requirement of such services beyond the year 2025. The HFRR will be a 30 MW (thermal) research reactor with a maximum thermal neutron flux of 5.5 x 10^{14} n/cm^2/sec. The reactor will be fuelled with Low Enriched Uranium (19.75% w/w) dispersion type plate fuel and will use demineralised water as coolant and moderator. The reactor core will be surrounded by an annular heavy water reflector tank to achieve a high neutron flux over a large radial distance to maximize the number of irradiation positions available for isotope production and material irradiation. Most of the irradiation positions will be accommodated in the heavy water reflector tank surrounding the core. Salient features of all reactors are shown in Table-1.

In the research reactors at Trombay, several irradiation

facilities in the form of tray rods, self serve, adjuster rod and pneumatic carrier are provided for isotope production. From time to time to augment the production of isotopes, new irradiation facilities were conceived and designed. Various reactor operational practices for enhancing the production of radio-isotopes were also evolved. For example, removal of the tray rods from the core was carried out in reactor shut down condition once a month till 1971. In 1972, new tools were designed, developed and tested successfully to carry out removal of tray rod on stream; i.e. without shutting down the reactor and sample changes are carried out once a week, thus increasing the frequency of supply of samples. The introduction of on-power tray rod facility and improvement in tray-rod design has proved a mile-stone in increasing radio-isotopes production on regular basis. Based on the sample volume, irradiation duration and specific activity requirement, a relevant facility is chosen. Various facilities, with their specific features, used for production of radioisotopes are given below:

Table-1: Salient features of research reactors

Parameters	**1 MW Apsara**	**40 MW CIRUS**	**100 MW Dhurva**	**2 MW Upgraded Apsara**	**30 MW HFRR**
Reactor type	Swimming pool type, thermal	Vertical tank type, thermal	Vertical tank type, thermal	Swimming pool type, thermal	Swimming pool type, thermal
Date of criticality	4th August, 1956	10th July, 1960	8th August, 1985	To be commissioned	To be commissioned
Maximum reactor power	1 MW	40 MW	100 MW	2 MW	30 MW
Fuel material	Enriched (~93%) uranium-aluminum alloy	Natural uranium metal	Natural uranium metal	Enriched (17%) uranium-silicide dispersion fuel	Enriched (~19.75%) uranium silicide dispersion fuel
Type of fuel element	Plate	Pin	Pin	Plate	Plate
Fuel cladding	Aluminum	Aluminum	Aluminum	Aluminum	Aluminum
Total fuel mass	4.5 Kg.	10.0 Tonne	6.7 Tonne	27.8 Kg. LEU	48 Kg LEU
Moderator	Light water	Heavy water	Heavy water	Light water	Light water
Coolant	Light water	Light water	Heavy water	Light water	Light water
Reflector	Light Water	Graphite	Heavy Water	BeO + Light Water	Heavy Water
Maximum neutron flux in n/cm²/sec (type of flux)	1×10^{13} (Thermal)	6.5×10^{13} (Thermal)	1.8×10^{14} (Thermal)	6.1×10^{13} (Thermal) 1.4×10^{13} (Fast)	6.7×10^{14} (Thermal) 1.8×10^{14} (Fast)
Shut off rod material	Cadmium	Boron	Cadmium	Hafnium	Hafnium
Number of shut off rods	3 CSRs 1 FCR	6 SORs	9 (SORs)	4 (2 CSRs and 2 SORs)	6 (2 SORs and 4 CSRs)
Number of	4 (Irr. Positions)	5 (tray rods)	3 (Tray rod), 1	7 (tray rods)8	2 :In core irradiation -
irradiation position (Type of irradiation position)	6 beam tubes	1 PCF 1 PWL 22 Beam tubes 5 Self servs	(Pneumatic carrier) and 2 (Engineering loop)	Beam tubes1 shielding corner for shielding experiments1 Thermal column for detector testing	position; In reflector26 : Irradiation position 1 Pneumatic carrier 2 NTD Si 2 Engineering loops

Utilization:

Based on the sample volume, irradiation duration and specific activity requirement, a relevant facility is chosen. Various facilities, with their specific features, used for production of radioisotopes are given below:

1. Isotope Tray Rods

These are specially designed irradiation assemblies used for irradiation of samples in high volumes and for longer durations. They are hollow rods, with trays mounted at various elevations for supporting the sample capsules and cut out

windows which provide access to these capsules. This portion of the tray rod is called the tray section. The number of tray rods in a reactor is limited by the amount of excess reactivity available, depending on other experiments being carried out. Individual target samples are housed in a 1.6 mm thick ASTM-A-SB-221-TP-1060 aluminium capsule measuring 22 mm in diameter and 46 mm in height. The weight of the empty capsule is about 15 gm [1]. There are 2 to 3 tray rods in Dhruva a maximum thermal neutron flux of 1.8×10^{14} n/cm^2/sec. In each rod there are 30 axial positions and at each position 3 capsules, 120 degree apart from each other, can be accommodated. Thus each tray rod can accommodate up to 90 capsules at a time. The tray rods are cooled with heavy water with a flow - 80 lpm.

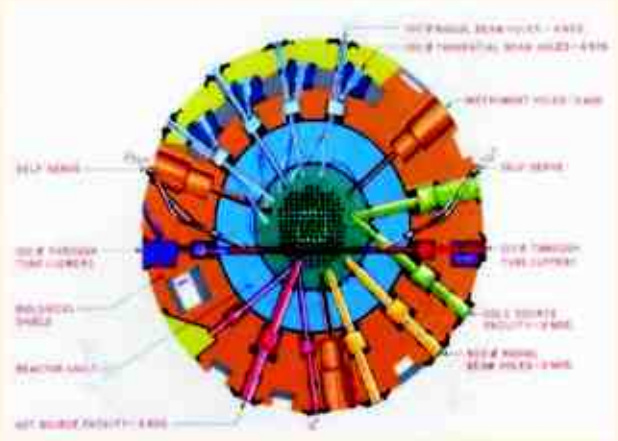

Figure-1: Dhruva experimental and irradiation facility

During the year 2011 radioisotopes of about 54000 Ci activity, including radiopharmaceuticals of about 2800 Ci activity, were produced in Dhruva. At present BRIT supplies only about 20% of the total radioisotope demand in the country. Nuclear medicine practitioners have to import the remaining isotopes. Out of the total radiopharmaceuticals produced in Dhruva ^{99}Mo and ^{131}I constitute about 60% and 30% respectively. Other isotopes supplied include ^{177}Lu, ^{153}Sm, ^{32}P, ^{51}Cr, ^{35}S, ^{192}Ir, ^{203}Hg etc. After the shutdown of Cirus reactor, an additional isotope assembly has been loaded in Dhruva with a view to increase the irradiation capability. Meanwhile, import of radioisotopes by BRIT has increased by about 25% in the last 2 years to cope up with the demand within the country.

A total of 1212 units of irradiations were carried out in Dhruva reactor during the year 2012, which corresponds to ~25% increase in number of irradiation units compared to last year. Utilization of the three tray rods in the Dhruva reactor for isotope production was above 95%. 3650 Ci of radioisotopes were processed for medical, industrial, agricultural and other applications. The activity produced exceeded the production in 2009 (3078 Ci) and 2010 (3600 Ci), when both CIRUS and Dhruva reactor were working. The isotope production could be much higher, if demand increases. 70700 Ci of ^{192}Ir was produced during 2012 in Dhruva by irradiating 82 cans of iridium pellets. Irradiation coordination was done by RPhD. The Unloaded activity was handed over to BRIT for processing. The amount of activity produced is higher than earlier years [61395 Ci in 2009, 63,339 Ci in 2010, 66737 Ci in 2011). Cobalt-60 was produced for the first time in the Dhruva reactor. 60 cans of cobalt slugs were unloaded with an estimated activity of 10,100 Ci and delivered to BRIT. The specific activity of the Co-60 produced in Dhruva is suitable for Blood Irradiator and gamma chamber.55 service irradiations were carried out for different researchers inside and outside BARC. Special irradiation services were provided to various divisions (LWRD, Material Science Division) in BARC.

2. Self Serve Positions

Dhruva has 5 numbers of self serve units each of which can accommodate 5 irradiation capsules. The standard irradiation capsules are enclosed in a specially designed spherical ball (**Figure-2**), which is rolled into the irradiation position under gravity. At the end of irradiation, the ball is rolled out into a special lead shielding container. Irradiation of targets in self serve units can be carried out without affecting the operation of the reactor for any pre-determined period. The self serve facility is ideally suited for the production of short lived radioisotopes. The maximum thermal neutron flux available in self serve position is about 1.5×10^{13} n /cm^2/sec.

Figure-2: Tray rod capsule & Self Serve Aluminium Sphere and capsule

3. Pneumatic Carrier Facility

This air cooled facility is used for short time irradiation of samples in reactor and is available in Dhruva. The design permits users to SEND/RECEIVE the samples to be irradiated in polypropylene capsules, to and from the reactor, pneumatically from PCF rooms located in annexe building/ attached. The maximum thermal neutron fluxes available in Dhruva is 9.0×10^{13} n/cm2/sec. The irradiation time in Dhruva is limited to 1 minute. The time limits on irradiation are based on the assessment of temperatures and pressures likely to be reached during irradiation. The facility is mainly used for neutron activation analysis. This technique provides not only rapid quantitative simultaneous analysis down to ppb level or below but also provides critical validation support to other techniques. The growth and success has been mainly due to the availability of research reactors with high neutron flux

and to the advances in high neutron spectrometry systems. A wide variety of samples were irradiated in PCF for application in material sciences, environmental and life sciences, forensic science and archaeology. PCF has also been used for determination of uranium by solid state nuclear track detector (SSNTD) using fission track analysis (FTA). NAA used for detection of trace elements in variety of materials such as geological, biological, archaeological, environmental, high purity materials, nuclear pure materials and forensic samples.

4.0 Specially Designed Assemblies

In Dhruva three cobalt slug rods were irradiated in a specially designed assembly. Cobalt metal slugs of dimensions 6 mm diameter and 75 mm height, sheathed in 1 mm thick aluminium, were arranged in tires around the central rod. The rod had 24 tires with each having 5 slugs. With the high neutron flux available in Dhruva, Cobalt-60 with intermediate specific activity of 50 ci/gm was obtained in a period of 3 to 4 years. Recently, Dhruva Adjuster rod has been commissioned which is very useful to produce high specific activity of Cobalt (250 Ci/gm) and to be used for xenon over-ride.

^{125}I is increasingly used in prostate cancer brachytherapy owing to its more favorable decay characteristics. Invariably this is accompanied by the formation of substantial amounts of other isotopes of iodine especially ^{126}I (T ½ - 13.03 days) which later require long decay periods to bring down the levels of ^{126}I to acceptable levels. This step also results into the loss of ^{125}I. A simple method of production of ^{125}I from irradiation of natural Xe gas was thought of and implemented in Cirus and in Dhruva. Even though the natural abundance of ^{124}Xe is low (0.094%), it could be used to produce ^{125}I provided the neutron flux and irradiation times are adequate. The resulting ^{125}I product is found to be suitable for RIA applications. The nuclear reaction involved is as follow: ^{124} Xe(n,ā) ^{125}Xe —>E.C. (18 hr)—>^{125}I—>E.C. (60.06 d)——> ^{125}Te (stable)

Radio-isotopes produced in Dhuva

The following Table lists the major isotopes that are being produced since the past few decades in Dhruva. This aspect has been advantageously used in production of isotopes such as ^{32}P.

Radionuclide produced	Target and the reaction	Typical Amount and frequency	Application
^{99}Mo	Natural MoO_3 ^{98}Mo(n,γ)^{99}Mo	1-1.3 TBq(30-40 Ci)/ wk	Medicine; ^{99m}Tc is obtained from ^{99}Mo-^{99m}Tc generator
^{131}I	Natural TeO_2 ^{130}Te(n,γ)^{131}Te(β-)^{131}I	0.7-1TBq(20-30 Ci)/ wk	Medicine; for management of thyroid disorders
^{32}P	Natural Sulphur ^{32}S(n,p)^{32}P	1.11GBq(3Ci)/15d	Medicine-therapy Agriculture, Molecular Biology
^{153}Sm	^{152}Sm(n,γ)^{153}Sm	222GBq(6Ci)/ month	Medicine-therapy
^{177}Lu	Enriched ^{176}Lu(n,γ)^{177}Lu	222GBq (6Ci)/month	Medicine-therapy
^{125}I	^{124}Xe(n,γ)^{125}Xe (EC)^{125}I	18.5GBq (500 mCi) bi-monthly	Brachytherapy and Radiometric assays
^{45}Ca	Nat.$CaCO_3$ ^{44}Ca(n,γ)^{45}Ca	As required	Research
^{35}S	Nat. KCl ^{35}Cl(n,p)^{35}S	As required	Research
^{203}Hg	Natural target ^{202}Hg(n,γ)^{203}Hg	As required	Industry-radiotracer
^{82}Br	Natural NH_4Br ^{81}Br(n,γ)^{82}Br	55.5GBq(mCi)as required	Industry-radiotracer
^{46}Sc	Natural Sc_2O_3 ^{45}Sc(n,γ)^{46}Sc	As per the reuqirement	Industry-radiotracer
^{140}La	Natural target ^{139}La(n,γ)^{140}La	As per the requirement	Industry-radiotracer
^{60}Co	Natural Cobalt ^{59}Co(n,γ)^{60}Co	Long irradiation; as required	Industry-radiography, radiation source
^{192}Ir	Natural Iridium ^{191}Ir(n,γ)^{192}Ir	37TBq/ wk	Industrial Radiography
^{115}Cd	Natural target ^{114}Cd(n,γ)^{115}Cd	As required	Research
^{115m}Cd	^{114}Cd(n,γ)^{115m}Cd	As required	Research
^{65}Zn	^{64}Zn(n,γ)^{65}Zn	As required	Research
$^{85+89}$Sr	$^{84+88}$Sr(n,γ)$^{85+89}$Sr	As required	Research

Safety Evaluation of samples

An isotope sample when put inside the reactor for irradiation, causes reactivity load on the reactor due to parasitic absorption of neutron in it. So reactivity load of the sample is an important parameter to be evaluated before its installation in the reactor. An isotope sample absorbs alpha, beta and gamma radiations present in the reactor and also produced in the sample itself causing a heat load which must be within the permissible limit. Thus heating in the sample must be evaluated before its installation in the reactor. A Sample, after irradiation, becomes radioactive and emits alpha, beta and gamma radiations. Without proper protection, these irradiated samples can cause harm to the personnel handling it. Thus for safety of the concerned personnel, it is required to assess the dose rate at the surface of the sample which should be less than 200 mR/hr. To meet the dose rate criterion, it is important to evaluate shielding and cooling requirement for the sample. All the safety evaluations of PIR are done by a computer code ORPAC (Operational Reactor Physics Analysis Code) developed in house. The overall heating in a sample, limits the mass of the sample in each capsule. For the sample being irradiated in the Dhruva reactor, the nuclear heating in the sample including capsule is limited to 100 watts. Related formulas to carry the calculations by PIR (Pile Irradiation Request) evaluation code ORPAC [2] are given in the following Table-2 & Table-3.

Table-2 Formulas used in ORPAC

Flux Depression Factor	$f = \frac{\bar{\phi}}{\phi_0}$, $f = \frac{\int_V \phi(\bar{r})d\bar{r}}{\int_V \phi_0 d\bar{r}}$
Capture gamma heating	$H = C_0 E_0 S_v (\psi_0 + a_1\psi_1)\frac{\mu_A}{\mu}\frac{M}{\rho}$
Decay gamma heating	$H = C_0 E_0 A(\psi_0 + a_1\psi_1)\frac{\mu_A}{\mu}\frac{M}{\rho}$
Core gamma Heating	$H_{(core)} = \sum_E \mu_{air}(E) E \varnothing_r(r,E) R(E)$, $R(E) = \frac{1}{\mu_{air}\lambda}(1-e^{-\mu_{air}(E)\lambda})$ $H_{FN} = \sum_n \Sigma_{xi}(\varphi_{ni})(\Delta E)_n = \frac{2A}{(A+1)^2}\sum_n \Sigma_{xi}\varphi_{ni}E_n$
Fast neutrons heating	$H_{FN} = \sum_n \Sigma_{(coolt)}(\Delta E)_n = \frac{2A}{(A+1)^2}\sum_n \Sigma_{(coolt)} E_n$
Heating in the sample post irradiation	$H_{gamma} = A \times E \times 1.6 \times 10^{-13}(1-e^{-\mu x})$ watts for gamma heating $H_{gamma} = A \times E \times 1.6 \times 10^{-13}$ watts for alpha and beta heating
Reactivity Load	$\frac{\delta K}{K} = -0.0258 f \delta\Sigma_A V_s \frac{\phi_s^2}{\phi_m^2} mk$
Activity First order case	$N_1 = N_1^0 e^{-\sigma_{A_1}\phi t}$ $N_2 = N_1^0 \sigma_{C_{12}}\phi\left[\frac{e^{-\sigma_{A_1}\phi t} - e^{-(\lambda_2+\sigma_{A_2}\phi)t}}{\lambda_2 + (\sigma_{A_2} - \sigma_{A_1})\phi}\right]$ $A_2 = \lambda_2 N_2$ $N_1 = N_1^0 e^{-\sigma_{A_1}\phi t}$
Second order case	$N_2 = N_1^0 \sigma_{C_{12}}\phi\left[\frac{e^{-\sigma_{A_1}\phi t} - e^{-(\lambda_2+\sigma_{A_2}\phi)t}}{\lambda_2 + (\sigma_{A_2} - \sigma_{A_1})\phi}\right]$ $N_3 = B\left[\frac{e^{-\sigma_{A_1}\phi t} - e^{-(\lambda_3+\sigma_{A_1}\phi)t}}{\lambda_3 + (\sigma_{A_3} - \sigma_{A_1})\phi}\right] + D\left[\frac{e^{-(\lambda_2+\sigma_{A_2}\phi)t} - e^{-(\lambda_3+\sigma_{A_3}\phi)t}}{\lambda_3 - \lambda_2 + (\sigma_{A_3} - \sigma_{A_2})\phi}\right]$ $B = \phi N_1^0\left[\sigma_{C_{13}} + \frac{\lambda_2\sigma_{C_{12}}}{\lambda_2 + (\sigma_{A_2} - \sigma_{A_1})\phi}\right]$ $D = \frac{\phi N_1^0 \lambda_2 \sigma_{C_{12}}}{\lambda_2 + (\sigma_{A_2} - \sigma_{A_1})\phi}$ $A(t_c) = \lambda_2 N_2 e^{-\lambda_2 t_c} + \lambda_3 N_3 e^{-\lambda_3 t_c}$
Dose Rate	$D = 5574C\sum_v E_v f_v e^{-\mu x} B(E_v, \mu x)$
Dose rate due to capsule activity	$D = D_0\frac{\phi}{\phi_0}(1-e^{-\lambda t_i})e^{-\lambda t_c}$

Table-3 Abbreviations used

f	flux depression factor
ϕ	average flux in the sample
ϕ_0	flux at outer surface
$\phi(r)$	neuron flux at position
C_n	1.6×10^{-11} (WS/Mev) a conversion factor
A_1	0.65
E_0	average energy of photons (MeV)
S_v	no. of gamma photons / cc/sec
μ_{E_0}	energy deposition coefficient for energy E_0 (cm^{-1})
μ	total linear attenuation coefficient (cm^{-1})
M	Mass of a sample
ρ	Density of sample
A	Specific activity (Bq/gm)
μ_m	total attenuation coefficient of the irradiated sample material
μ_{en}	absorption coefficient of gamma rays in the sample material
l	mean chord length of the sample
E	average energy of gamma/ beta/alpha particle in MeV,
$\varphi_{n(E)}$	neutron flux of energy group n
$\sum_{s(}$	macroscopic scattering cross section of the sample
E_n	mean energy of group n
A	Atomic Mass
V_s	Sample Volume
N_1, N_2, N_3	number density of isotope X_1 X_2 X_3
φ_{a1}	absorption cross section of nuclides
φ_{a2}	absorption cross section of nuclides
$\lambda_1, \lambda_2, \lambda_3$	Decay Constants (sec^{-1})
D	Shielded dose rate at a distance of 1foot (mR/hr)
D_0	Bare Dose rate(mR/hr)

Future prospects/plans for isotope production

There are various plans of augmentation of isotope production in Dhruva and in proposed new research reactors viz modified 2 MW Apsara and 30 MW HFRR. Following gives the salient points about future plans of enhancing isotope production in Indian research reactors.

(a) Fission molybdenum production in Dhruva

Technetium-99m, the daughter product of Molybdenum-99 (^{99}Mo), is the most commonly utilized medical radioisotope in the world. ^{99m}Tc (half life=6 hrs) is very much suited for medical diagnostic applications because of its soft gamma (140-keV). ^{99}Mo (half life 67 hrs) the parent isotope of ^{99m}Tc can be produced in two ways. First way to produce it is by irradiating natural molybdenum in the reactor through neutron capture reaction. Since fission yield of ^{99}Mo is around 6%, nuclear fission method is the other way to produce ^{99}Mo. By this route one can produce Mo^{99} of very high specific activity.

A preliminary analysis for production of fission moly in Dhruva reactor has been carried out. LEU-Al alloy has been considered as a target material for this purpose. The enrichment of U-235 has been assumed to be 20%. Fuel position has been considered for placing the target for irradiation. Total of two targets have been assumed to be loaded at fuel position. Expected activity/two week will about 1500 to 2000 Ci.

Conclusions:

Programme of isotope production in India has been quite successful and these isotopes have been used extensively in various areas such as medicine, agriculture, forensic science, neutron activation analysis, radiography. To overcome the shortfall expected due to decommissioning of Apsara and Cirus, 100 MW Dhruva will meet the growing demand of radio-isotopes in India. With the proposed fission moly production in Dhruva reactor will serve the high specific activity requirement of this isotope.

References:

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Author Indormation

Dr. P.V. Varde is B.E.(Mech.) from Government Engineering College Rewa, Madhya Pradesh and joined Reactor Operations Division of Dhruva as shift engineer in 1984 after completion of one year orientation course in Nuclear Engineering from 27th batch of BARC training school. He did his PhD in reliability engineering. from IIT Mumbai. He also did post-doctoral at Korea Atomic Energy Research Institute, South Korea in 2002. His areas of expertise are Probabilistic Safety Assessment, Development of Artificial Neural Network Based Applications, Root Cause Analysis, Safety Performance Evaluation of Nuclear Plants, Risk-Based ISI, Nuclear Plant Operations, Physics of Failure approach for electronic components. He worked as specialists / consultant to many international organizations.. He is founder of Society for Reliability and Safety. Presently he is Senior Professor at Homi Bhabha National Institute and Head, Research Reactor Services Division of Bhabha Atomic Research Centre, Mumbai (India).

Tej Singh, a post graduate in Physics from Agra University, Uttar Pradesh, joined Research Reactor Services Division in the year 1990 after completion of one year orientation course in Nuclear Engineering from 33rd batch (Physics Discipline), BARC training school. At present, he is heading the Reactor Physics and Nuclear Engineering Section of Research Reactor Services Division. He is responsible to provide Reactor Physics support for safe and smooth operation of the research reactors at Trombay, Mumbai. He is also responsible for Reactor Physics and shielding design of upcoming Research Reactors, like upgraded Apsara, High Flux Research Reactor (HFRR) and 125 MW Thermal Research Reactor. He has also developed computer codes NEMSQR and HEXNEM, based on nodal expansion method, for reactor core design calculations and safety analysis codes RITAC and SACRIT based on point kinetics model coupled with thermal hydraulics.

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Shri H.G Gujar is B.Tech (Mech) from Engineering College, Karad Maharashtra and joined Reactor Operations Division of Dhruva as shift engineer in 1986 after completion of one year orientation course in Nuclear Engineering from 29th batch of BARC training school. His areas of expertise are Research reactor operations including Surveillance, Performance monitoring, Refuelling, Performance review, Safety review, Safety evaluation, Modifications of new systems/components and Ageing Management. Currently he is heading Engineering Services Section of RRSD. He is responsible for Review of utilization of RRs, Safety review of irradiation proposals, Design & development of irradiation facilities, Design review & implementation of modifications, Commissioning of system/equipments, Conducting of periodic Safety Review and Ageing Management.

Neutron Irradiation of Target for Radioisotope Production

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Introduction:

Radioisotopes have a wide range of applications in diverse fields like health care which includes diagnostic and therapeutic usage, industrial engineering involving radiographic imagining of materials, agriculture sector which includes food security and sterilization through irradiation, age estimation of the geological samples and compositional characterization through activation analysis –just to name a few. The time line of radioisotopes dates back to the discovery of neutron which is accredited to James Chadwick in 1932.

Soon after its discovery, neutron found its applications in scientific investigations related to physics, material science, biology, and chemistry. Fermi bombarded heavier elements with these neutrons which enabled him to induce radioactivity in elements of high atomic number. This work earned Fermi his Noble Prize in Physics "for his demonstrations of the existence of new radioactive elements produced by neutron irradiation and for his related discovery of nuclear reactions brought about by slow neutrons" in 1938.

Before the discovery of nuclear fission, the strength of neutrons available for inducing radioactivity was limited to just 10^3 -10^6n/cm^2/s. As a consequence the amount and quantity of radioactivity that could be produced by such neutrons remained very low. But after the development of nuclear technology, neutron flux in the range of 10^{12}-10^{15}n/cm^2/s high amount of radioactivity became accessible to researchers which facilitated the production of radioisotopes. The source of this neutron strength was nuclear research reactor.

With the world's first research reactor Brookhaven graphite Research Reactor (BGRR), becoming operational in 1950, an intense neutron source became available which could induce nuclear reactions across the entire periodic table for isotope production and activation analysis Presently there are more than 1600 radioisotopes which are being artificially produced.

In India radioisotope production programme started under the peaceful purpose programme of DAE, with the commissioning of the swimming pool Apsara reactor in August 1956. To make the country self-sufficient, a programme for radioisotope production was undertaken and the Isotope Division was established in 1957. Small quantities of ^{131}I and ^{32}P were produced and handled in the production facility set up in the Isotope laboratories. As the demand increased for variety of radioisotopes and experience gained, Cirus was commissioned and went critical in 1960 for production of almost all the reactor produced radioisotopes of medium to high specific activity.

The regular supply of radioisotopes for application in the fields of medicine, industry agriculture and research was commenced in 1962-63. Cirus has been in operation for over five decades and has been used extensively for production of variety of radioisotopes. At present Dhruva is operating at 100MW and successfully catering the radioisotope needs of our nation.

Production of Radioisotopes

Radioisotopes are produced by exposing suitable target material to the neutron flux in nuclear reactor for an appropriate time. Target materials to be irradiated are sealed in some container preferably in aluminium container and then loaded in the irradiation facility. The radioisotope production typically involves several interrelated activities such as target preparation, irradiation in nuclear reactor, transportation of irradiated target to radioactive laboratory for radiochemical processing or encapsulation in sealed source and quality control followed by its transportation to the end user. The crucial characteristic of radioisotope for its application is the magnitude of its specific activity.

Production of radioisotopes having high specific activity depends on parameters like target and irradiation conditions, the rate of the nuclear reaction which in turn depends on the energy of the neutrons, neutron flux and characteristic of the target material and activation cross section for the desired nuclear reaction.

Classification of Neutrons

The neutrons are classified on the basis of their energy in to following categories:

Cold neutrons : The neutron with the energy range from 0.0ev to 0.025 eV are considered as cold neutrons.

Thermal neutron : Thermal neutrons are those which are in thermal equilibrium with the molecules/atoms of the surrounding medium. The energy distribution of this group of neutrons is represented by Maxwellian distribution. The thermal neutron has energy of about 0.025eV at the temperature of 20°C.

Epithermal neutrons : The neutrons which are having energy normally in keV range and obey the 1/E law are epithermal energy neutron. The energy range of these neutrons varies from 0.025eV to 0.4eV.

Resonance neutrons : The neutrons having the energy between 10 to 300eV are referred as resonance neutrons.

Intermediate neutrons : The energy range of intermediate neutrons is between 300eV to 1MeV.

Fast neutrons : Neutrons which are having energy more than 1MeV are considered to be fast neutron. They are having the distribution similar to that of fission neutrons.

It is important to note that in a nuclear reactor the distribution of the neutron energy group will be different in different parts of the reactor. At the centre of the core, the distribution of fast neutron will be more compared to the periphery of the reactor. Majority of the neutrons that are available from reactor are thermal.

The quantity of radioisotope produced in a reactor during a typical irradiation schedule depends of on various parameters that are described below.

Yield of radioisotope

There are different types of nuclear reaction which can take place by the interaction of neutron inside the reactor. These are (n,p), (n,α), (n, γ) with beta decay. The yield of radioisotope can be calculated by the following equations

When any target is exposed to neutrons in the reactor the activation of the radioisotope produced is given by

$$\frac{dN}{dt} = N_T \sigma \varphi$$

N_T is the total number of atoms present in the target

ϕ is neutron flux in n/cm^2/s

σ is the neutron cross section in barn

λN is the number of atom activated

In the above equation the neutron flux is considered to be isotropic and average value of the flux is considered. For the decay of the radioisotope while irradiation, the net growth rate of the active atoms is given by

$$\frac{dN}{dt} = N_T \sigma \varphi - \lambda N$$

λN denotes the decay of the product nucleus

The above equation can be solve for the specific activity (Ci/gm) and the final form of the equation after simplifying can be given as follows

Specific activity =

$$\frac{0.6 \times \sigma \times \varphi}{3.7 \times 10^{10} \times A}\left(1 - e^{-\lambda t}\right) Ci/g$$

where A is the mass number of the parent nuclei, λ is decay constant, t is time of irradiation. Activity is in Curie per unit gram of radionuclide. When the time of irradiation is very large compared to the half life of the daughter then we get saturation activity as

Specific activity =

The activity reaches the saturation value limited to the flux of the neutron in the reactor.

The activity induced can be reduced because of the following factor

Self-shielding factor

Activation calculation assumes the uniform neutron flux inside the target which is practically not there, therefore it must be corrected to take into account the fact that for strong absorbers, the inner portions of target are exposed to a lower flux than the outer ones, because of neutron absorption in the latter. This correction can be made by defining a self shielding factor f such that $A=fA_u$, where A_u is the specific activity of an irradiated infinite dilution target and A is the specific activity of the irradiated target. Infinite dilution refers to an extremely low density N of target atoms, such that the fractional neutron absorption in a volume element, which is proportional to the density N and the absorption cross section is negligible.

The correction factor f depends upon the geometry of target and can be evaluated theoretically. [1]

Power variation in the reactor

The power of the reactor varies during the operation and it is difficult to evaluate theoretically the effect of power variation on the activity of buildup except by following the operation of the reactor and applying decay correction.

Corrections to the activation

Correction has to be applied for the flux depression due to adjacent target and for the burn up of the target material with time and destruction of the product nucleus due to subsequent neutron capture. This is effective for long term irradiation of targets and the targets are having high activation cross section.

Irradiation efficiency

The ratio of the activity actually produced in the target to the activity calculated is referred to as the irradiation efficiency. It depends on all the effects of the factors above. This factor should be experimentally determined by trial irradiation. The irradiation efficiency varies between 90% to as low as a value as 10%. [2]

Irradiation of targets

For the production of the above radioisotopes targets are irradiated for more than two half lives of the activation product of interest in high flux position of reactor. In practice, actual activity produced is different from the theoretically calculated activity. This is because the actual flux, self shielding factor of the target, burn up, power variation in the reactor operation, flux depression due to adjacent target and depletion of the product nucleus due to subsequent neutron capture. In certain cases, contribution from epithermal neutrons leads to enhancement in the activity produced as compared to the theoretical calculation.

Table 1. Major radioisotopes produced in nuclear reactor with nuclear reaction

Radioisotope	Half-life($T_{1/2}$)	Nuclear reaction
Mo-99	66 h	$^{98}Mo(n,\gamma)^{99}Mo$
I-131	8.02 d	$^{130}Te(n,\gamma)^{131}Te \rightarrow ^{131}I$
I-125	59.41d	$^{124}Xe(n,\gamma)^{125}Xe \rightarrow ^{125}I$
Lu-177	6.71d	$^{176}Lu(n,\gamma)^{177}Lu$
Sm-153	46.27 h	$^{152}Sm(n,\gamma)^{153}Sm$
Ir-192	73.83d	$^{191}Ir(n,\gamma)^{192}Ir$
Co-60	5.272y	$^{59}Co(n,\gamma)^{60}Co$
P-32	14.26d	$^{32}S(n,p)^{32}P$
Br-82	35.34h	$^{81}Br(n,\gamma)^{82}Br$
Sc-46	83.82d	$^{45}Sc(n,\gamma)^{46}Sc$

Table 2. Detail production parameters of various useful radioisotopes by neutron irradiation in research reactor [3]

Sr.No	Parent nuclide	% Nat. Abund	Radioisotope	Cross section (barn)	Half Life	Theoretical Sp.Activity	Saturation(100% $1x10^{14}n/cm^2/s$ enrichment)
1.	$^{98}Mo_{42}$	24.13	^{99}Mo	0.130 ± 0.006	67h	470KCi/g	346mCi/g
2.	$^{130}Te_{52}$	34.08	^{131}I	0.29 ± 0.06	8.04d	124mCi/μg	Carrier free
3.	$^{32}S_{16}$	95.02	^{32}P	70mb	14.3d	9100Ci/millimol	Carrier free
4.	$^{191}Ir_{77}$	37.3	^{192}Ir	954 ± 10	74d	9.23KCi/g	1.17KCi/g
5.	$^{176}Lu_{71}$	2.59	^{177}Lu	2090 ± 70	6.7d	110KCi/g	19.25KCi/g
6.	$^{152}Sm_{62}$	26.75	^{153}Sm	206 ± 6	47h	436KCi/g	0.105KCi/g
7.	$^{81}Br_{35}$	49.31	^{82}Br	2.7 ± 0.2	35.4h	1074KCi/g	15.77Ci/g
8.	$^{44}Ca_{20}$	2.09	^{45}Ca	0.88 ± 0.05	165d	16.32KCi/g	32.4Ci/g
9.	$^{50}Cr_{24}$	4.34	^{51}Cr	15.9 ± 0.2	27.8d	93.7KCi/g	515.6Ci/g
10.	$^{59}Co_{27}$	100	^{60}Co	37.18 ± 0.06	5.26y	1.15KCi/g	1.034KCi/g
11.	$^{124}Xe_{54}$	0.095	^{125}I	165 ± 11	60d	17.5mCi/ μg	Carrier free
12.	-	-	Fiss. ^{99}Mo		66h	470KCi/g	-

For the safe operation of reactor, it is necessary to restrict the maximum weight of target inside the aluminum can to a certain limit.

Following are the considerations by the safety evaluation group of Dhruva research reactor for the irradiation of target in reactor:

a) Only solid samples which remain stable during neutron irradiation should be considered.

b) The permissible mass of the sample has been calculated for the maximum neutron flux position in the irradiation facility to ensure safety even in case of errors in handling/ loading and post irradiation samples

c) The heating rate in the sample due to core radiations, capture gammas and other radiations such as alpha and beta radiations, dose should not exceed 25 Watt/cm of length of target material in the capsule. This value is specific to reactor and depends upon the structure of individual reactor.

d) The target material in a capsule should not occupy more than 90% of the capsule volume to account for the liberation of gases or dimensional changes due to heat or irradiation.

e) During post irradiation handling of irradiated sample, cooling should be provided at least 30 minutes for decaying of short lived radioactive nuclides before transferring the capsules to Hot cell facility.

f) Nuclear heating in a capsule during post irradiation handling should not exceed 1.5 Watt after 30 minutes of radioactive cooling.

g) The maximum value of weight of the target material that can be irradiated in a rector is strictly governed by reactor safety considerations and is specific to a particular reactor.

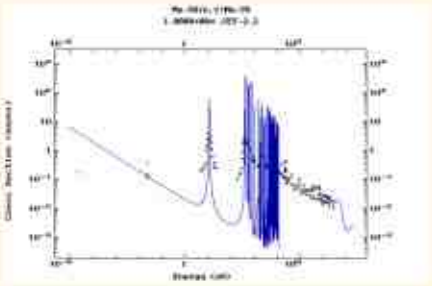
Production of major radioisotopes

Molybdenum-99

Mo-99 is a medically important radionuclide, is extensively used in diagnostic in the form of ^{99m}Tc-radiopharmaceuticals and is the workhorse of nuclear medicine.Mo-99 is produced by neutron irradiation of natural MoO_3 target. ^{99m}Tc is separated at hospital radioparmacies from ^{99}Mo-^{99m}Tc generators. There are seven isotopes of molybdenum with different natural abundance. The abundance of Mo-98 is 24.19% which is maximum of all the isotopes. For production of Mo-99, metal target is not preferred for irradiation but oxide of molybdenum is irradiated because of the simple chemistry of dissolution. High specific activity ^{99}Mo can be produced using enriched target in ^{98}Mo(>98 atoms%) in high flux reactor or by fission of enriched uranium-235. The cost of highly enriched target of Mo-98 is very high and cannot be practicable. The cross section of Mo-98 is 0.13b for thermal neutron which cannot yield high specific activity. But from the excitation function(Fig.1) of the (n,γ) reaction it can be observed that the cross section are having resonance in the epithermal energy and therefore the yield of ^{99}Mo can be increases. The effective cross section of ^{98}Mo(n,γ)^{99}Mo can be possibly increase upto 700mb owing to contribution of the resonance part of the neutron spectra. Specific activity of 3.4Ci/g for the natural molybdenum sample can be obtained if the target is exposed only to the epithermal region. [4]

Due to presence of other trace impure elements in the target, other radioisotopes are formed which is unavoidable unless highly enriched target is used. This formation of other radioisotopes will results in radionuclidic impurity. The most probable impurities are chromium and tungsten. Presence of tungsten impurity in the target would lead to the production of respective ^{186}Re and ^{188}Re radioisotopes on neutron activation of ^{184}W and ^{186}W isotopes. Since technetium and rhenium are chemically same radiation due to rhenium isotope may cause radiation to patient during diagnostic studies. Other impurities presents are Fe, Co, Cs and Sb. If these impurities are present in considerable quantity then it is concern in radiopharmaceutical formulation. Long lived radionuclide will be of great concern necessitating stringent pharmacopoeia specifications of the product.

Direct neutron irradiation of molybdenum is the least complex route of access to Mo-99. Given the existence of severe limitations on the specific activity attainable, the method of ^{98}Mo(n,γ)^{99}Mo is still particularly suited to use in developing countries. Figure 1 below shows the absorption neutron cross section as neutron energy



Iodine-131

I-131 is radioisotope with very good potential use in nuclear medicine for diagnostic and therapy. I-131 decays with half life of 8.04d with prominent emission of 364keV to stable Te-131. I-131 can be produced in reactor with moderate to high thermal neutron flux by irradiation of TeO_2 powder as target. The nuclear reaction for the production of I-131 is ^{130}Te(n,γ)^{131}Te. The cross section for the above reaction is 0.29 ± 0.06b. The neutron cross section is very low and if the tellurium target in Te-130 is enriched then the yield can be enhanced. Te-131 after beta decay forms I-131. It produces carrier free I-131 with high specific activity of 124mCi/μg. I-127 and I-129 are produced from ^{126}Te(n,γ)^{127}Te($T_{1/2}$=9.35h) and ^{128}Te(n,γ)^{129}Te($T_{1/2}$=69.6m) during the natural Te. Natural Tellurium has eight isotopes with different natural abundance. I-131 is produced by neutron irradiation of Te-130 with abundance as 34.08%, which is high among the other isotopes. Te-126(18.84%) and Te-128(31.74%) will result in stable I-127 and long lived I-129($T_{1/2}$:1.57X10^7 years) isotopes. Presence of iodine in tellurium will reduce the specific activity of I-131. Selenium and antimony if presence will produce long lived Se-75($T_{1/2}$ 121d) and Sb-125($T_{1/2}$ 2.7 y) which will pose problem for post handling and disposal problem. Other impurities such as Hg,Au and Ag will create problem in recovering I-131.

Lutetium-177

Lu-177 owing to suitable nuclear decay properties and favourable production logistic and good coordination chemistry is been effectively used in targeted therapy. Lu-177 has a half life of 6.65days with $E_{\beta(max)}$=497k (78.6%); 385 keV(9.1%); 176keV(12.2%); Eβ =208keV(11.0%) 113keV(6.4%) which is suitable for the application. The specific activity produced through (n,γ) route is important for labelling the bio-molecules. For labelling purpose at least 20Ci/mg of specific activity is required. Lu-177 can be produced by two route, one by thermal neutron activation of enriched(inLu-176, two isotopes of lutetium one Lu-175 with abundance 97.41% and other Lu-176 with abundance of 2.59%) lutetium target and thermal neutron activation of enriched(in Yb-176) ytterbium target leading to formation of Lu-177 from beta decay of the short lived activation product. Yb-177($T_{1/2}$ =1.9h) could be utilize to produce Lu-177 having specific activity more than 20Ci/mg. Indirect method of production of Lu-177 through the irradiation of Ytterbium target yield less Lu-177 due to complex radiochemical procedure. Direct (n,γ) route can produce large quantity of Lu-177 with adequate specific activity for labelling, with a thermal flux of ~ 1X10^{14}n/cm^2/s or higher and using enriched target(> 80%, Lu-176). This can be possible because of very high thermal neutron capture cross section (σ =2090β) and neutron capture cross section of Lu-176 does not follow 1/v law and there is strong resonance near to thermal region. The maximum yield of Lu-177 is achieved after a 14 days of irradiation and maximum specific activity is attained after 21 days. Since the actual mass of lutetium after post irradiation is different from the initial mass of the target irradiated, applying the burn up of the target the exact specific activity can be calculated. The period of

irradiation at which the maximum yield of Lu-177 per mg is achieved does not provide the highest available specific activity [5]. There is possibility of formation of Lu-177m which is having a half life of, $T_{1/2}$=160.5d. Limits of tolerance for Lu-177m in Lu-177 would be defined upon the irradiation conditions of the target.

Smarium-153

^{153}Sm is an attractive therapeutic radionuclide in nuclear medicine with half life of 46.27h, $E_{\beta max}$=0.81 MeV, E_γ = 103(28%). ^{153}Sm can be produced by neutron irradiation of both natural Sm_2O_3 and enriched $^{152}Sm_2O_3$ targets. The neutron absorption cross section of ^{152}Sm is 206b. The composition of the natural samarium target is: ^{154}Sm, 22.75%; ^{152}Sm, 26.75%; ^{150}Sm, 7.38%; ^{149}Sm, 13.82%; ^{148}Sm, 11.24%; ^{147}Sm, 14.99%; ^{144}Sm, 3.07%. Irradiation of natural samarium target will lead to long lived radionuclide impurity of ^{154}Eu, ^{155}Eu and ^{156}Eu and low specific activity of ^{153}Sm. During irradiation, ^{153}Sm formed will decay by beta to ^{153}Eu(stable). ^{153}Eu with a neutron absorption cross section of 390b will form ^{154}Eu($T_{1/2}$ =8.8y) as an impurity. ^{154}Sm(nat.abun. 22.75%) after absorption of neutron with cross section of 7.5b will form ^{155}Sm which after beta decay gives ^{155}Eu($T_{1/2}$ = 4.76yr) as another impurity. ^{155}Eu with very high absorption cross section of 3900b will produce ^{156}Eu ($T_{1/2}$=15.2d). Therefore by irradiation of natural Samarium target, europium impurities with long lived isotopes will form. To get high specific activity with less impurity, it is desirable to irradiate enrich ^{152}Sm target. By irradiation of 98% enriched target the europium impurities can be decreased considerably and the specific activity can be increased to three to four fold times. Ion exchange chromatography can be use to separate Sm-153 from Europium impurities.

The use of ^{153}Sm from natural targets which is easy and can be produce with less expense can be use for therapeutic application if there are no stringent conditions. To reduce the $^{155+156}$Eu impurity moderately enriched ^{152}Sm target will be suffice, instead of very highly enriched(>98%)^{152}Sm target.[6]

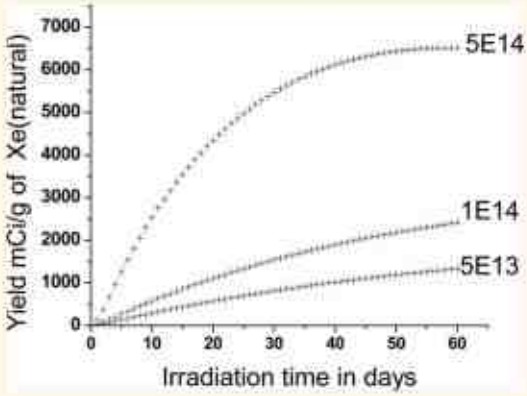
Iodine -125

I-125 is an attractive and widely used radionuclide in numerous diagnostic and therapeutic applications. I-125 produces high quality thyroid scans almost indistinguishable from those produced using I-131. In recent years, I-125 has become the radionuclide of choice for the preparation of brachytherapy seeds for the treatment of prostate and ocular cancers.

I-125 has a 60-days half-life and decays by EC, producing in the process the 27.4keV X-rays and the 35.4 keV gamma ray which are easily absorbed in conveniently small and light detectors. The X- ray and gamma radiations emitted are relatively soft. This makes these isotopes with much higher gamma ray merit ratio(defined as the ratio of the usable signals to energy absorbed locally) than I-131 for many in vitro and in vivo applications.

The initial production of I-125 was carried out in the MIT cyclotron when natural elemental tellurium was irradiated with 14.5 MeV deuteron. The other route for the production of I-125 is using thermal neutron activation of Xenon. It had made available relatively large amounts of I-125 of much greater purity.

The general I-125 production route is through the neutron irradiation of Xe-124 gas to form Xe-125, followed by the decay to form I-125. Natural Xenon has nine isotopes. The isotopes of xenon with natural abundances are Xe-124(0.10%), Xe-126(0.09%), Xe-128(1.91%), Xe-129(26.40%), Xe-130(4.10%), Xe-131(21.20%), Xe-132(26.90%), Xe-134(10.40%), Xe-136(8.90%). Xe-124, Xe-126, Xe-132, Xe-134 and Xe-136 isotopes will become radioactive with formation of Xe-125($T_{1/2}$=16.9h), Xe-127($T_{1/2}$=36.4d), Xe-133($T_{1/2}$=5.25d), Xe-137($T_{1/2}$=3.83m). Xe-125 after decay will form I-125($T_{1/2}$= 59.41d), Xe-127 decay to I-127(stable), Xe-133 to I-133($T_{1/2}$= 20.9h). I-127 will form by double neutron capture of I-125, $^{125}Xe(n,\gamma)^{126}Xe(n,\gamma)\ ^{127}Xe$ —(EC)→^{127}I and direct neutron capture $^{126}Xe(n,\gamma)^{127}Xe$—(EC)→^{127}I. Xe-125 after decay to I-125 will form I-126 with high neutron absorption cross section of 900b and activation integral of ~13730±90 barn. I-126($T_{1/2}$=13.11d) is having neutron absorption cross section of 5960b which will form I-127(stable) isotope. The I-125 activity produced at the end of neutron irradiation as a function of irradiation time at different thermal neutron fluxes is shown in Figure 1. From the figure it is evident that for higher neutron flux the time of irradiation is shorter for required activity. Although the activity of I-125 is higher after long irradiation the contribution from I-126 and I-127 form is significant which decreases the specific activity of I-125. For maximum production of I-125 neutron flux and irradiation time has to be optimized. For irradiation time of 15days and neutron flux of $5X10^{13}$n/cm^2/s the production of I-126 is minimum. Since the half life of I-126 is much less than I-125, a reduction of the radionuclide contamination of I-126 in I-125 can be achieved through the effective use of cooling time. For a contamination of I-126 below 1-2% a cooling of ~50days is required. The formation of Xe-133 and Xe-137 leads to the formation of Cs-134 and Cs-137 which are the prominent radionuclidic impurities in the product. Small amounts of other activation products are simultaneously generated. Among them, caesium, iodine, barium and tellurium radioisotopes are important. I-126 impurity content in I-125 samples is not permitted to exceed about 1% at the time of application. Two general methods are used for maximizing the output of I-125 during neutron irradiation. By increasing the enrichment of Xe-124 in the irradiated gas and by pressurizing the gas [7].



Iridium- 192

Ir-192 is one of the important radioisotopes used in industry mainly for radiography. There are two stable isotopes of iridium, 191,193 with 37.30% and 62.70% natural abundance respectively. The neutron absorption cross section is 954 b for Ir-191 nuclide. The half life of Ir-192 is 74 days and therefore it is irradiated for at least two months in high flux position inside the reactor. The specific activity comes to be approximately 350Ci/gm. Since the neutron cross section of Ir-191 is very high therefore neutron flux in the volume will be decreasing if the geometry of the target material is not properly arranged. For the irradiation of iridium the target is made in the form of thin pellets with thickness 0.3mm and arranged in a cylindrical form so that there is minimum self shielding to get high specific activity.

Conclusion

Most of the radioisotopes are produced by exposing various targets to neutrons in nuclear reactor. Large volume radioisotopes can be produce in research reactor because of high neutron flux and volume available. Specific activity of the radioisotope is an important requirement for their application in various fields such as health care, industry, agriculture and research. High specific activity targets can be achieved by irradiating the target in high neutron flux, with enrich target, specific geometry to avoid self shielding, less burn up by optimize irradiation, irradiation under continuous reactor operation and high irradiation efficiency. For target irradiation with high specific activity all the above parameters are to be optimize so that high specific activity can be produced. Thus irradiation of targets in Dhruva research reactor at Trombay which provides high neutron flux(10^{13} to 10^{14}n/cm^2/s) and optimizing the above parameter can produce indigenously radioisotopes with high specific activity that will cater various societal needs.

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K.C. Jagadeesan *joined BARC in 1983 after obtaining B.Sc. Degree in Physics from Calicut University. He is mainly involved in the production of radioisotopes by neutron irradiation. His job involves planning, target preparation, organizing the irradiations, and coordination between different groups such as reactors and BRIT. His current fields of work are production of radioisotopes, neutron activation analysis and neutron flux measurement and R&D in related fields. He has many publications in international journal and conferences.*

Production of Radioisotopes for Human Healthcare Utilizing Dhruva Research Reactor

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1. Introduction

Radioisotope production programme at Isotope Production and Applications Division (IP&AD) has come a long way since its inception in India in 1958. Establishment of Radiological Laboratories at Trombay in 1969 and availability of CIRUS reactor marked the modest beginning of radioisotope production at a commercial scale in India. Availability of 100 MWD DHRUVA research reactor in 1985 was an important milestone in the development and implementation of indigenous nuclear technology in the field of radioisotope production, which resulted in augmentation of production capacity. Radioisotopes find extensive applications in several fields that include medicine, industry, agriculture and research. Radioisotope production to service different sectors of economic significance constitutes an important ongoing activity at Radiopharmaceuticals Division (RPhD), BARC. Radiochemicals Section, RPhD, BARC shoulders the responsibility for the steady availability of reactor produced radioisotopes in ready to use radiochemical form.

The technique of radioisotope production and radiochemical separations is being continually improved, and its application is being demonstrated in important areas of public interest, such as Energy production, Agriculture, Food preservation, Industry-Radiography, Industrial process monitoring/trouble shooting, Research, Defence, Geology, Environment-Pollution monitoring etc. Radioisotopes have become an indispensable tool in most area of human endeavour. Radioisotope production is extremely important and prominent peaceful uses of atomic energy. One of the most important contributions of nuclear science has been the vital application of radioisotopes in medicine, for both diagnosis and therapy.

Last couple of decade has witnessed momentous development in the field of health care sector; both diagnostic and therapeutic radiopharmaceuticals using a variety of radionuclides have contributed to this. The field of radiopharmaceuticals has witnessed continuous evolution thanks to the contributions of scientists from diverse yet related disciplines such as chemistry, physiology, molecular biology, pharmacology etc. Currently, a large number of radiopharmaceuticals are produced and supplied by commercial manufacturers for patient application in the hospitals. Availability of radionuclides with attractive decay characteristics in suitable radiochemical form have contributed to the accelerated growth of nuclear medicine. In recent times, the therapeutic products have come into greater prominence. With the revival of interest in therapeutic applications, identification of additional radionuclides having attractive features suitable for radiotherapy, their production and radiochemical preparation has assumed importance.

In this article, we discuss the production, radiochemical processing and supply aspects of medically important radionuclides ^{99}Mo, ^{131}I, ^{32}P, ^{153}Sm and ^{177}Lu. Apart from these, there are a few upcoming reactor produced medically useful radioisotopes namely ^{64}Cu, ^{90}Y, ^{166}Ho and ^{170}Tm.

2. Radioisotope production utilizing Dhruva reactor for nuclear medicine

Radioisotopes are produced by thermal neutron activation of suitable target chemical in Dhruva research reactor, Trombay. Target chemicals are neutron irradiated from few days to several weeks and months at neutron flux in the range of 1×10^{13} n.cm^{-2}s^{-1} to 1.8×10^{14} n.cm^{-2}.s^{-1}. Measured amounts of respective target to be irradiated in the reactor for production of radioisotopes are weighed and sealed in standard aluminum capsules (inner dia. 19 mm, 38 mm height) by cold welding (**Fig. 1**). The amount of target is calculated and optimized for obtaining the desired radioactivity content on irradiation at a known neutron flux for adequate length of time duration.

Fig. 1. Standard 1S Aluminum cans, target encapsulation and a typical target

Activity of the radionuclide produced by thermal neurtron activation depends on various factors such as isotopic abundance of the target nuclide, activation cross-section for neutron absorption and the neutron flux, the duration of irradiation and half life of the product radionuclide.

Presently, irradiations for radioisotope production are done over one-week cycle duration in Dhruva reactor. Two tray rods K-09 and H-07 are dedicated for radioisotope production. **Table 1** enlists medically useful radionuclides produced in Dhruva research reactor along with target chemicals, nuclear reactions involved in their production and probable impurities coproduced from competing reactions arising from trace impurities in the target chemical.

Table 1. List of medically useful radionuclides produced in Dhruva reactor

Radio isotope	Target used	Activation cross section (b)	Natural abundance (%)	Nuclear reaction	Radionuclidic impurities
Routinely produced medically important radionuclides					
^{99}Mo	MoO_3	0.13	^{98}Mo-24.4%	$^{98}Mo(n,\gamma)^{99}Mo$ ^{99m}Tc	^{93m}Mo, ^{93}Mo, ^{101}Mo, ^{101}Tc, ^{99}Tc, $^{186+188}Re$
^{131}I	TeO_2	0.2	^{130}Te-34.5%	$^{130}Te(n,\gamma)^{131}Te$ ^{131}I	^{129}I, ^{75}Se, ^{125}Sb, ^{198}Au, $^{197+203}Hg$
^{32}P	P Elemental	0.172	^{31}P-100%	$^{32}P(n,\gamma)^{32}P$	^{76}As, ^{122}Sb, ^{124}Sb,
^{153}Sm	Sm_2O_3	206	^{152}Sm-26.7%	$^{152}Sm(n,\gamma)^{153}Sm$	^{145}Sm, ^{151}Sm, ^{155}Sm, $^{154+155}Eu$
Recently approved medical radionuclide					
^{177}Lu	Lu_2O_3	2100	^{176}Lu-2.59%	$^{176}Lu(n,\gamma)^{177}Lu$	^{177m}Lu
Upcoming medically useful radionuclides					
^{64}Cu	CuO	4.5	^{63}Cu-69.17%	$^{63}Cu(n,\gamma)^{64}Cu$	^{65}Zn, ^{59}Fe, ^{60}Co
^{90}Y	Y_2O_3	1.28	^{89}Y-100%	$^{89}Y(n,\gamma)^{90}Y$	^{89}Sr, ^{91}Y
^{166}Ho	Ho_2O_3	64.7	^{165}Ho-100%	$^{165}Ho(n,\gamma)^{166}Ho$	^{166m}Ho
^{170}Tm	Tm_2O_3	103	^{169}Tm-100%	$^{169}Tm(n,\gamma)^{170}Tm$	^{171}Tm

2.1. Production of Molybdenum-99 by direct (n,γ) reactions on MoO_3 targets

Molybdenum-99 is the parent radionuclide for ^{99m}Tc [$T_{1/2}$ = 6.02 h and E_g = 140 keV], which is estimated to be used in about 30 million medical diagnoses annually throughout the world and is considered as the workhorse of nuclear medicine procedures. Availability of ^{99m}Tc for preparation of diagnostic agents is ensured in the form of $^{99}Mo/^{99m}Tc$ generator system from which ^{99m}Tc is separated under aseptic conditions. ^{99}Mo for this purpose is produced by thermal neutron activation of natural MoO_3 target and 900 GBq (~25 Ci) of ^{99}Mo is processed and supplied weekly from our laboratory for nuclear medicine applications. The neutron irradiated target is chemically processed and supplied as ^{99}Mo-sodium molybdate (product code: Mo-3) to facilitate preparation of $^{99}Mo/^{99m}Tc$ generators. The specific activity of ^{99}Mo obtained is about 26-37 GBq (700-1000 mCi)/g of Mo. Large scale regular production of ^{99}Mo and its customized optimization for requirements have yielded in its successful utilizaton in preparation of 18.5 GBq (500 mCi) $^{99}Mo/^{99m}Tc$ gel generators (Geltech generators). Considering the diagnostic value provided by ^{99m}Tc based imaging agents, it is expected that ^{99m}Tc will continue its central role in diagnostic nuclear medicine into the future [1]. Our process procedure serves as a good stead for ensuring the large scale availability of medium specific activity ^{99}Mo with requisite radionuclide purity. The nature and cost of facilities to be set up for availing ^{99}Mo using (n,g) route of production method is less demanding and relatively less expensive as compared to many other proposed techniques.

2.2. Production of Iodine-131 from neutron irradiated TeO_2 by dry distillation

Iodine-131 in the form of $Na^{131}I$ radiochemical is extensively used in the diagnosis and treatment of thyroid disorders including differentiated thyroid cancer. Iodine-131 decays by emission of both b-particles with a maximum energy of 0.61 MeV and g photons [principal g photon energy 364

keV (81%)]. The 8.1 day half life is logistically favorable for shipment of ^{131}I radiopharmaceuticals to places far away from the reactors. With expanding areas of applications and growing interest in the use of ^{131}I labeled radiopharmaceuticals, the domestic demands of ^{131}I has increased several folds over the last decade. In the quest for an effective method for large-scale routine production of ^{131}I to cater the increasing domestic requirements, we turned our focus towards the use of dry distillation technology owing to its appealing attributes. The dry distillation technology developed at RPhD, BARC is facile, robust, efficient, easily up scalable, generates minimum amount of radioactive waste and cost effective. Briefly, the procedure involves heating of neutron irradiated high purity TeO_2 target, purging the ^{131}I released using an inactive carrier gas and trapping it in NaOH solution containing Na_2SO_3 to obtain ^{131}I as radiochemically pure $Na^{131}I$ solution [2]. The reported method has been successfully used for the routine production of 1.48-2.22 TBq (40-60 Ci) of ^{131}I. Iodine-131 produced is utilized for the preparation of ^{131}I-MIBG, ^{131}I-NaI therapeutic capsules, ^{131}I-Rituximab, ^{131}I-lipiodol and other ^{131}I labeled biomolecules apart from its regular use as orally administered doses of ^{131}I-NaI solution.

2.3. Production of Phosphorus-32 for medical applications

Phosphorus-32 [$T_{1/2}$ = 14.26 d, $E_{b(max)}$ = 1.71 MeV] in the form of sodium orthophosphate was the first systemic radionuclide to be used for the treatment of bone metastases, which continues till date for palliative care of painful skeletal metastases. The classical route of production of ^{32}P by (n,p) reaction on high purity elemental sulfur yields no-carrier-added (NCA) ^{32}P and has been used over the years for preparation of ^{32}P-sodium orthophosphate injection for bone pain palliation. Since the formulation of the required dose of ^{32}P-sodium orthophosphate for bone pain palliation does not require very high specific activity ^{32}P, an alternate production route by radiative neutron capture of elemental phosphorus target [$^{31}P(n,g)^{32}P$] was envisaged. Its suitability for use in bone pain palliation was comprehensively evaluated and subsequently approved by Radiopharmaceuticals Committee (RPC), India for human clinical use in 2012. Production of ^{32}P following the $^{31}P(n,g)^{32}P$ route is straight forward, offers the scope of using inexpensive mononuclidic natural elemental phosphorus (100% in ^{31}P) target material and needs a very simple chemical treatment after neutron irradiation [3]. For production of ^{32}P following (n,g) route, about 0.35 g of red phosphorus encapsulated by cold-press welding in an aluminum container is irradiated in Dhruva reactor at a thermal neutron flux of 1×10^{14} n.cm^{-2}.s^{-1} for 60 days. Under the stated optimized conditions of irradiation, batches yielded ^{32}P with a specific activity of 230 ± 15 MBq/mg (6.2 ± 0.4 mCi/mg) at the EOI.

2.4. Production of Samarium-153 for management of metastatic bone pain

Samarium-153 [$T_{1/2}$ = 47 h] decays by emission of both b-particles with a maximum energy of 0.81 MeV and g photons [principal g photon energy 103 keV (28%)]. Favorable nuclear characteristics coupled with feasibility of its large-scale production made this radioisotope a good choice for palliative care of painful skeletal metastases. From a modest beginning of 1 batch per month in year 1998, we are currently (year 2016) producing 370 GBq (10 Ci) ^{153}Sm weekly for formulation of ^{153}Sm-EDTMP (EDTMP = Ethylenediaminetetramethylenephosphonicacid) radiopharmaceutical. Both natural and enriched ^{152}Sm targets are useful for the production of medically useful ^{153}Sm suitable for therapeutic purposes [4]. However, we have opted for ^{153}Sm production by neutron irradiation of enriched Sm_2O_3 target (I.E 99.8% in ^{152}Sm) utilizing Dhruva research reactor facility. For production of ^{153}Sm by (n,g) route, about 15 mg enriched Sm_2O_3 encapsulated by cold-press welding in an aluminum container is irradiated in Dhruva reactor at a thermal neutron flux of 1.4×10^{14} n.cm^{-2}.s^{-1} for 3-7 days. Under the stated optimized conditions of irradiation, batches yielded ^{153}Sm with a specific activity of 44 GBq/mg (1200 mCi/mg) at the EOI.

2.5. Lutetium-177: A recently approved radionuclide for nuclear medicine applications [5,6]

Lutetium-177 is relatively new in the field of targeted radionuclide therapy and this therapeutic radionuclide has emerged as a promising candidate during the last decade by virtue of its attractive nuclear decay properties, favourable production logistics and straightforward coordination chemistry. Presently, there is a great deal of interest in the use of ^{177}Lu for *in vivo* targeted therapy including peptide receptor radionuclide therapy (PRRT), bone pain palliation and radioimmonu therapy. Targeted radionuclide therapy with ^{177}Lu-DOTA-TATE has shown considerable increase in overall survival and significant improvement in the quality of life of patients suffering from neuroendocrine tumors (NETs).

Lutetium-177 decays to stable ^{177}Hf with a half-life of 6.65 d by emission of b$^-$ particles having E_{max} of 497 keV (78.6%), 384 keV (9.1%) and 176 keV (12.2%). The emission of low-energy gamma photons [E_g=113 keV (6.6%), 208 keV (11%)] enable imaging and therapy with the same radiolabeled preparation and allow dosimetry to be performed before and during treatment as well. Two different strategies, namely, (i) direct thermal neutron activation of enriched (in ^{176}Lu) lutetium target and (ii) thermal neutron activation enriched (in ^{176}Yb) ytterbium target leading to the formation of ^{177}Lu from the b$^-$ decay of the short-lived activation product ^{177}Yb ($T_{½}$ = 1.9 h) could be utilized to produce ^{177}Lu having specific activity more than 740 GBq/mg. While the indirect method of production using enriched ^{176}Yb provides no-carrier-added (NCA) ^{177}Lu (theoretical specific activity 40.33 TBq/mg, 1090 Ci/mg), implicit need of a complex radiochemical separation procedure to isolate ^{177}Lu of requisite purity and poor yield of ^{177}Lu per mg of highly enriched ^{176}Yb target are the major impediments. Direct (n,g) route offers large-scale ^{177}Lu production with specific activity adequate for targeted tumor

therapy in nuclear reactors having thermal neutron flux of ~1.0×10^{14} n/cm^2.s or higher using enriched target (80% or more in ^{176}Lu). This is the least intricate route to access ^{177}Lu in the desired chemical form with minimum generation of radioactive waste, apart from being inexpensive. In order to tap the potential of (n,g)^{177}Lu production method for application of ^{177}Lu in the preparation of receptor-specific therapeutic radiopharmaceuticals, we have worked on feasibility of producing ^{177}Lu in adequate specific activity and in requisite purity by careful optimization of the irradiation parameters.

The variation of yield of ^{177}Lu per mg of target irradiated with duration of irradiation is shown in **Fig. 2** when enriched (82% in ^{176}Lu) target is irradiated at a thermal neutron flux of 1.4×10^{14} n.cm^{-2}.s^{-1}. It is evident from the figure that the maximum yield of ^{177}Lu per mg of target irradiated is achievable when the irradiation is carried out for a duration of ~14 d at the above specified thermal neutron flux.

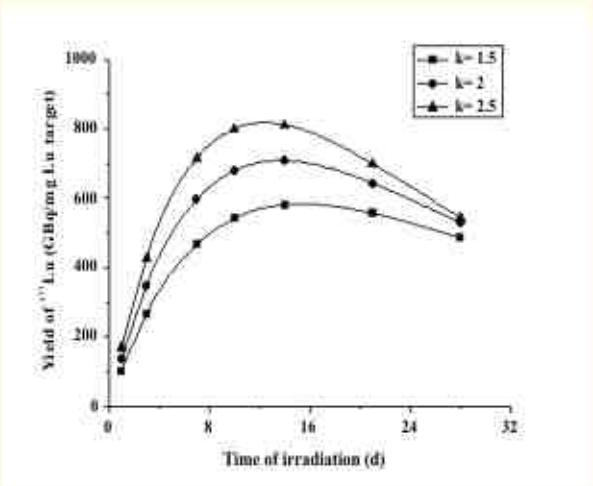

Fig 2. Variation of specific activity of ^{177}Lu, theoretically calculated using k = 1.5, 2.0 and 2.5, with duration of irradiation when enriched (82% in ^{176}Lu) target is irradiated at a thermal neutron flux of 1.4×10^{14} n.cm^{-2}.s^{-1}

Our pursuit of (n,γ)^{177}Lu method of production of ^{177}Lu for targeted tumor therapy in India was driven mainly by the need to provide the required activity of ^{177}Lu for its use in the treatment of patients suffering from neuroendocrine tumor (NET) at an affordable cost. Evolution and continued success of ^{177}Lu-labeled DOTA-TATE therapy in our country, has been, in large part, due to the cost effective availability of ^{177}Lu of required quality. The specific activity of indigenously produced ^{177}Lu available every week at nuclear medicine clinics in India is around 740-900 GBq/mg, considering the decay loss of 48 h during transit. This is adequate to formulate ^{177}Lu-labeled somtatostatin (SST) analogue peptides, such as DOTA-TATE with specific activity of 37 MBq/μg of peptide conjugate with high radiochemical purity [5].

RPhD is currently supplying 296-370 GBq (8-10 Ci) of radiopharmaceutical grade [^{177}Lu]$LuCl_3$ radiochemical every week to the leading nuclear medicine centres across India. More than 2000 cancer patients have received ^{177}Lu-DOTA-TATE treatment using BARC [^{177}Lu]$LuCl_3$. A typical post-therapy scan of a patient suffering from neuroendocrine originated cancer with liver metastases recorded 24 h after administration of therapeutic dose of ^{177}Lu-DOTA-TATE is given in **Fig. 3** emphasizing the clinical utility of BARC [^{177}Lu]$LuCl_3$.

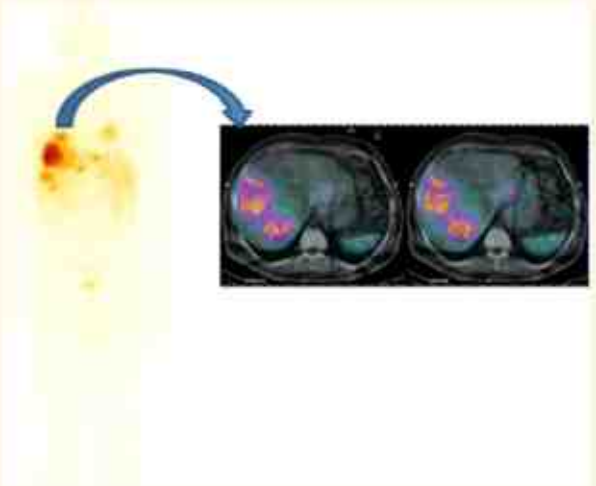

Fig 3. A typical post-therapy scan of a patent suffering from neuroendocrine originated cancer with liver metastases 24 h after administration of therapeutic dose of ^{177}Lu-DOTA-TATE

The specifications of radiochemical products regularly prepared and deployed by RPhD for medical use are given in Table 2. A comparative overview of the volume of activity of four major radiosiopes produced and supplied from RPhD in the last five years is depicted in **Fig. 4.**

Table 2. Specifications of the radiochemical products

Radioisotope	Parameters						
	Code	Radiochemical form	Appearance	pH	Radionuclidic purity	Radiochemical purity	Specific activity
Mo-99	Mo-3	$[^{99}Mo]Na_2MoO_4$	Colorless liquid	~10	>99.9%	>95%	> 15 $GBq.g^{-1}$
I-131	I-2	$[^{131}I]NaI$	Colorless liquid	8-10	>99.9%	>95%	NCA
P-32	P-3	$[^{32}P]H_3PO_4$	Colorless liquid	~2	>99.9%	>95%	> 185 $GBq.g^{-1}$
Sm-153	Sm-1	$[^{153}Sm]SmCl_3$	Colorless liquid	1-2	>99.9%	>98%	> 20 $TBq.g^{-1}$
Lu-177	Lu-2	$[^{177}Lu]LuCl_3$	Colorless liquid	~2	>99.9%	>98%	> 600 $TBq.g^{-1}$

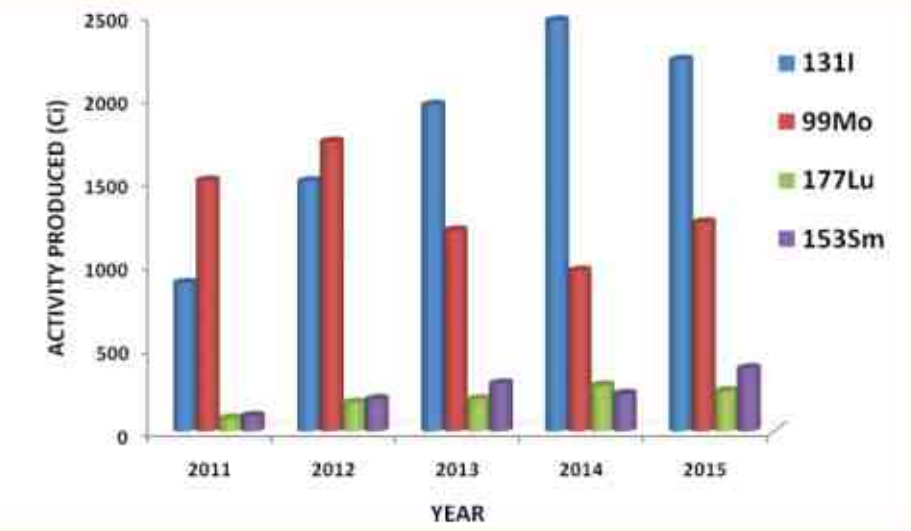

Fig 4. A comparative overview of the volume of activity of four major radioisotopes produced and supplied from Isotope Production and Applications Division in the last five years

2.6. Reactor produced ^{64}Cu, ^{90}Y, ^{166}Ho and ^{170}Tm: the way ahead

With the successful utilization of radionuclides in various nuclear medicine procedures including radionuclide therapy (RNT) applications, efforts are on to identify and establish newer radioisotopes with attractive radionuclide features and production feasibility. In this regards, reactor produced radionuclides such as ^{64}Cu, ^{90}Y and ^{166}Ho and ^{170}Tm are our focus of attention.

Copper-64 [$T_{½}$ = 12.7 h., EC 45%, β 37.1%, β⁺ 17.9%) is a promising radionuclide for positron emission tomography (PET) imaging, which is generally produced by $^{64}Ni(p,n)^{64}Cu$ reaction in a cyclotron. Despite excellent attributes of ^{64}Cu for PET imaging, utility of this radioisotope is still limited to countries having good cyclotron facilities and excellent production logistics. We have explored the feasibility of using ^{64}Cu produced in a research reactor by (n,γ) route, in the form of $^{64}CuCl_2$, as a probe for tumor imaging by PET [7]. The production strategy has been optimized to obtain $^{64}CuCl_2$ with adequate specific activity and radionuclidic purity suitable for clinical use. We have, for the first time, successfully demonstrated the suitability of ^{90}Y [$T_{1/2}$ = 64.1 h, $E_{\beta(max)}$ = 2.28 MeV] produced by neutron activation route in Dhruva reactor in the treatment of arthritis of knee joints in the form of ^{90}Y-labeled hydroxyapatite (HA) microparticles [8]. The treatment efficacy of this product is clearly demonstrated in **Fig. 5,** which shows the bone scans of the arthritic knee joints of a patient at different time post administration of 185 MBq of ^{90}Y-HA preparation. Holmium-166 [$T_{1/2}$ = 26.9 h, $E_{\beta(max)}$ = 1.85 MeV, E_γ = 81 keV(6.4%)] also holds good promise as a therapeutic radioisotope in India, thanks to the feasibility of its large-scale production in adequate specific activity. We have demonstrated its potential in treatment of

arthritis [9], which could be extended to the treatment of multiple myeloma. Thulium-170 [$t_{½}$ = 128.4 days, E (β_{max}) = 968 keV, Eγ = 84.3 keV (3.26%)] is a new entrant in the arena of therapeutic radioisotopes with potential for use in palliation of bone pain due cancer metastases as a cost-effective alternative to ^{89}Sr [10]. The clinical utility of this radioisotope was proposed from our group for the first time. An optimized production strategy based on trade-off between various neutron irradiation parameters to obtain ^{170}Tm with adequate specific activity and radionuclidic purity in Dhruva has been carried out [11]. Preliminary clinical studies carried out using the ^{170}Tm-EDTMP prepared from indigenously produced ^{170}Tm has shown promising clinical outcome [11].

After treatment After 3 months After 6 months

Fig 5. Bone scans of the arthritic knee joints of a patient at different time post administration of 185 MBq of ^{90}Y-hydroxyapatite showing the therapeutic efficacy of the preparation

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Radioisotope Production in FBTR, Kalpakkam

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Introduction

A large number of radioisotopes find extensive applications today in almost all the fields like Industry, Geology, Chemical Science, Medicine, agriculture, space etc. Many of them are even providing unique and exclusive solutions for the challenges in different areas. Even though there are radioisotopes available in nature, they do not have sufficient scope to satisfy the specific requirements of a wide range of radiation characteristics varying with the field of their applications. Hence the concept of tailor-made radioisotopes for such applications is always inevitable. Fortunately there are many methods available to produce the radioisotopes artificially with the desirable radiation characteristics. The stability of an isotope is based on its neutron to proton ratio and the same can be disturbed to make it a radioactive isotope by making it artificially either neutron excess by irradiating with neutron in a nuclear reactor or neutron deficient by irradiating with high energy charged particles in an accelerator. Hence the sources of artificial radioisotopes can be from nuclear fission, radionuclide generator, nuclear reactor and accelerator. The focus of this article is on the feasibility studies of producing some radioisotopes useful for medical applications using the only fast reactor available in India, the Fast Breeder Test Reactor (FBTR), Indira Gandhi Centre for Atomic Research (IGCAR), Kalpakkam.The reactor was made available only recently for the above study even though it became critical in October, 1985 with the objectives developing fast reactor technology *[1]*.

The type and quantity of isotope produced in a nuclear reactor depends on the nature of reactor, neutron energy, neutron flux, target used in the irradiation, neutron absorption cross section and types of nuclear reactions the target can undergo. The radioactivity of the desirable radioisotope that can be produced in a nuclear reactor [2] is given by

$$A = N\sigma\phi(1-e^{-\lambda t}) \text{ Bq}$$

where A - Activity of the radioisotopes produced of the target irradiated in a nuclear reactor, σ- the neutron activation cross-section leading to the production of radioisotope of interest in barn, ϕ-the flux in n $cm^{-2}s^{-1}$, t- the time of irradiation, λ- the decay constant = $0.693/t_{½}$ of the radioisotope produced in the reactor.

However with the condition $t >> t_{½}$, the saturated activity becomes

$$A = N\sigma\phi \text{ Bq}$$

This clearly shows that the growth of activity in a target under irradiation is exponential in nature and reaches a saturation value limited by the neutron flux in the reactor.

Most of the reactor-produced radioisotopes are products of the (n, γ) reaction which is primarily a thermal neutron reaction. The product is another isotope but of the target element itself and hence it is difficult to separate. This results into the production of a radioactive isotope of low specific activity. However the reactions of the type (n,p), (n,α) etc use neutrons of higher energy called threshold energy and hence involve primarily the use of fast neutrons. The purification of the radioisotope of interest in these cases involves easier elemental separation resulting into a higher specific activity or carrier free product.

Initial venture of producing radioisotopes using FBTR was started with one of the important isotopes ^{89}Sr which is medically useful especially for the treatment of bone pain palliation in the cancer patients. This essay summarizes the efforts to establish the flow sheet for the production of ^{89}Sr after irradiating the target yttria in FBTR. Similarly the feasibility study of producing another isotope ^{32}P in FBTR which is also useful in the medical field, especially again bone pain palliation and also some biological applications was studied but using the small fast flux neutron available in the research reactor KAMINI in Kalpakkam.

Radioisotopes used for bone pain palliation

Majority of the cancers such as prostate, breast, lung, thyroid, and kidney cancers in their advanced stage develop into bone metastases. The metastasis is a very painful clinical condition and is a challenge for the quality of life of the cancer patient. Radionuclide therapy is a commonly used technique for the bone pain palliation. The desirable characteristics of the radioisotope for such application include that it should have selective absorption in the bone, cause minimum damage to the normal cells, have optimum biological half-life, be easily available, be affordable etc. The efforts are in progress to identify and establish the most suitable radioisotope for the purpose [3]. Bone consists of calcium hydroxyl apatite, $Ca_5(PO_4)_3(OH)$ [4,5] and hence the radiopharmaceuticals targeted towards bone lesions can take either the Ca or P route. The bone seeking radionuclides used for the bone pain palliation are mainly short lived in nature and are associated with high energy beta emission such as ^{89}Sr, ^{153}Sm, ^{166}Ho, ^{186}Re, and ^{188}Re or alpha emitters (^{223}Ra) [3]. Among the various radiopharmaceuticals, US Food and Drug Administration (US FDA) has approved only three radiopharmaceuticals [6] which are ^{89}Sr-Strontium chloride, ^{32}P-Orthophosphate, and ^{153}Sm-Ethylenediaminetrimethylene phosphonic acid (EDTMP). ^{32}P was the first radionuclide widely used in bone pain palliation therapy which is

intravenously injected to the bone metastatic cancer patients as orthophosphate in dilute hydrochloric acid medium. However, the use of these radionuclides results into a mild to severe bone marrow suppression [7,8], which is not observed in the case of ^{89}Sr [9-11]. Being an alkaline earth element, Sr is biological analogues to Ca and has a high affinity for metabolically active bone. After its intravenous injection, it selectively concentrates at sites of increased osteoplastic activity. The whole body retention of Sr was found to be 11–88% in 90d after the injection depending upon the skeletal tumors burden [12]. The biological half-life exceeds 50d in osteoplastic metastases even though it is only 14d in normal bone [12]. The recurrent bone pain can be safely treated at 3 months intervals but the toxicity is cumulative [13]. ^{89}Sr has a relatively longer half-life that helps in its comfortable supply. $^{89}SrCl_2$ is marketed by the name METASTRON® worldwide. ^{32}P and ^{153}Sm are the alternative candidate materials for bone pain palliation which may be utilized under different conditions.

Production of ^{89}Sr

The radioisotope ^{89}Sr is a β^- emitter with $E_{\beta max}$ of 1.495 MeV and half-life of 50.57 days with a very low intensity gamma emission i.e. 0.0095% of 909.15 keV [14]. There are mainly three methods by which ^{89}Sr can be obtained i.e. i) ^{88}Sr(n,γ) ^{89}Sr reaction in thermal reactor [15,16], ii) Using gaseous ^{89}Kr from solution reactor [17,18] and iii) ^{89}Y(n, p) ^{89}Sr reaction in Fast reactor [19-21]. However these methods have their own advantages and limitations.

^{88}Sr (n,γ) ^{89}Sr using thermal neutron irradiation facility

Natural strontium is not mono-isotopic but consists of ^{84}Sr, ^{86}Sr, ^{87}Sr and ^{88}Sr with their associated abundance of 0.56%, 9.9%, 7.0% and 82.6% respectively. The Sr-89 radioisotope is formed in the target containing strontium carbonate or metallic strontium by the neutron capture reaction, ^{88}Sr (n, γ) ^{89}Sr in a thermal nuclear reactor. A highly enriched target containing ^{88}Sr>99.9% is used for the elimination of the undesirable ^{85}Sr from ^{84}Sr (n, γ) ^{85}Sr, as well as for the better yield of ^{89}Sr. The cross section of the reaction ^{88}Sr (n, γ) ^{89}Sr is found to be as low as 5.8 mb which is the limitation of this method of production. This method offers ^{89}Sr source with carrier ^{88}Sr due to the challenging task of its isotopic separation.

Solution reactor

^{89}Sr is generated in significant quantities in the fission process associated with the heavy nuclei. But the accumulation of ^{90}Sr in much higher content compared to the required purity of less than 2×10^{-4}% makes it unsuitable source for the medical application. However ^{89}Sr is selectively extracted from a fuel of solution reactor. It is obtained from the gaseous radionuclide ^{89}Kr ($T_{1/2}$=190.7 s) in the decay chain ^{89}Se→^{89}Br→^{89}Kr→^{89}Rb→^{89}Sr which is free from ^{90}Sr. The pure ^{89}Sr source is obtained from the separated gaseous precursor ^{89}Kr from the solution reactor containing water solution of uranyl sulfate UO_2SO_4. However the solution reactor is not commonly available.

^{89}Y(n,p)^{89}Sr using fast neutron irradiation facility

This method is based on the threshold reaction ^{89}Y (n, p) ^{89}Sr which uses the fast neutron flux of a fast nuclear reactor with a cross section of 75.5 micro barn and a threshold energy of 720 keV. A target containing natural mono-isotope ^{89}Y is irradiated in a nuclear reactor with fast neutron spectrum and is subsequently subjected to radiochemical reprocessing for the separation and purification of the ^{89}Sr source so produced. This method offers the advantage of obtaining ^{89}Sr source of high specific activity as it involves elemental separation of Sr from Y target. However the production route demands an irradiation facility of fast reactor and hence depends upon the availability of the fast reactor technology.

Production of ^{89}Sr isotope in FBTR

IGCAR has a fast reactor facility i.e. Fast Breeder Test Reactor (FBTR) and ^{89}Sr production was taken up using the fast neutron irradiation facility available in the reactor. The following sections describe the feasibility study [1] carried out in FBTR to produce ^{89}Sr source using ^{89}Y (n, p) ^{89}Sr.

Target preparation and Irradiation

Yttria powder obtained from various sources (Indian Rare Earths Limited 99.9% purity, Alfa Aesar. 99.999% purity) was used without further purification. Pellets were prepared by using either addition or no addition of sintering aid (ZnO, 0.1 wt%). The pellets were sintered at 1600°C for 5 hours with uniform heating and cooling rate of 5°C/min. The pellets were loaded to a stainless steel (SS) irradiation capsule which was filled with He gas and weld sealed. The irradiation capsule was then locked into the special irradiation sub-assembly IFZ100 and loaded into the FBTR [1]. However the irradiation was carried out for various durations and at various positions of FBTR in different campaigns based on the availability of the reactor. After the irradiation, the capsule was removed and transferred to a hot cell and cut using a laser cutting machine. The irradiated pellets were removed into an SS container. Standardization of the chemical reprocessing procedures in an analytical scale was carried out by using a single pellet before proceeding for bulk operation. The contact dose per yttria pellet of ~1g of FBTR irradiated at core centre was observed to be 20mSv/hr when it was removed after a month from the end of irradiation. The dose level was again different for the pellets irradiated at different locations and different duration as the neutron flux seen by them was different.

Dissolution

The analytical scale dissolution of the irradiated yttria pellet of ~1g was accomplished in conc. HNO_3 under reflux condition [19] in fume hood. However the bulk dissolution of irradiated yttria pellet of about 25g was carried out in 9M

HNO_3 medium under high pressure and temperature inside the hot cell facility using a Ti container. This was necessary because of the high dose associated from the by-product ^{88}Y, an intense gamma emitter. The acidity of the dissolver solution was subsequently adjusted to 12M HNO_3 for the better extraction efficiency. The dissolver solution contained various radio-isotopic impurities [22] such as the activated products of i) the target impurities i.e. ^{160}Tb, ^{154}Eu and $^{139,141}Ce$ ii) the clad material in FBTR i.e. ^{58}Co and ^{54}Mn and iii) the sintering aid ZnO used during the target preparation i.e. ^{65}Zn along with the by-products ^{88}Y and ^{86}Rb as shown (Fig.1).

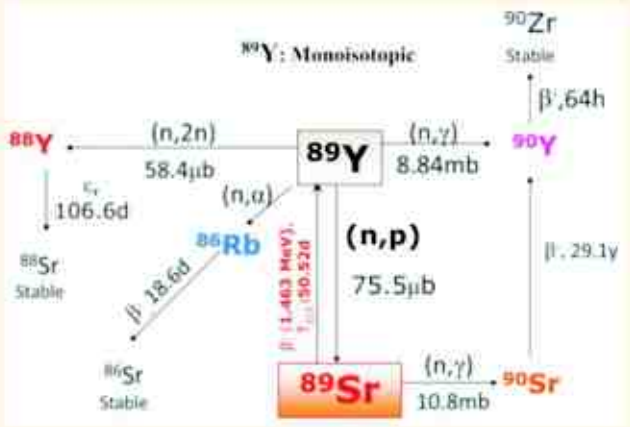


Figure 1 Production scheme of ^{89}Sr along with other accompanying reactions [21]

Purification methods

Purification of ^{89}Sr from the yttrium matrix of the dissolver solution was carried out by two methods i.e i) solvent extraction using TBP in which the bulk yttrium matrix was separated followed by the purification of Sr source by cation exchange chromatography using Dowex 50Wx8 resin [19] and ii) Solvent extraction using the Sr-Specific Crown Ether 4,4'(5') tert-butyl cyclo-hexano-18-Crown-6 (DtBuCH18C6) in which the Sr was selectively removed from the matrix element yttrium and other associated impurities [22]. In both the cases the final Sr fraction was concentrated and the source was made up to a known volume in the desired medium. The Sr-source was quantified by radiometric techniques and was subjected to the recommended quality control (QC) evaluations.

Purification of ^{89}Sr source using Solvent Extraction followed by cation exchange chromatography

Solvent Extraction

The distribution coefficient,D(Y) for the extraction of yttrium with TBP increases with increased [HNO_3] [23], a favourable condition for the direct extraction of yttrium from the dissolver solution of higher acidity medium. The separation of yttrium from the dissolver solution by solvent extraction using TBP was carried out for both analytical scale as well as bulk scale. In the analytical scale operation, the dissolver solution of a single irradiated yttria pellet was subjected to solvent extraction using pre-equilibrated TBP with conc. HNO_3 in a fume hood facility. The aqueous phase was extracted thrice using every time fresh organic medium of TBP- HNO_3. This resulted into the complete removal of ^{160}Tb, a near complete removal of Y and only a partial removal of ^{141}Ce into the organic phase (Fig.2).

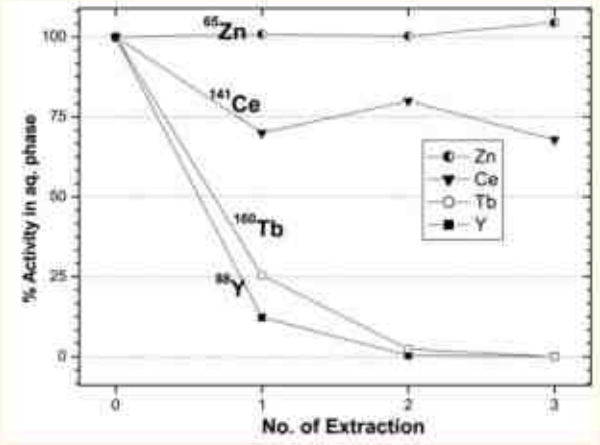


Figure 2 Analytical scale solvent extraction profile of d dissolver solution with neat TBP-HNO_3, Aq. phase: 16M HNO_3

However the aqueous phase of the dissolver solution retained complete ^{65}Zn and partial yttrium along with the total $^{89+85}Sr$. In order to standardize the procedure in the analytical scale, the Sr tracer containing $^{89+85}Sr$ was added into the dissolver solution so that the Sr assay was easily accomplished using the gamma signature of ^{85}Sr as the ^{89}Sr produced in the target is a pure beta emitter. The relative insignificant increase of ^{65}Zn activity observed in the aqueous phase after 2nd extraction is attributed to the activity fluctuation inherent to the radiometric techniques. However the extraction for the dissolver solution of 12M HNO_3 in the bulk scale separation was carried out five times using pre equilibrated TBP-HNO_3 medium which was added freshly every time in the hot cell facility through master-slave operator. This resulted into a near complete removal of the matrix element yttrium along with the partial removal of other radio-isotopic impurities to different levels (Fig.3).

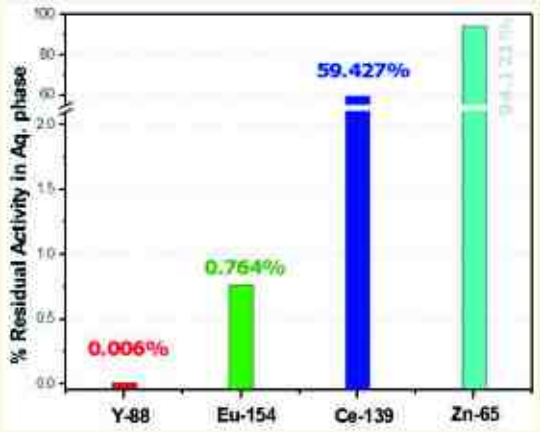


Figure 3 Bulk scale solvent extraction profile of dissolver solution with neat TBP-HNO_3, Aq. phase: 12M HNO_3

Ion Exchange

The aqueous fraction obtained from the above solvent extraction experiment contained ^{89}Sr along with a number of radioactive impurities such as ^{86}Rb, ^{85}Sr, ^{54}Mn, ^{65}Zn, ^{58}Co, ^{88}Y and ^{141}Ce. The ^{89}Sr source was therefore further purified using cationic exchange chromatography. The purification was established in the analytical scale where the pure beta active ^{89}Sr was traced using the corresponding gamma emitting Sr tracer $^{85+89}$Sr. Based on the reported distribution coefficient data [19], column experiments were carried out using 1M HNO_3 as eluant.

The feed solution in 0.1M HNO_3 containing $^{85+89}$Sr tracer was loaded onto the glass column containing the slurry of Dowex 50Wx8 (100-200 mesh) resin pre-conditioned using 0.1M HNO_3. The elution was carried out using 1M HNO_3. The addition of the Sr tracer facilitated the easy sample assay by gamma spectrometry to establish the separation profiles (Fig.4).A clear base-line separation of Sr source from the other radioactive impurities was obtained by this method. However the elution of the yttrium held in the column was carried out using a higher acidity i.e. 3M HNO_3 to shorten the elution time. The same method of purification was used to obtain pure ^{89}Sr source from bulk scale dissolver solution also with some minor modifications or fine tuning for a faster completion of the separation.

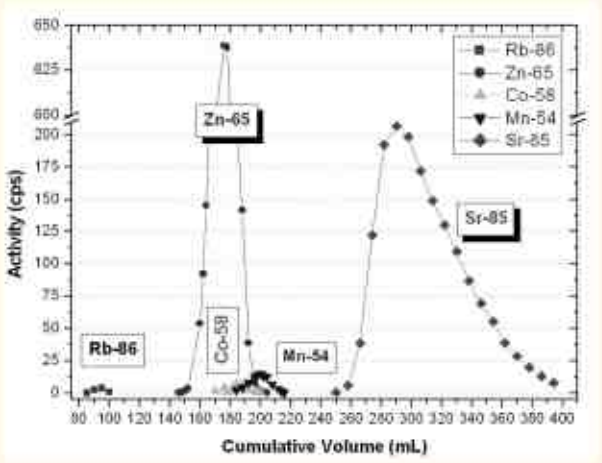


Figure 4 Analytical Scale cation exchange chromatography for the separation of Sr source

The elution profile of the various radioactive isotopes was established using their assay by radiometric techniques such as gamma spectrometry by HPGe detector for monitoring gamma emitting nuclides and beta assay of ^{89}Sr by Cerenkov detector.

Purification of ^{89}Sr source using Solvent Extraction (crown ether)

The Crown ether and the associated diluent were chosen for the purification of Sr from Y matrix based on the reported data in the literature [19,24]. For the analytical scale purification, the separation of ^{89}Sr was carried out using 0.2M DtBuCH18C6/octanol from the dissolver solution of the irradiated yttria in 12M HNO_3 medium. The dissolver solution contained 0.17M of bulk Y and the associated activated impurities produced during the irradiation. The dissolver solution was equilibrated twice with fresh 0.2M DtBuCH18C6/ octanol every time maintaining both organic and aqueous phase of equal volume (Fig.5.). At the end of the solvent extraction the cumulative volume of org. phase was scrubbed twice with equal volume of 12M HNO_3 to remove the other trace impurities co-extracted with ^{89}Sr. The ^{89}Sr in the organic phase was then back extracted thrice using fresh pH 3 HNO_3 solution every time in which the ratio of organic to aqueous phase was always maintained 1:8. In all these cases, the equilibration and phase separation time were always maintained 10 min each. The cumulative aq. phase collected together was kept for evaporation under IR heating. The dried mass was brought into the solution of 1M HNO_3. The activity of ^{89}Sr was measured by Cerenkov counting.

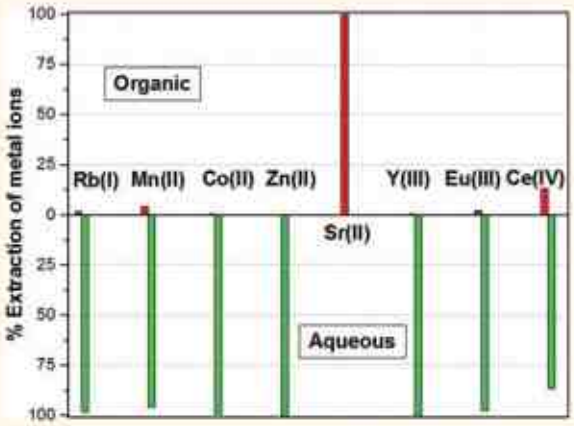


Figure 5 Analytical Scale Crown Ether extraction of Sr from dissolver solution (prior to scrubbing stage)

Subsequent analysis of the scrubbed organic phase showed the presence of only ^{89}Sr (II) which was free from the other impurities present in the dissolver solution. The other impurities such as Ce(IV), Y(III), Eu(III), Mn(II), Co(II) and Rb(I) were already removed during the scrubbing with pH 3 HNO_3 but along with about 12% Sr.This procedure established the pure fraction ^{89}Sr obtained by Sr-specific crown ether DtBuCH18C6 even though encountered some loss of Sr source during the scrubbing stage. In order to mitigate this problem, the repeated extraction of the Sr from the scrubbing reagent is being investigated. Alternately the purification by cationic exchange chromatography using Dowex resin as in the case of the other purification method is also being investigated. While the retention of Sr(II) in the crown ether organic phase can be attributed to its 1:1 complex formation ,the low extraction of Ce and other impurities are attributed to the possible formation of weak perching type complex and no complex formation respectively [22]. In bulk scale operation, 0.1M DtBuCH18C6/octanol was used with the dissolver solution in 9M HNO_3.The purification of the ^{89}Sr source in the case of bulk scale was accomplished using the same procedure standardized for the analytical scale as described above.

Quantification of the ^{89}Sr

Since ^{89}Sr is a pure beta emitter with very low intensity of gamma rays [15], it was quantified using various radiometric techniques such as beta gas proportional counter, liquid scintillation counter, Cerenkov counter and Gamma spectrometry. The assay by GM counter involved the following procedure i.e. first the efficiency calibration of the G.M counter was established using standard beta sources such as ^{60}Co (β_{max} 0.31 MeV), ^{210}Bi (β_{max} 1.17 MeV) and ^{90}Sr-^{90}Y (β_{max} 2.2 MeV). The efficiency for ^{89}Sr source of (β_{max} 1.495 MeV) was obtained by interpolating the efficiencies obtained for the standard sources ^{210}Bi and ^{90}Sr-Y. A fraction of ^{89}Sr solution was used to prepare the planchet for the assay. Similarly the efficiency calibration of Cerenkov and LSC Counting system of HIDEX make was also established using the standard sources of ^{3}H, ^{99}Tc, ^{204}Tl, ^{89}Sr, ^{32}P and ^{90}Y (^{90}Sr).The weak-intensity gamma energy of 909 keV of ^{89}Sr source was also useful for its quantification by high resolution gamma spectrometry using HPGe detector. The yield of ^{89}Sr was obtained for different campaigns (Table.1).

Table.1. ^{89}Sr production in different campaigns

Irr No.	Irradiation position FBTR	*Cumulative duration/ Irradiation	Total Activity ^{89}Sr/ run
1st	Core Centre	73 d	1.1Ci
2nd	4th Ring	114d	45mCi
3rd	5th Ring	31d	20mCi
• *All activities are as on end of Irradiation*			

The activities of the various radioactive impurities were also quantified using high resolution gamma spectrometry. The flow sheet for the purification of ^{89}Sr source from its irradiated Yttria pellets by the above two methods in the bulk scale can thus be represented as shown in Fig.6.

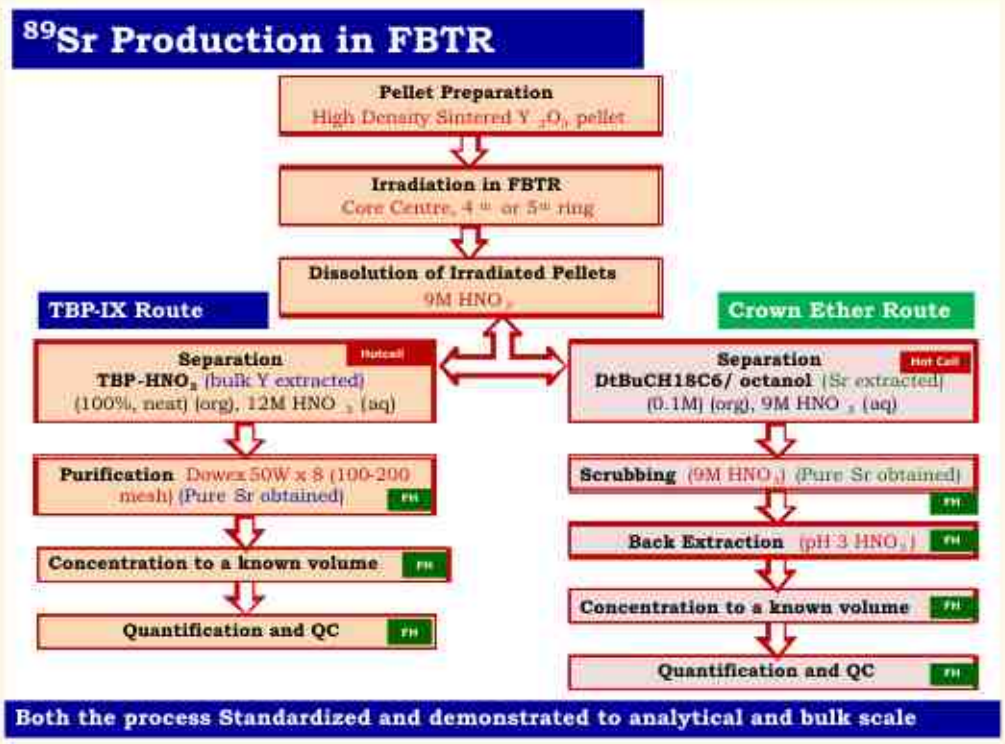


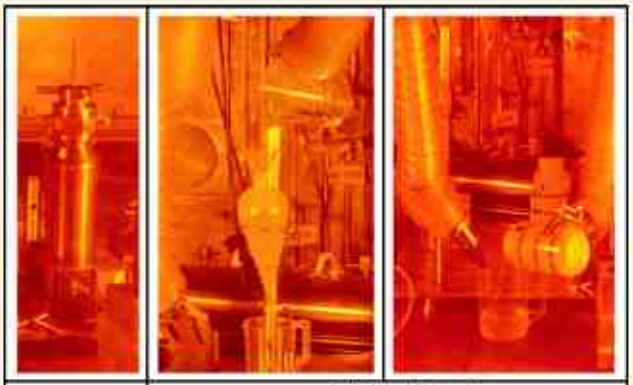
Figure 6 ^{89}Sr production flow chart by both TBP-Ion Exchange and Crown Ether processes for bulk scale operation (FH: Fume hood)

Quality Control

Various quality control measures such as measurements of pH, residual NO_3^- ion content, radioactive and non-radioactive impurities were carried out using a range of established techniques. The radionuclidic purity of the ^{89}Sr source obtained above was established by measuring experimentally the half-life of the source by plotting the activity variation with time using Cerenkov counting and obtaining its half-live from the profile. The half-life obtained from the graph drawn Ln(Activity) Vs Time was found to be 50 days which was in good agreement with the reported value of 50.57 days [25]. The results of the measurement of the various quality control parameters were found to be satisfactory as per the recommended values (Table.2). Biological quality control studies such as apyrogenicity, sterility and bacterial endotoxin. were carried out with simulated sample and found to be in accordance with the required QC norms and hence satisfactory. However the overall qualification of the actual source with respect to the biological quality control criteria is in progress.

Table.2: Quality control parameters of ^{89}Sr produced in FBTR

S.No.	QC parameter	^{89}Sr source from the above purification (2nd campaign)	Recommended
1.	Radiochemical Purity: [NO_3^-]	<10ppb*	<19ppb
2.	Radionuclidic Purity :		
	a. Other ā emitter impurities (%)	3.3×10^{-3}%	<0.4%
	b. Presence of ^{90}Sr alone	$<9.1 \times 10^{-5}$%	$<2.3 \times 10^{-4}$%
3.	Chemical Purity [Inactive Impurities i.e. Al, Fe and Pb]	1 ppm	<12ppm
4.	Specific Activity [A(^{89}Sr)/g of Sr]	3×10^{7} Ci/g	>80mCi/g
*Using only Simulated sample			



a. Dissolution | *b. Solvent Extraction (by TBP/Crown Ether)*

Figure. 7.Dissolution and solvent extraction in hot-cell facility

Conclusion

The flow sheet for the purification of ^{89}Sr source from FBTR-irradiated yttria target has been established. The flow sheet was based on the results from the analytical scale purification using a single pellet of ~1g of the yttria target as well as from the bulk scale purification using ~77g of the irradiated pellets in a dedicated hot cell facility [(Fig.7.)The evaluation of the quality control aspects of the source obtained above was satisfactory.However the biological quality control was found to be satisfactory only for the simulated solution and the same is yet to be confirmed for the actual ^{89}Sr source.

The final irradiation campaign is in progress for the total qualification of the source.

Trial Production of ^{32}P isotope in KAMINI Reactor

^{32}P is a pure beta emitter with a half-life of 14.3 d and a typical whole body biological half-life of 39.2 d. Apart from its usage for bone pain palliation therapy, it is also a treatment of choice for polycythemia vera and thrombocythaemia [26]. As a tracer, ^{32}P has several other applications in the field of plant physiology, soil chemistry and the mechanism of nutrient uptake in the plants [27]. This can be produced from the reaction ^{31}P(n,ā)^{32}P by irradiating phosphorus in a thermal reactor or from the reaction ^{32}S(n,p)^{32}P by irradiating sulphur bearing targets with fast neutrons [28]. The former method has a high yield but gives a product of low specific activity. However various other isotopes are also produced simultaneously during the irradiation of sulphur with neutrons (Fig.8).

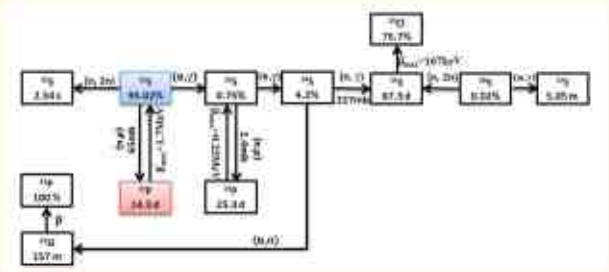


Figure 8 Production pattern of different isotopes during the irradiation sulphur

But the latter method renders ^{32}P of high specific activity because of the feasible and simple elemental chemical separation. Therefore it is possible to produce carrier free ^{32}P of high specific activity through ^{32}S(n,p)^{32}P using the fast neutron flux available in FBTR, Kalpakkam. However the required flow sheet for the processing of the irradiated targets was developed using the small fast flux available in the KAMINI research reactor, IGCAR, Kalpakkam.

Development of flow sheet

Even though the sulphur powder as the target results into the maximum yield for ^{32}P, the possible vapour pressure increase during its irradiation at the high temperature in FBTR may be of a concern and the safety aspects are to be addressed before proceeding with its usage as the target. Hence the flow sheet was developed for the other alternate targets such as magnesium sulphate and strontium sulphate beside the sulphur powder itself [29]. The feasibility of ^{32}P production via ^{32}S (n, p) ^{32}P reaction using the above sulphur bearing targets was established by irradiating them with the small fast flux available in the research reactor KAMINI, Kalpakkam. The flow sheet established in the experiments is to be utilized for the large scale production using FBTR irradiation facility in future. The flow sheet developed using these targets are described in the following sections.

Magnesium sulphate as Target

10 g of magnesium sulphate (99 %) was irradiated in KAMINI reactor for ~ 4.5 h at south thimble position that has the thermal neutron flux of 3.6E8 n cm^{-2} s^{-1}. ^{32}P produced during the irradiation of $MgSO_4.7H_2O$ target in KAMINI reactor was converted into phosphate by addition of H_2O_2 in dil.HNO_3 medium which was subsequently precipitated as Struvite using ammonium hydroxide at pH 8-10 [30].

$$Mg^{2+} + NH_4^+ + PO_4^{3-} \xrightarrow{6H_2O} Mg(NH_4)PO_4.6H_2O \downarrow (Struvite)$$

The Cerenkov analysis showed that ~80 % of ^{32}P was precipitated as struvite and ~20 % of ^{32}P in the supernatant. The ^{32}P in the supernatant was recovered subsequently by precipitating it again as struvite and by repeating the method. The ^{32}P in its phosphate form in HCl medium was separated from Mg in the dissolved struvite solution using cation exchange chromatography with DOWEX 50WX8 (100–200 mesh) resin (Fig. 9).

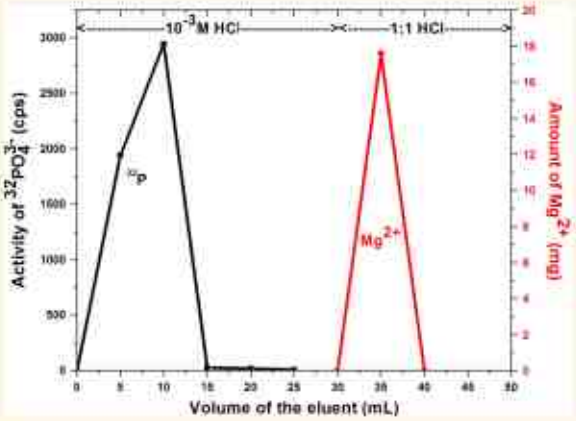


Figure 9 Elution profile of ^{32}P (phosphate) separated from Mg by cation-exchange chromatography

The sample fractions were analyzed for ^{32}P content using Cerenkov counting and Mg content by complexometric titration using EDTA. Over 99 % of the initial activity of ^{32}P was eluted in the first 2 fractions of about 10mL volume of 10^{-3}M HCl itself. Mg was subsequently eluted using 1:1 HCl. The separated ^{32}P from both struvite precipitate and the supernatant solution was quantified using Cerenkov detection. About 83 nCi of ^{32}P was produced per 10 g of magnesium sulphate target in KAMINI reactor at south thimble position. The purity of ^{32}P was confirmed by observing its comparable half-life with that of reported value in literature.

Strontium sulphate as target

About 1g of $SrSO_4$ (99 %) was irradiated for 6h in KAMINI reactor at pneumatic fast transfer system (PFTS), with thermal neutron flux of 1.6E11 ncm^{-2}s^{-1}. The irradiated $SrSO_4$ target was dissolved in water by converting it into its carbonate precipitate by adding sodium carbonate [31]

$$SrSO_4 + Na_2CO_3 \xrightarrow{\Delta, Stirring} SrCO_3 \downarrow + Na_2SO_4$$

The $SrCO_3$ precipitate was dissolved in HCl and converted into $SrCl_2$. Further ^{32}P in the $SrCl_2$ solution was co-precipitated as ferric phosphate along with ferric hydroxide on addition of ferric chloride and ammonium hydroxide. The same is followed in the case of filtrate also i.e.

$$FeCl_3 + 3NH_4OH \longrightarrow Fe(OH)_3 \downarrow + 3NH_4Cl$$

$$FeCl_3 + PO_4^{3-} \longrightarrow FePO_4 \downarrow + 3Cl^-$$

The conditioned solutions from residue and filtrate were combined as the feed for cation exchange chromatography using Dowex 50WX8 (100–200) resin to purify ^{32}P from Sr and Fe. ^{32}P was eluted by 0.1M HCl and Sr and Fe by 3M HCl. The eluted samples were assayed by Cerenkov counting to quantify ^{32}P. The elution profile of ^{85}Sr and ^{89}Sr produced during the irradiation was established by the assay of ^{85}Sr by HPGe detector and ^{89}Sr by Cerenkov counting. Fe content of the samples was profiled using ICP-OES. A clear base line separation of ^{32}P from Fe and Sr was achieved (Fig.10).

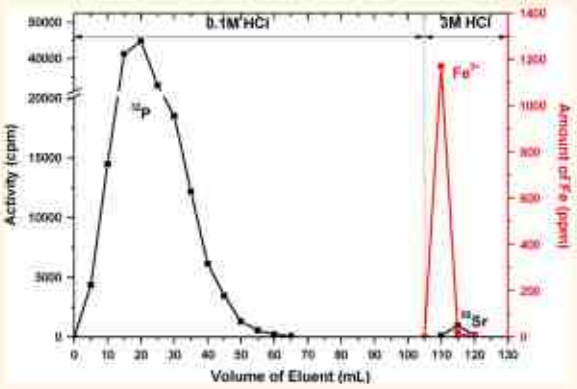


Figure 10 Elution profile of ^{32}P (phosphate) separated from Fe & Sr by cation-exchange chromatography.

On repeating the method separately for the residue and the filtrate, the ^{32}P found in the residue fraction accounted for 75 % of the total ^{32}P produced while the rest was found to be present in the filtrate fraction. The amount of ^{32}P obtained together in both residue and filtrate by this method was 7.57 iCi/g of target which accounted for 99.8 % of the calculated yield of ^{32}P. The purity of ^{32}P was confirmed by obtaining its characteristic half-life by from its decay profile established using Cerenkov counting assay. The gamma spectrometric analysis of the sample also confirmed the absence of any gamma impurities.

Elemental Sulphur as target

About 5g of elemental sulphur powder (98 %) was irradiated in KAMINI reactor at north thimble position for 6h with thermal a neutron flux of 1.1E10 ncm^{-2}s^{-1}. ~1g of the irradiated target was added with 10mL of glacial acetic acid and the mixture was heated to the boiling point of the medium i.e. 120°C for 20min [32]. During this process the sulphur melted resulting into the release of the phosphorous as phosphate into the acetic acid. The mixture was allowed to cool to room temperature. The Sulphur was solidified and the supernatant which contained ^{32}P was filtered using whatman 542 filter paper. The Sulphur was again treated similarly with fresh glacial acetic acid four times to extract the ^{32}P completely. The ^{32}P was assayed by Cerenkov counting. Another similar process was standardized where rapid cooling of molten Sulphur was carried out to recover the ^{32}P. The separated ^{32}P was conditioned to 0.1M HCl and was used as feed to purify the source by cationic exchange chromatography using Dowex 50WX8 (100-200 mesh) resin. The feed solution was introduced into the column and the elution was started using 0.1M of HCl followed by 6M of HCl. The analysis of the eluted samples was carried out using Cerenkov counting for

^{32}P. A clear base line separation of ^{32}P from the cationic impurities was observed (Fig.11).

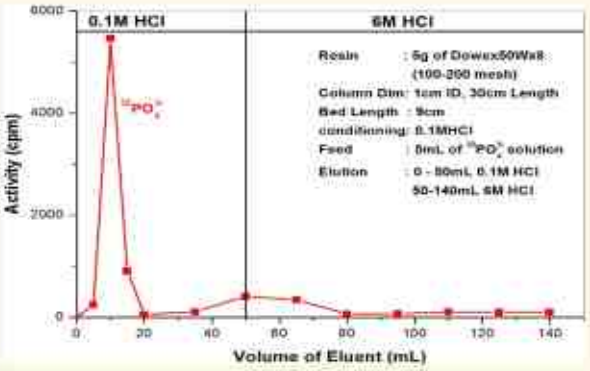


Figure 11 Elution profile of ^{32}P (phosphate) in cation-exchange chromatography

The total recovery was found to be ~96% of the calculated value of ^{32}P content produced in the case where natural cooling was implemented and 99 % of recovery was observed in rapid cooling method. The amount of ^{32}P produced was found to be 0.43 Ci/g of Sulphur in this case.

Conclusion

A flow sheet has been standardized for the separation of ^{32}P from the various targets i.e. magnesium sulphate, strontium sulphate and elemental sulphur powder irradiated at KAMINI reactor using its small fast flux neutrons available. The procedure can be extended for the large scale production of ^{32}P in FBTR owing to its high fast flux neutrons. The most desirable target would be the elemental sulphur but the choice will depend on its technical clearance for its irradiation in FBTR. Else the strontium sulphate or magnesium sulphate can be used as the target for the production of ^{32}P.

Future program

There are various other radioisotopes can be produced in Fast Breeder Test Reactor. Some of them include ^{60}Co, ^{117m}Sn, ^{64}Zn etc. These isotopes can be produced through $^{60}Ni(n,p)^{60}Co$, $^{117}Sn(n,n')^{117m}Sn$ and $^{64}Cu(n,p)^{64}Zn$ reactions. Standardization of the flow sheet for the production of ^{60}Co is in progress.

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Cyclotron Production of Radioisotopes and Their Medical Applications

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Introduction

Radioisotopes have various applications. However, their most important application is in health care, where radioisotopes are used to assess the function of an organ in disease and health. They are also used in therapy of disease such as cancer. Nuclear medicine is the branch of medical science which uses radioisotopes for diagnostic or therapeutic purpose by administering radioisotope in a suitable chemical form, called radiopharmaceutical (RPS). Hungarian chemist George Charles de Hevesy proposed the tracer principle and published in 1923 the first study on the use of the naturally radioactive ^{212}Pb as radioactive tracer to follow the absorption and translocation of lead by plant [1], which paved the way for use of radioisotopes as a diagnostic tool. U.S. physician, Hermann Blumgart first studied the velocity of blood in veins by injecting a solution of ^{214}Bi [2].

Radioisotopes used in nuclear medicine are artificially produced in a nuclear reactor or in a charged particle accelerator, usually a cyclotron. Historically radioisotopes were first produced in cyclotron after its invention by Lawrence and Livingstone in the year 1931[3]. In 1941 the first commercial medical cyclotron was installed at the Washington University, St. Louis for the purpose of production and supply of various radioisotopes. Soon the demand of radioisotope increased and existing cyclotrons were unable to cope with. The situation changed after the World War-II. The nuclear reactors at Oak Ridge and Los Alamos which were set up to make atom bomb were used to supply huge quantities of radioisotopes at a cheap cost. Because of these reasons cyclotron produced radioisotopes were neglected for some time. With the rapid growth of nuclear medicine, it was soon realised that in certain cases reactor produced radioisotopes could not satisfy all the growing demands. Since reactor produced radioisotopes are generated mainly by using the (n,γ) reaction, the range of radioisotopes that could be produced is limited and all are of 'n rich' type which undergo β^- decay. The importance of cyclotron was therefore felt and today it is the only tool for the production of certain 'n deficient' radioisotopes.

In nuclear medicine about 90% of the radioisotopes are employed in diagnostic procedures [4]. The most common radioisotope used in diagnosis is ^{99m}Tc (technetium-99m), accounting for 80% of all nuclear medicine procedures worldwide. It has been reported that out of all the radioisotopes used in nuclear medicine, more than 80% are produced by research reactors. The remaining radioisotopes are produced by particle accelerators. However, the importance of radioisotope production in cyclotron is growing. Radioisotope production in cyclotron has several advantages. Compared to cyclotrons, reactor complex is a huge facility, produce lot of radioactive waste, commonly used (n,γ) reaction produce radioisotope of low specific activity which are unsuitable for certain applications. On the other hand cyclotron produced radioisotopes are mostly carrier free and hence have high specific activity. Positron emitting radioisotopes are produced only in cyclotron. Finally, cyclotrons pose no risk in relation to nuclear weapons proliferation since they do not use high-enriched uranium (HEU) targets. Medical radioisotopes are produced by half a dozen reactors which are more than 40 years old. As a result of this, frequent shut down of these reactors adversely affected the steady supply of radioisotopes during 2008-2010. This prompted the policy makers to study the medical radioisotope production feasibility without a nuclear reactor. With this goal in mind, significant progress has been made by the Canadian scientists, particularly in the production of ^{99m}Tc in a cyclotron [5, 6].

Salient Features of Radioisotope Production in Cyclotron

Radioisotope production in cyclotron is much complicated compared to that in a nuclear reactor and hence requires special attention to several aspects in preparing the target and the target irradiation chamber. When accelerated charged particle of high intensity (several tens or hundreds of μA) hits a target vertically, large amount of heat is generated in a small area which may cause melting/evaporation of the target material. Addressing this problem requires, i) target cooling, ii) irradiation of the target at a grazing angle (~7°) using an wobbling beam, iii) selection of target material having good thermal conductivity and high melting point. Simultaneous production of various isotopes (both stable and radioactive) from various nuclear channels is a common feature in target irradiation in a cyclotron. Undesired nuclear reaction products may be minimized by i) selecting the optimum energy window for the irradiation (requires the knowledge of the nuclear reaction data for the production of the desired radioisotope as well as that of the impurity radioisotopes) and ii) using enriched / monoisotopic target material. While using costly enriched target material, it is imperative to recover and reuse the target material in order to keep the production cost low. While irradiating liquid or gas target in cyclotron, the target material is enclosed in airtight chamber, the front side of which is made up of a thin foil through which the beam enters and irradiate the target. In selecting the window foil, following parameters should be considered: i) its thermal conductivity, ii) its tensile strength, iii) its chemical inertness, iv) its energy degradation property, v) its susceptibility to radioactive activation and vi) its melting point. Some of the above material properties should also be kept in mind while selecting the material of construction for the target chamber.

Cyclotron Produced Diagnostic Radioisotopes

Diagnostic radiopharmaceuticals (RPS) are radiolabelled with a radioisotopes emitting low energy gamma (100-250 keV) or with a positron emitter. The 1st categories of radioisotopes are imaged with a planar gamma camera or with a Single Photon Emission Computed Tomography (SPECT) camera and the 2nd category with a Positron Emission Tomography (PET) camera. The photons emitted from the RPS, distributed over a tissue, are detected with these cameras and give a 2D or 3D image of radioisotope distribution on that particular tissue. Radiopharmaceuticals are prepared by adopting various radiochemical synthetic approaches which is out of the scope of this article. Summary of production route of major cyclotron produced radioisotopes, for diagnostic application is given in Table-1.

More information on some of the important diagnostic radioisotopes and the applications of the RPS prepared with them are given below.

^{201}Tl

Enriched ^{203}Tl electroplated targets are used for the production. ^{201}Tl is obtained by the decay of the directly produced ^{201}Pb. The most important RPS of this radioisotope is [^{201}Tl]thallous chloride. It is used in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction. Analysis of stress and rest image taken with [^{201}Tl]thallous chloride may be used to differentiate between myocardial infarction and ischemia. [^{201}Tl]thallous chloride is indicated also for the localization of sites of parathyroid hyperactivity in patients with elevated serum calcium and parathyroid hormone levels. It may also be useful in pre-operative screening to localize extrathyroidal and mediastinal sites of parathyroid hyperactivity and for post-surgical re-examination. Now-a-days [^{201}Tl]thallous chloride has been largely replaced by ^{99m}Tc based compounds (like ^{99m}Tc labelled methoxy isobutylisonitrile, MIBI).

^{123}I

Radioiodine, ^{131}I, is one of the oldest radioisotopes used in nuclear medicine. ^{131}I is being used for both diagnostic and therapeutic applications. However, it is not an ideal radioisotope for diagnostic application. On the other hand ^{123}I is one among the ideal radioisotopes used in diagnostic nuclear medicine. Its application is, however, limited due to the logistic problem in producing it with acceptable radionuclidic purity. Purest ^{123}I is produced by proton irradiation of pressurised enriched ^{124}Xe gas target. Iodine uptake studies with [^{123}I]sodium iodide may be used for the diagnosis of hyperthyroidism and hypothyroidism. [^{123}I]mIBG (metaiodobenzylguanidine) is used for the neuroendocrine tumour imaging. Malignant tissue may be imaged with specific monoclonal antibody or their fragment labelled with ^{123}I. Peptide receptors, over expressed in certain tumour cells, may be imaged effectively with the specific peptide radiolabelled with ^{123}I. ^{123}I labelled fatty acid, beta methyl p-iodo phenyl pentadecanoic acid (^{123}I-BMIPP), may be used for myocardial imaging.

^{67}Ga

Enriched ^{68}Zn electroplated targets are used in its production. Its most important radiopharmaceutical is [^{67}Ga]gallium citrate which may be useful in demonstrating the presence of the following malignancies: Hodgkins disease, lymphomas and bronchogenic carcinoma. It may also be useful as an aid in detecting some acute inflammatory lesions.

^{111}In

Enriched ^{112}Cd electroplated targets are used for its production. Several RPS of ^{111}In are available. [^{111}In]-leukocyte may be used for infection imaging. Octreotide radiolabelled with ^{111}In is used in imaging cancer cells over expressing somatostatin receptors. Monoclonal antibody or their fragments may be radiolabelled with ^{111}In for cancer imaging. [^{111}In]DTPA may be used in cisternography to find the leakage of cerebrospinal fluid from the central nervous system.

^{81m}Kr

This radioisotope is obtained from the ^{81}Rb/^{81m}Kr radioisotope generator. The parent radioisotope, ^{81}Rb, has 4.57h half life. The daughter radioisotope, ^{81m}Kr, may be eluted as gas or in aqueous solution. In gaseous form it is used in lung ventilation imaging and in aqueous solution for lung, myocardial and cerebral perfusion studies.

^{18}F

^{18}F is an attractive radioisotope for use in positron emission tomography (PET). Its 110 min half-life allows complex or multistep organic synthesis and the RPS produced can be utilised at sites moderately distant from their production centre. ^{18}F as fluoride is obtained by irradiation of ^{18}O-enriched water with proton or by deuteron irradiation of neon gas containing small amount of H_2 in a small cyclotron. ^{18}F as carrier added [^{18}F]F_2 gas is produced by deuteron irradiation of neon gas containing small amount of F_2. The relatively long physical half-life of ^{18}F permits PET studies of moderately slow physiological processes. Comparatively lower positron energy (E_{max} = 0.635 MeV) of ^{18}F, having a short mean range (2.39mm in water), provides better image resolution. Detailed discussion on preparation of ^{18}F-labelled compounds is beyond the scope of this article, however, excellent review articles on this are available [31, 32]. Briefly, ^{18}F-labelled compounds generally prepared through (p, n) reaction on enriched ^{18}O-water target. For this reason nucleophilic fluorination produces a product with high specific activity. Many important ^{18}F-RPS including FDG,

Table 1: Nuclear data and production routes of few cyclotron produced diagnostic radioisotopes

Radioisotope, $t_{1/2}$	Decay mode	Production route	Target	Ep, MeV	Yield at EOB mCi/μAh	Ref.
^{201}Tl, 73.01h	EC	^{203}Tl(p, 3n)^{201}Pb →^{201}Tl	En. ^{203}Tl	28.5	120 mCi/μA[1]	7
^{123}I, 13.22h	EC	^{124}Xe(p, 2n)^{123}Cs→ ^{123}Xe→^{123}I	En. ^{124}Xe	30	12	8
		^{123}Te(p, n)^{123}I	En. ^{123}Te	014.5→11	3.7	9
^{67}Ga, 78.28h	EC	^{68}Zn(p, 2n)^{67}Ga	En. ^{68}Zn	28.5	40 mCi/μA[1]	7
^{111}In, 67.2h	EC	^{112}Cd(p, 2n) ^{111}In	En. ^{112}Cd	28.5	45 mCi/μA[1]	7
^{57}Co, 271.74d		^{59}Co(p, 3n)^{57}Ni→^{57}Co	Nat. Co	40→24	2	10
		^{58}Ni(p, 2p)^{57}Co	En. ^{58}Ni	20→15	10.8	11
^{81m}Kr[a], 13.1s	IT	Kr(p, x)^{81}Rb→^{81m}Kr	Nat. Kr	27→19	48[2]	12
^{87m}Sr[b], 2.81h	IT	^{88}Sr(p, 2n)^{87}Y→^{87m}Sr	Nat. $SrCl_2$+SrO	26→20	270-400mCi/C[2]	13
^{18}F, 109.77min	β$^+$(97) EC (3)	^{18}O(p, n)^{18}F as $^{18}F^-$	En.[^{18}O]H_2O	18	165mCi/μA[3]	14
		^{20}Ne(d, α) ^{18}F as ^{18}F	Nat. Ne + H_2	8→2	17[4]	15
		^{20}Ne(d, α) ^{18}F as $^{18}F_2$	Nat. Ne+2% F_2	14→2	28[4]	15
^{11}C, 20.33min	β$^+$(99.7)	^{14}N(p, α)^{11}C as $^{11}CO_2$	Nat. N_2+0.5% O_2	18	225mCi/μA[5]	16
^{13}N, 9.96min	β$^+$(99.8)	^{16}O(p, α)^{13}N as $^{13}NH_3$	Nat. H_2O + 5m Mol ethanol	16	20mCi/μA[6]	14 17
^{15}O, 2.04min	β$^+$(99.9)	^{16}O(p, pn)^{15}O	Nat. O_2 gas	30-2626.5-25	35mCi/μA/min[7] 16mCi/μA/5min	14 18
^{68}Ga[c], 67.71min	β$^+$(88.9) EC(11.1)	^{69}Ga(p, 2n)^{68}Ge→^{68}Ga	Nat. Ga	45	14 μCi/μAh[2]	19
^{64}Cu, 12.70h	EC(43.9) β$^+$(17.6) β$^-$(38.5)	^{64}Ni(p, n)^{64}Cu	En. ^{64}Ni	12	1.98	20
			En. ^{64}Ni	15.5	2.3-5	21
^{62}Cu[d], 9.67min	β$^+$(97.8) EC(2.2)	^{63}Cu(p, 2n)^{62}Zn→^{62}Cu	Nat. Cu	30→15	5.9[2]	22
^{61}Cu, 3.33h	β$^+$ (61.4) EC (38.6)24	^{61}Ni(p, n)^{61}Cu	En. ^{61}Ni	15→7	38.3[4]	23
		^{64}Zn(p, x)^{61}Cu	Nat. Zn	19→10	9.9	24
^{82}Rb[e], 1.25m	β$^+$ 95.4 EC 4.6	Mo(p, spall)^{82}Sr→^{82}Rb	Nat. Mo	500-700	20-30 Ci[8]	25
		^{85}Rb(p, 4n)^{82}Sr→^{82}Rb	Nat. RbCl	561-39	0.24[2]	26
^{124}I, 4.17d	EC 77.3 β$^+$ 22.7	^{124}Te(p, n)	En. ^{124}Te	14.1	0.57	27, 7
^{74}As, 17.77d	EC 66 β$^+$ 34	^{nat}Ge(p, x)	Nat. Ge	15.5	0.28	28
^{75}Br, 96.7min	β$^+$(75) EC(25)	^{76}Se(p, 2n)	En. ^{76}Se (96.5%)	30→22	100	15
^{76}Br, 16.2h	β$^+$(54) EC(46)	^{76}Se(p, n)	En. ^{76}Se	16→8	1.7-1.9	29
^{89}Zr, 78.4h1	EC (77) β$^+$ (23)	^{89}Y(p, n)	Nat. ^{89}Y	15	1.52	30

[a]Obtained from ^{81}Rb-^{81m}Kr generator, [b]Obtained from ^{87}Y-^{87m}Sr generator, [c]Obtained from ^{68}Ge-^{68}Ga generator, [d]Obtained from ^{62}Zn-^{62}Cu generator, [e]Obtained from ^{82}Sr-^{82}Rb generator, [1]Yield as metal chloride at the end of radiochemical separation, [2]Yield of the parent radioisotope, [3]Yield at the end of 1h irradiation, [4]Yield calculated from the excitation function curve, [5]Yield of $^{11}C[CO_2]$ at saturation, [6]Yield of $[^{13}N]NH_3$ at the end of 15min irradiation, [7]Online continuous production as $[^{15}O]O_2$, [8]Yield at EOI with 500 μA proton irradiation for one month.

FLT, FAZA, FMISO are prepared by nucleophilic and electrophilic reactions, the former being the preferred method. Nucleophilic substitution reaction (SN2 or SNAr) is carried out with no carrier added [^{18}F]fluoride as the nucleophile etc. have been prepared by the nucleophilic substitution reaction. Electrophilic fuorination utilises [^{18}F]F_2 or milder reagents prepared from it. [^{18}F]F_2 is produced through ^{20}Ne(d,α)^{18}F

reaction in carrier-added form as a small amount of inactive natural F_2 is required to be mixed with the Ne gas used for the irradiation. Hence, ^{18}F-RPS with high specific activity cannot be prepared by this method. The most important electrophilic fluorinating agent is acetyl hypofluorite, CH_3COOF. The selective electropilic aromatic substitution may be carried out by displacement of a metallic (Hg, Sn) substituent (^{18}F-fluorodemetallation). ^{18}F-fluorodestannylation is now the preferred demetallation for the electrophilic route of production of [^{18}F]6-fluoro-L-DOPA in which the trimethyltin group at 6 position is replaced by the electrophilic ^{18}F. Applications of few important ^{18}F- RPS are listed in the Table-2.

^{11}C

^{11}C is produced by proton irradiation of natural N_2 gas in a small cyclotron. Short half life of ^{11}C limits the total synthesis time available in preparing a RPS. This in turn limits the number of RPS that can be produced. Its short half life also requires handling large amount of radioactivity which poses problems related to radiation hazard during synthesis. Automation of the synthesis process is therefore necessary to reduce the risk of radiation hazard as well as the total synthesis time. The radiochemical form of ^{11}C often used in the synthesis of various precursors for the preparation of ^{11}C-RPS are [^{11}C]CO_2, [^{11}C]CH_3I, [^{11}C]HCN etc. Applications of a few ^{11}C based RPS are listed in the Table-3.

^{13}N

The most important RPS of ^{13}N is [^{13}N]NH_3. [^{13}N]NH_3 is directly produced when 1-5 mmol solution of ethanol in water is irradiated with 15 MeV proton beam. Yield of [^{13}N]NH_3 is more than 95%. About 400 mCi product is obtained in 15m irradiation at 20mA. [^{13}N]NH_3 is used in myocardial perfusion studies using PET camera [45].

^{15}O

^{15}O is produced by proton irradiation of O_2 gas in a small cyclotron. Important RPS of ^{15}O are [^{15}O]H_2O, [^{15}O]CO_2 and [^{15}O]CO. Production of all these three RPS involves one step process and requires few minutes for completion. For example in production of [^{15}O]water, a stream of helium gas carrying [^{15}O]O_2 from the target is mixed with hydrogen and air and passed through a converter containing palladium catalyst (at 150°C). [^{15}O]water is produced by combustion of ^{15}O with hydrogen. The synthesis takes 2 minutes and the yield is 70-80%. [^{15}O]O_2 may be converted to [^{15}O]CO_2 by passing [^{15}O]O_2 through a furnace (500°C) containing activated carbon and copper powder. Decay corrected yield is 80%. [^{15}O]CO_2 may be converted to [^{15}O]CO by passingthrough a furnace (900°C) containing.

Table 2: Applications of a few important ^{18}F-radiopharmaceuticals

Radiopharmaceuticals	Application	Ref.
[^{18}F]FDG	Study of regional glucose metabolism; useful in oncology, brain and cardiac function studies	33,34
^{18}F]FLT	Cell proliferation	35
[^{18}F]FET	Amino acid transport rate	36
[^{18}F]FMISO	Tumour hypoxia	37
[^{18}F]FAZA	Timor hypoxia	38
[^{18}F]NaF	Skeletal metastasis	39
[^{18}F]FDOPA	Presynaptic dopaminergic function	40

Abbreviations: FDG= Fluorodeoxy glucose, FLT= Fluorothymidine, FET= Fluoroethyl-L-tyrosine, FMISO= Fluoromisonidazole, FAZA= Fluoroazomycinarabinoside, FDOPA= 6-fluoro-L-3,4-dihydroxyphenylalnin.

Table 3: Applications of a few ^{11}C based radiopharmaceutical

Radiopharmaceuticals	Application	Ref.
[^{11}C]Choline	Identification of the location of recurrence prostate cancer	41
[^{11}C]Raclopride	Determination of dopamine (D_2) receptor density in the human brain	42
[^{11}C]PiB(PiB =Pittsburgh Compound B)	Imaging amyloid neuritic plaques that are associated with Alzheimer's Disease (AD) and mild cognitive impairment (MCI)	43
[^{11}C]carfentanil	Imaging brain μ-opioid receptors	44

activated charcoal. Residual CO_2 is trapped on a soda lime trap. Decay corrected yield is 70%. While [^{15}O]H_2O is used in blood flow studies in brain and heart [46, 47, 48], [^{15}O]O_2 is used to measure metabolic rate of oxygen in brain[48]. [^{15}O]CO and [^{15}O]CO_2 are used to estimate cerebral blood volume [48] and flow [49], respectively.

^{68}Ga

^{68}Ga is obtained from the ^{68}Ge/^{68}Ga radioisotope generator [50]. Parent radioisotope, ^{68}Ge, is mostly produced

by proton irradiation of natural gallium target in a medium energy cyclotron. Specially designed target chamber is required for the irradiation of Ga metal as it is in liquid state above 30 °C and also due to its reactivity with most metals under the irradiation condition. ^{68}Ge/^{68}Ga generator was developed long back. But early generators produced ^{68}Ga as ^{68}Ga-EDTA complex which makes it difficult to prepare other RPS. This is one reason why this generator did not gain wide acceptance at that time. In the modern generator ^{68}Ga can be eluted in simple ionic form suitable for preparing various RPS. The most widely used ^{68}Ga RPS are based on somatostatin analog (^{68}Ga–DOTATOC, ^{68}Ga–DOTATATE etc.), which target tumours that over express somatostatin receptors. RPS for many other receptors (CCK/gastrin receptor, glucagon like peptide receptor, gastrin releasing peptide receptor etc.), which are over expressed in various other types of cancer, are in different stages of development/ clinical trial. ^{68}Ga labelled RGD peptide, which targets prostate cancer cells, has undergone preclinical testing. Certain ^{68}Ga bifunctional ligands used for tumour imaging can be employed for therapeutic purpose by replacing ^{68}Ga with therapeutic radionuclides of trivalent metals, e.g. ^{90}Y, ^{177}Lu, ^{213}Bi, and thus ^{68}Ga is also a product of theragnostic interest currently. With the existing ^{68}Ga based RPS, and many new pharmaceuticals under development, ^{68}Ge/^{68}Ga generator based RPS will play an increasing role in future, similar to that of ^{99m}Tc and ^{18}F products. Sangeeta Ray Banerjee et al. have published [51]an excellent review article on the clinical applications of ^{68}Ga RPS.

^{64}Cu

^{64}Cu is one of the very few radioisotopes in which all the three decay modes, namely, EC (43.9%), β^+(17.6%), β^- (38.5%) coexist. As a result of this, ^{64}Cu has potential use in PET diagnostic imaging as well as in therapy. Electron capture decay with its associated Auger electrons makes ^{64}Cu more efficient in cell killing. Its 12.7 hour half-life allows PET evaluation of biochemical pathways whose rates are too slow to be analysed using readily available short-lived positron emitting radionuclides such as ^{18}F, ^{11}C. The advantageous chelating chemistry of copper makes ^{64}Cu useful for labelling biomolecules through the formation of stable complexes with bifunctional chelators like cyclic polyamines (cyclam) and cyclic polyaminocarboxilates (DOTA, TETA, NOTA). Applications of few ^{64}Cu-radiopharmaceuticas are listed in the Table-4.

^{82}Rb

^{82}Rb is a positron emitting radioisotope obtained from a radioactive generator system by decay of its parent radioisotope, ^{82}Sr. ^{82}Rb, analogue of potassium is taken up by the viable myocardium and is therefore used (as [^{82}Rb]rubidium chloride) in assessing blood flow in myocardial tissue. ^{82}Rb has certain distinct advantages over other SPECT (^{201}Tl, ^{99m}Tc) or PET (^{15}O, ^{13}N, ^{38}K) radioisotopes for myocardial perfusion imaging. Compared to other SPECT radioisotopes it offers high imaging resolution and less dose. Unlike ^{15}O, ^{13}N, ^{38}K it is available to the facilities without a cyclotron. 25.34 d half life of its parent, ^{82}Sr, with decay by electron capture (100%), is convenient for shipping and provides useful radioactivity in a generator for at least a month of frequent elutions. However, the production of ^{82}Sr requires high proton energy (50 MeV and above) and is only produced in few large accelerator facilities.

Table 4: Diagnostic applications of ^{64}Cu-radiopharmaceuticals

Radiopharmaceuticals	Application	Ref.
[^{64}Cu]ATSM	Hypoxia imaging	52, 53
[^{64}Cu]PTSM	Quantification of myocardial, cerebral, renal, and tumour blood flow	54
^{64}Cu-DOTA-cetuximab	PET-imaging agent for epidermal growth-factor receptor-positive (EGFR) tumours	55
[^{64}Cu]Octreotide	PET imaging and therapy of tumour which over-express somatostatin receptor on cell surface	56
[^{64}Cu]RGD peptide	PET imaging and therapy of tumours where 5_v5_3 integrin is upregulated	57

Abbreviations: ATSM= diacetyl-bis(N4-methylthiosemicarbazone, PTSM= diacetyl-bis(N4-methylthiosemi- carba zone.

^{124}I

As stated earlier, radioisotopes of iodine hold a special position in nuclear medicine. Since the chemistry of iodine based RPS is well known for more than sixty years and many radiopharmaceuticals of ^{131}I are in use for a long time, it is easy to prepare similar RPS by just taking the required radioiodine during the synthesis. ^{124}I decays by both positron emission and electron capture. Being a positron emitter, its RPS offer all the benefits of PET imaging. Emission of Auger electrons resulting from its electron capture decay mode makes it a potential therapeutic nuclide. Diagnostic applications of some important RPS of ^{124}I are listed in the Table-5.

^{89}Zr

^{89}Zr which decays by positron emission (23%) and electron capture (77%), has attractive characteristics for immunoPET applications. It can be produced in high purity,

specific activity and yield in a small cyclotron. Its 3.3 d half life is ideally suited for targeting cancer cells in immunoPET imaging which utilizes monoclonal antibody-based (mAb) RPS. ^{89}Zr images are comparable to those observed with the ^{18}F and ^{64}Cu. ^{89}Zr labeling of antibodies can be achieved primarily through the bifunctional chelating agent such as desferrioxamine B (Df) or its various derivatives. Few ^{89}Zr based RPS developed have imaging applications as listed in the Table-6.

Cyclotron produced therapeutic radioisotopes

Rapidly dividing cells are particularly sensitive to damage by radiation. Hence, some cancerous growths can be controlled or eliminated by irradiating the diseased area. With sealed radiation source this has been achieved through high energy gamma radiation sources such as ^{60}Co (teletherapy) or by planting a suitable sealed gamma/β^- source such as ^{192}Ir in the region of cancer growth (brachytherapy). In therapeutic nuclear medicine, targeted radiotherapy approach is followed. Here, a suitable carrier molecule is labelled with a radioisotope emitting β/γ/Auger electron. These particulate radiatons have high linear energy transfer (LET) value compared to energetic photons. Hence, they have the potential to kill the malignant cells very effectively, sparing the healthy cells around them. Table-7 lists the production routes of a few cyclotron produced radioisotopes that can be employed for this purpose.

Table 5: Diagnostic applications of few ^{124}I-radiopharmaceuticals

Radiopharmaceuticals	Application	Ref.
[^{124}I]mIBG	Cardiovascular imaging, diagnosis, and dosimetry of neuroblastoma, paraganglioma, pheochromocytoma, and carcinoids.	58
[^{124}I]-cG250 (^{124}I labelled antibody chimeric G250)	To identify renal cell cancer	59
[^{124}I]IAZG	Imaging of hypoxia in tissue	60
[^{124}I]IUdR	Functional imaging of cell proliferation	61
[^{124}I]Annexin V	Apoptosis imaging	62
[^{124}I]âCIT	Early diagnosis of Parkinson's disease	63
[^{124}I]NaI	PET imaging in thyroid gland diseases and for evaluating the spread of metastatic thyroid carcinoma	64
[^{124}I]fatty acid	PET imaging of myocardial metabolism, marker of viability	65

Abbreviations: mIBG=m-iodobenzylguanidine, IAZG= iodine azomycin galactoside, IUdR= 5- Iodo-2-deoxyuridine, âCIT= â-carbomethoxy-3â(4-iodophenyl)tropane.

Table 6: Diagnostic applications of few ^{89}Zr based radiopharmaceuticals

Radiopharmaceuticals	Application	Ref.
^{89}Zr- trastuzumab	HER2-positive breast cancer	66
^{89}Zr-cetuximab	PET surrogate radioisotope for scouting biodistribution of the therapeutic radiometals ^{90}Y and ^{177}Lu in RIT	67
^{89}Zr-labeled anti-PSMA mAb, J591	To identify and quantify PSMA-positive prostate tumours	68
^{89}Zr-cmAb (cU36)	Head and neck tumours as well as metastases in the neck; Scouting of therapeutic doses of ^{90}Y-labeled mAbs	69,70

*Abbreviations: trastuzumab = anti-HER2 mAb, cetuximab = chimeric IgG1 mAb, PSMA = prostate- specific membrane antigen, cmAb = chimeric mAb.*Additional information on some of the therapeutic radioisotopes and the applications of the radiopharmaceuticals prepared from them are given below.

^{103}Pd

^{103}Pd is used as brachytherapy source for the treatment of prostate cancer. The source is encapsulated in a tiny titanium tube to form 'seed'. These seeds are permanently implanted in the prostate. ^{125}I is also used for this purpose. However, ^{103}Pd has more favourable physical properties, including its low energy rapid dose fall-off, short half-life and total cumulative dose delivery at a higher dose rate than ^{125}I.

^{211}At

Targeted alpha therapy (TAT) is a cancer treatment modality which selectively destroys malignant cells with alpha emitter tagged with a carrier molecule such as a monoclonal antibody or a peptide. Due to the high LET of alpha particle, a large fraction of its energy is deposited in the targeted cell. ^{211}At has many attractive features for TAT. Its 7.21 h half life is well matched to the pharmacokinetics of a variety of molecular entities, including peptides, monoclonal antibody fragments, and small molecules. Several researchers have

developed the techniques of radiolabelling of a variety of targeting molecule [76]. Clinical trials have also been done on some of the ^{211}At labelled monoclonal antibodies [77, 78].

^{67}Cu

^{67}Cu is one of the best-suited radioisotopes used for radioimmunotherapy. Its 61.9 h half-life matches with the biological half-life of many antibodies and therefore good biodistribution of the RPS is obtained. Its relatively low gamma radiation abundance imparts less radiation dose to the patient as well as the medical personnel. Excellent chelating chemistry of copper makes preparation of RPS a simple procedure. Some of the RPS of ^{67}Cu developed for radioimmunotherapy are listed in the Table-8.

^{47}Sc

Nuclear properties of ^{47}Sc (half-life, 3.34 d; average β^- energy, 162 keV; Eā, 159 keV) make it a potential radioisotope for therapeutic application and for SPECT imaging. The potential of ^{47}Sc as a therapeutic radioisotope has been demonstrated recently [83] with ^{47}Sc-cm10 (cm10= DOTA-folate conjugate) in a preclinical setting. Moreover, ^{47}Sc is in particular attractive as part of the theragnostic principle together with ^{44}Sc (a potential PET imaging radioisotope), which may be used for pre-therapeutic imaging as well as therapy planning and monitoring.

^{213}Bi

^{213}Bi is a promising radioisotope for TAT. It is obtained from a radioisotope generator through the decay chain of its parent, ^{225}Ac ($t_{½}$ =10 d).This generator has an effective life of several weeks. Each decay of ^{213}Bi produces an alpha particle. The C595 and PAI2-alpha conjugates (with ^{213}Bi) are found to be suitable for the treatment of micro-metastatic pancreatic cancer with over-expression of MUC1 and uPA receptors [84]. Feasibility of targeted particle immunotherapy with ^{213}Bi for the treatment of myeloid leukemia has been reported [85]. Several pre-clinical and clinical studies show the potential of ^{213}Bi in treatment of various types of cancer [86] and infectious disease [87]

Table-7: Nuclear data and production routes of few cyclotron produced therapeutic radioisotopes

Radioisotope, $t_{½}$	Decay mode	Production route	Target	Ep, MeV	Yield μCi/μAh at EOB	Ref.
^{103}Pd, 16.99d	EC	^{103}Rh(p, n)	Nat. Rh	1621	57mCi/μA[a]625	71
^{211}At, 7.21h	EC(58)/α(42)	^{209}Bi(a, 2n)	Nat. Bi	28	1.1	72
^{67}Cu, 61.9h	β^-	^{nat}Zn(p, x)	Nat. ZnO	200	13.6	73
^{47}Sc, 3.34d	β^-	^{nat}Ti(p, x)	Nat, Ti	30	0.2[b]	74
^{213}Bi[c], 45.6min	β^- (97.8)/γ(2.2)	^{226}Ra(p,2n)^{225}Ac^{213}Bi	$^{226}RaCl_2$	16	6.2[d]	75

[a]*Yield at the end of 6 day long irradiation;* [b]Estimated from the measured cross-sections; [c]*Obtained from* ^{225}Ac-^{213}Bi *generator;* [d]*Target thickness15mg/cm^2 & yield at the end of 45h irradiation.*

Table 8: Applications of some of the radiopharmaceuticals of ^{67}Cu in radioimmunotherapy

Radiopharmaceuticals	Application	Ref.
^{67}Cu- chCE7	Neuroblastoma, ovarian, and some renal carcinoma therapy	79
^{67}Cu- Lym-1	Non-Hodgkin's lymphoma	80, 81
^{67}Cu- C595	Bladder cancer	82

Abbreviations: chCE7= anti-L1-cell adhesion molecule antibody, Lym-1= monoclonal antibody against human B cell lymphoma, C595= anti-MUC1 mucin antibody.

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Recent Advances in Radionuclide Generator Technology

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Introduction

Over the last 5 decades, radionuclide generators have attracted substantial attentions, indeed close scrutiny of the nuclear medicine community owing to their ability to provide short-lived radioisotopes without the need for on-site nuclear reactor or accelerator facilities for preparation of a myriad of diagnostic and therapeutic radiopharmaceuticals [1]. Not only do they provide no-carrier-added (NCA) radionuclides on-demand basis, but also in a cost-effective way where the payoff of benefits is substantial and invaluable [1]. Nuclear medicine and radionuclide generator feed off of one another, thereby, propelling both forward. Utility of radionuclide generators has virtually pervaded most areas of activities in the field of nuclear medicine and their importance has been well demonstrated and recognized [1].

The current importance and success of diagnostic imaging in nuclear medicine is primarily due to ^{99}Mo/^{99m}Tc generator [1]. A large number of the nuclear medicine procedures in remote areas far from the site of a cyclotron or reactor facility would not have been possible but for the availability of this radionuclide generator [1]. It would not be an exaggeration to state that the field of nuclear medicine owes its existence to the development of this generator in 1957 at Brookhaven National Laboratory in United States [1]. The subsequent years have seen an enormous increase in the use of generators such as ^{90}Sr/^{90}Y and ^{188}W/^{188}Re generators to provide therapeutic radionuclides, which has paralleled the development of complementary strategies for targeted radiotherapy [2-4]. With the recent advances in clinical positron emission tomography (PET), use of the ^{68}Ge/^{68}Ga generator is showing enormous potential as a source of positron-emitting ^{68}Ga which can be used for preparation of a wide variety of radiopharmaceuticals [5, 6].

Basic Concept of Radionuclide Generator

A radionuclide generator is a self-contained system housing an equilibrium mixture of a parent / daughter radionuclide pair [1]. The system is designed to separate the daughter radionuclide formed by the decay of a parent radionuclide by virtue of their differences in chemical properties [1]. The parent-daughter nuclear relationships offer the possibility to separate the daughter radionuclide at suitable time intervals (**Figure 1**).

In a radionuclide generator, a 'parent' radionuclide (A) decays to a 'daughter' radionuclide ($\mathbf{B}$) which further decays to stable/nearly stable 'grand-daughter' nuclide (C). In this decay scheme λ_1 is the decay constant for A having $\mathbf{N_1^0}$ initial number of atoms and λ_2 the decay constant for B. For the sake of simplicity, it is generally assumed that $N_2(t=0) = N_2^0 = 0$ and $N_3(t=0) = N_3^0 = 0$ and the grand-daughter product C, as a stable nuclide characterized by $\lambda_3 = \mathbf{0}$.

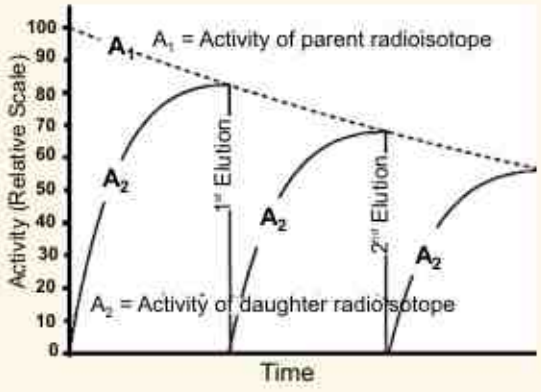

Figure 1: *Example of radionuclide daughter activity in-growth over repeated elutions. The radionuclide generator provides a reduced level of the daughter radionuclide activity by each subsequent elution.*

Then at any given time t, one can write the following differential equations:

$$dN_1(t) = -\lambda_1 N_1(t)dt \quad \text{or} \quad \frac{dN_1(t)}{dt} = A_1(t) = -\lambda_1 N_1(t) \qquad \text{.....(1)}$$

$$dN_2(t) = +\lambda_1 N_1(t)dt - \lambda_2 N_2(t)dt \quad \text{or}$$

$$\frac{dN_2(t)}{dt} = \lambda_1 N_1(t) - \lambda_2 N_2(t) \qquad \text{.....(2)}$$

$$\text{and} \qquad dN_3(t) = +\lambda_2 N_2(t)dt \quad \text{or}$$

$$\frac{dN_3(t)}{dt} = +\lambda_2 N_2(t) \qquad \text{.....(3)}$$

Equation 1 describes the rate of change of number of atoms of type A, supposing that the only source of these atoms is from the initial supply $\mathbf{N_1^0}$ at $t = 0$. Equation 2 describes the rate of change of the number of atoms of type B which is equal to the supply by the decay of atoms A corrected for the loss through its own decay. Equation 3 describes the rate of change of the number of atoms of type C fed by only the decay of atoms B (being stable, C is continuously accumulated). The solution of equation 1 leads

to the well-known decay equation of a single radionuclide i.e.:

$$N_1(t) = N_1^0 e^{-\lambda_1 t}$$ and

$$A_1(t) = \lambda_1 N_1^0 e^{-\lambda_1 t} = A_1^0 e^{-\lambda_1 t} \quad \text{.....(4)}$$

The solution of equation 2 leads to the following expression (assuming $N_2(0) = N_2^0 = 0$):

$$N_2(t) = N_1^0 \frac{\lambda_1}{\lambda_2 - \lambda_1}\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right) \quad \text{.....(5)}$$

Here, the activity $A_2(t)$ is given by the general definition of the activity. Therefore,

$$A_2(t) = \lambda_2 N_2(t) = N_1^0 \frac{\lambda_1 \lambda_2}{\lambda_2 - \lambda_1}\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right) \quad \text{.....(6)}$$

$$\text{or } A_2(t) = A_1^0 \frac{\lambda_2}{\lambda_2 - \lambda_1}\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right) \quad \text{.....(7)}$$

where, $A_1^0 = \lambda_1 N_1^0$.

Time Taken by the Daughter Radioisotope to Attain Maximum Radioactivity

The radioactivity of the daughter isotope reaches maxima when the feeding of the daughter atoms (B) exactly compensates their decay:

$$\text{i.e. when } A_1(t) = A_2(t) \quad \text{or} \quad \lambda_1 N_1(t) = \lambda_2 N_2(t)$$

$$\text{or when } \frac{dA_2(t)}{dt} = \frac{dN_2(t)}{dt} = 0 \quad \text{.....(8)}$$

Then one can write:

$$t_{max} = \frac{\ln(\lambda_2 / \lambda_1)}{\lambda_2 - \lambda_1} = \left(\frac{1.44 t_1 t_2}{t_1 - t_2}\right)\ln\left(\frac{t_1}{t_2}\right) \quad \text{.....(9)}$$

where, t_1 and t_2 are the half-lives of the parent and daughter radionuclides, respectively and t_{max} is the time taken by the daughter radioisotope to attain maximum radioactivity.

In-Growth and Isolation of Daughter Radionuclide from Parent Radionuclide

For practical considerations, radionuclide generators are eluted at periodic intervals depending on the daughter activity requirements. Often the separation of the daughter from the parent may not occur at the time the daughter activity is at its maximum as calculated using Equation (9). Owing to the decrease of the parent radionuclide activity within the time between two elution steps, the radionuclide generator is expected to provide a reduced level of the daughter radionuclide activity by each subsequent elution as shown in **Figure 1**. The growth and separation of the daughter radionuclide can be continued as long as there are useful activity levels of the parent radionuclide available. Separation may be performed any time before equilibrium is reached, and the activity levels of daughter recovered will depend on the time elapsed since the last separation. In-growth of the daughter species is continuous, and once the activity of the daughter is recovered from the mixture, the daughter activity increases until its activity level reaches a maximum and is in equilibrium with the parent radionuclide (**Figure 1**). The growth of the daughter depends on the half-life of the daughter radionuclide which also governs the frequency of its separation from the parent radionuclide. When the daughter radionuclide is relatively long-lived, periodic elution will take place prior to reaching the maximum equilibrium daughter activity levels and it is normal to use generators in this way. As an example, 50% daughter activity in-growth is detected in one half-life, 75% in two half-lives and the daughter activity reaches the activity of the parent radionuclide in 5-6 half lives.

Criteria for Selection of Parent/Daughter Pairs

While several factors contribute to the development of radionuclide generators, selection of an appropriate parent/daughter pair is a key determinant that underpins its success in nuclear medicine. While selecting a parent/daughter pair for making radionuclide generator, the following criteria need to be considered:

- ***Availability of parent radionuclide***: The production route for the parent radionuclide should be cost-effective. Parent radionuclide which exhibits attractive characteristics but lack a cost-effective production route might not be suitable for preparation of clinically useful radionuclide generators.
- ***Parent radionuclide half-life***: The physical half-life of the parent radionuclide should be long enough to ensure availability of daughter nuclide for an extended period of time.
- ***Daughter radionuclide half-life***: The physical half-life of the daughter radionuclide should be compatible with the *in vivo* pharmacokinetics of the radiolabeled targeting molecule.
- ***Emission and energy of the radiation of the daughter radionuclide***: The daughter product of a radionuclide generator will decay by any of the decay modes (isomeric transition, β^-, β^+, electron capture, γ decay) or by a combination of two or more decay modes. Consequently, the applications of generators vary depending on the decay characteristics. Gamma emitters, with gamma energy within the range of 100-250 keV are suitable for single photon emission computed tomography (SPECT) imaging. Particle emitting radionuclides (α particle, β^- particle or Auger electron emitters) are suitable for therapy. Positron (β^+) emitting radionuclides are needed for positron emission tomography (PET) imaging.

- ***Decay of daughter radionuclide***: In order to preclude radiation dose to the patient undergoing diagnosis or therapy, the daughter radionuclide should preferably decay to a stable or very long-lived product.
- ***Chemical characteristics of daughter radionuclide***: The daughter radionuclide should have chemistry amenable to its attachment with a broad class of carrier molecules and binding must exhibit high *in vivo* stability when attached to the radiopharmaceutical.

Methodologies for Separation of Daughter Radioisotope from the Parent/Daughter Equilibrium Mixture

While radionuclide generator technology "lives" at the interface of many disciplines, its dependence on separation science is arguably the strongest and is hence vital for its success. Over the last several decades, the separation methodologies applied for the development of are subjected to a continuous evolution, as indicated by the large volume of literature covering them [1, 7]. At one end of the spectrum are the current commercial systems, and at the opposite end are new concepts or processes, some of which are in the early stages of development, or perhaps as early as experiments in a research laboratory. The potentially useful separation methodologies for preparation of radionuclide generators are summarized in **Table 1**.

Quality Control of Radionuclide Generators prior to Clinical Use

Since generator derived radionuclides are intended for clinical use, it is imperative that the radionuclide generators undergo strict quality control procedures before being handed over to the nuclear medicine physicians [1]. Quality control involves specific tests and measurements that ensure the elution efficiency of the generator, product purity, biological safety and the efficacy of the radionuclide for the preparation of radiopharmaceuticals. These methods are briefly described below.

Elution efficiency of the radionuclide generator: The elution efficiency of the radionuclide generator is defined as the proportion of the daughter radioisotope present in the generator system that is separated during the elution process. Theoretically, the activity (A_2) of the daughter radioisotope present in the generator system at the time of elution is given by the equation (7). In practice, the activity of the daughter radioisotope eluted is less than that predicted by the theory. If the measured activity of the separated daughter radioisotope after allowing time 't' for its growth, is denoted by A_s, then the elution efficiency can be defined by the equation:

$$\%\,Elution\,efficiency = \frac{A_s}{A_2} \times 100 \quad \text{.....(10)}$$

For a radionuclide generator to be cost-effective, it is essential that its elution efficiency should be fairly high (not < 60%) and it should remain consistent during the stipulated period of utilization of the generator.

Radionuclidic purity of the separated daughter radioisotope: Radionuclidic purity is defined as the fraction of the total radioactivity in the form of the desired radionuclide. In the separated daughter radioisotope obtained from the radionuclide generator, the primary radionuclidic impurity that may be expected is the long-lived parent radioisotope. Sometimes, the parent radioisotope may be associated with other radionuclidic impurities which may also come in the separated daughter activity. Understandably, radionuclidic impurities are undesirable in the daughter product, as these can have various implications for its use in nuclear medicine, such as interference in the reaction for preparation of the radiopharmaceutical leading to poor yields or unwanted compounds, increase in the unwanted radiation exposure to the patient, obscure scintigraphic images, and possible radio-toxicity related issues [1]. Hence the radionuclidic purity of the intended radionuclide needs to be determined and the impurities ascertained to be well within the stipulated limits [1]. Determination of radionuclidic impurities in the separated daughter radioisotope is generally done by γ-ray spectrometry using high purity germanium detector (HPGe) detector coupled with a multi-channel analyzer [1]. This technique can be used for both qualitative as well as quantitative estimation of radionuclidic impurities in the daughter product obtained from the radionuclide generator.

Radiochemical purity of the separated daughter radioisotope: The radiochemical purity of a generator produced radionuclide may be defined as the fraction of the total radioactivity present in the desired chemical form [1]. Radiochemical impurities may arise in the daughter radionuclide during its separation from the parent or its subsequent storage due to several factors such as the action of the solvent and the effect of radiolysis, change in temperature or pH, presence of oxidizing or reducing agents [1]. The radiochemical impurities present in the daughter radionuclide may not be suitable for labeling with ligands and biomolecules. This may also affect the biological behavior of the radiopharmaceutical as the agent may not be selectively taken up by the target organs [1]. The presence of radiochemical impurities in generator produced radioisotopes can be detected and determined by various analytical methods. These include, paper chromatography, thin layer chromatography, paper electrophoresis, high performance liquid chromatography, gel filtration, gel chromatography, ion exchange chromatography, solvent extraction, inverse dilution and precipitation [1].

Chemical purity: Any unwanted chemical species (organic or inorganic) present in the daughter product is considered as chemical impurity. The presence of these chemical impurities may affect the chemistry of the radionuclide for the preparation of radiopharmaceuticals. The

chemical impurities may be introduced in the daughter radionuclide by a variety of ways. This includes the use of impure chemicals and use of radioactive parent solutions containing undesired chemicals introduced during its radiochemical processing. Also, in case of column chromatographic generators, the radiolytic or chemical degradation of the column matrix may lead to the addition of chemical impurities to the daughter radionuclide. The presence of these chemical impurities can be avoided by the use of highly pure chemicals and adoption of appropriate separation methodology. The level of these chemical impurities may be detected and determined by various analytical techniques like colorimetry, spot-tests, spectrophotometry, inductively coupled plasma atomic emission spectroscopy (ICP-AES) etc. [1].

Labeling efficacy: Generally, generator produced radionuclides are used for clinical application, only after radiolabeling a suitable ligand or a biomolecule with it. The suitability of a generator produced radionuclide for radiopharmaceutical applications can be demonstrated by its efficacy to prepare standard radiolabeled agents. This is also an indirect test of the chemical purity of the radionuclide as high chemical purity is required for the preparation of the radiolabeled agent with the NCA radionuclide.

Biological tests: Biological quality control tests are carried out to examine the sterility and apyrogenicity of the generator-produced radionuclide before the preparation of radiopharmaceuticals [1]. Sterility indicates the absence of any viable bacteria or microorganism in a radiochemical. It is essential to avail the daughter radionuclide from the generator in sterile form in order to prepare clinical grade radiopharmaceuticals. Administration of non-sterile radiopharmaceutical can cause a wide variety of infections leading to several physiological problems including death.

Pyrogens are either polysaccharides or proteins produced by metabolism of microorganisms and if present in a radiopharmaceutical can cause a wide variety of physiological problems, such as, fever, chills, malaise, leucopenia, flushing, sweating, headache and pain in joints. It is mandatory that all products intended for injection into the humans, including radiopharmaceuticals should have pyrogens below the stipulated limits. Pyrogen free radionuclides can be obtained from the generator without much difficulty using high quality chemicals and taking particular care during the preparation, operation and storage of the generator.

Shelf-Life of a Radionuclide Generator

The shelf-life of a radionuclide generator is the period for which the generator can safely be used for the designated clinical applications [1]. The shelf-life of a typical radionuclide generator is influenced by the following factors:

- Physical half-life of the parent radioisotope. The parent radioisotopes having longer physical half-lives are generally expected to have longer shelf-life.
- Generator performance which is monitored by measuring the elution yield, radioactive concentration and the purity of the daughter radioisotope.

However, the shelf-life of a radionuclide generator is also influenced by the procedure adopted for the separation of the parent-daughter pairs. The suitability of a separation procedure to withstand the effects of radiolysis and chemical degradation over a prolonged period of time enhances the shelf-life of the generator. Overall, the economics of production of short-lived radioisotopes via a radionuclide generator is decided by the shelf-life of the generator which in turn determines the cost of treatment using radiopharmaceuticals prepared using generator produced radionuclides.

Emerging Concepts in Radionuclide Generator Technology

As separation science is subject to continuous evolution, any revolutionary breakthrough in this subject represents not only an important driving force, but also lays the cornerstone towards the development of new radionuclide generators. With the emergence of professionally run centralized radiopharmacies, the use of radionuclide generator technology is pointing to an era of a paradigmatic shift from the present designs and user profiles. In order to sustain the nuclear medicine service using generator derived radionuclides, it is of utmost importance to nurture emerging separation technologies in an appropriate manner, both in absolute, as well as in relative, terms of missions, goals, and requirements, to respond to the foreseeable changes in radionuclide generator technology.

In the recent times, our group has introduced two new concepts in the field of radionuclide generators, which are poised to bring paradigm shift in nuclear medicine practices in the foreseeable future. While the first approach involves the use of electrochemical separation technique [8, 9], the second involves the use of sorbents based on nanomaterials for use as column chromatography matrices [10] for the preparation of radionuclide generators.

Electrochemical Separation

Electrochemical method provides a simple and convenient approach of performing a wide variety of metal ion separations. A mixture of metal ions having adequate difference in their formal potential values in an electrolytic medium can be mutually separated by selective electrodeposition of one metal on an electrode surface under the influence of controlled applied potential (**Figure 2**). *In-situ* electrodeposition of a daughter radionuclide is an attractive route to develop radionuclide generators. The major advantage of this approach is that the daughter radioisotope can be obtained with very high radionuclidic purity and radioactive concentration, irrespective of the specific activity of the parent radioisotope. This approach has been used for development of a variety of radionuclide generators, such as, ^{90}Sr/^{90}Y, ^{99}Mo/^{99m}Tc and ^{188}W/^{188}Re generators [8]. The

electrochemical reactions involved in the separation process are summarized in **Table 2**.

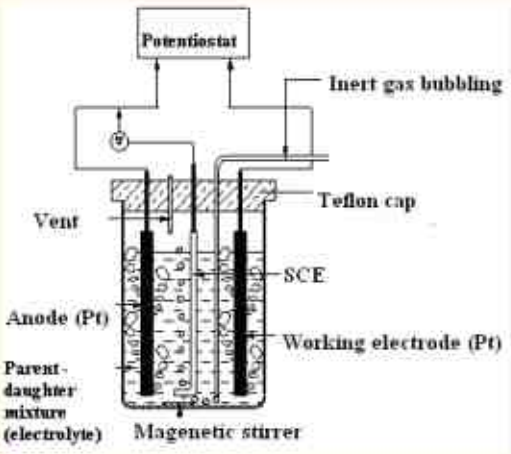

Figure 2: Schematic diagram of electrochemical radionuclide *generator*

Column Chromatography using Nanosorbents

The second approach is based on the use of nanomaterials based sorbents as column matrices for the preparation of generators relies on the unique morphological features, pore structure, high surface areas and high surface charge of nanomaterials [1,10]. Such sorbents demonstrate much higher sorption capacity and selectivity for sorption of the parent radioisotope compared to their bulk counterparts. The daughter activity can be obtained with appreciably high radioactive concentration and purity suitable for biomedical applications. Over the last 10 years, a wide variety of nanostructured metal oxides such as polymer embedded nanocrystalline titania (TiP), mixed phase nanocrystalline zirconia (nano-ZrO_2), tetragonal nanozircona (t-ZrO_2), nanocrystalline γ-alumina (γ-Al_2O_3), mesoporous alumina (MA) and nanoceria-polyacrylonitrile (CeO_2-PAN) composite have been synthesized by our group for preparation of ^{99}Mo/^{99m}Tc, ^{188}W/^{188}Re and ^{68}Ge/^{68}Ga generators (**Figure 3**) [10]. Synthesis procedures adopted and structural characteristics of these nanosorbents are summarized in **Table 3**. It is pertinent to point out that in case of all the nanosorbents used for preparation of radionuclide generators, the synthesis methods adopted were neither cumbersome nor used expensive precursors and was amenable for scale-up. All these nanomaterials exhibited good mechanical strength, granular properties and were amenable for column operations. However, all these sorbents consist of agglomerated nanoparticles (**Figure 4**). Agglomeration to a certain extent is essential for use of such materials as sorbent matrices in chromatographic columns. Very fine particles without agglomeration are not suitable for column chromatographic application as such materials are impervious to the flow of liquid through the column bed.

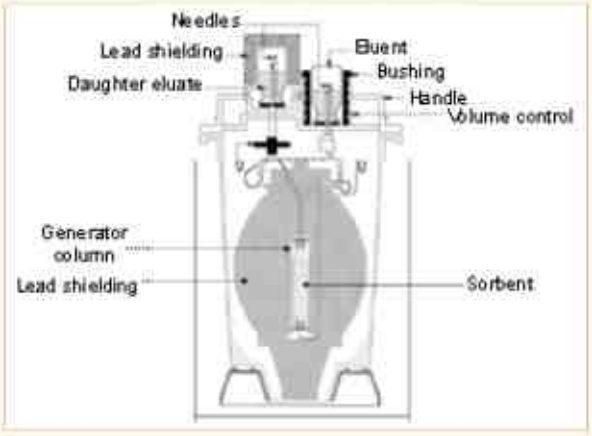

Figure 3: Schematic diagram of column chromatographic radionuclide generator.

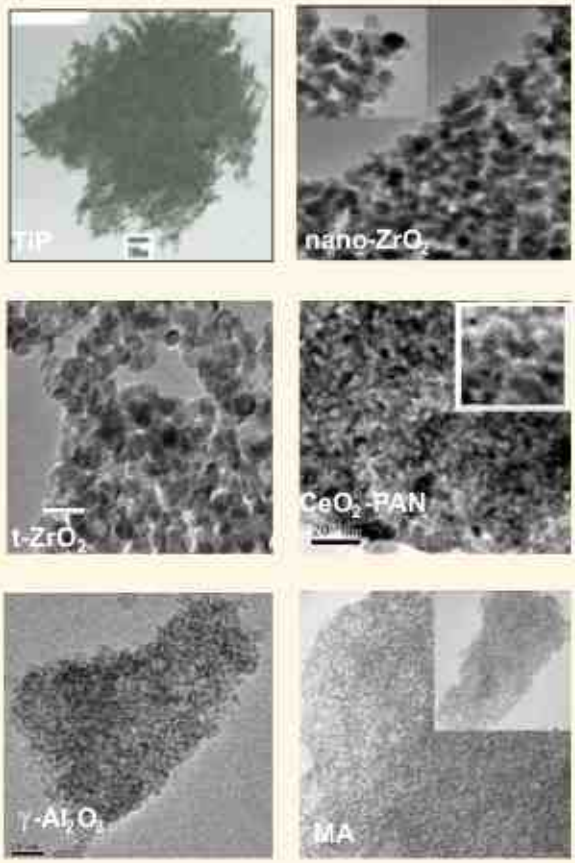

Figure 4: TEM *micrographs of nanosorbents used in preparation of column chromatographic radionuclide generators.*

The following sub sections provide an overview of the clinically useful radionuclide generators developed using the novel separation chemistry approaches described above.

^{99}Mo/^{99m}Tc generator

Over the last 5 decades, a variety of ^{99m}Tc/^{99}Mo generator systems have been thoroughly investigated all over the world due to the everlasting demand for ^{99m}Tc, which is the most

commonly used medical radioisotope [1, 3]. This radioisotope is considered as the 'workhorse' of diagnostic nuclear medicine and is used for approximately 20–25 million procedures annually, comprising ~80% of all diagnostic nuclear medicine procedures. The widespread interest in clinical utilization of this radioisotope is attributed to its attractive nuclear decay characteristics ($t_{½}$ = 6 h, emission of 140 keV γ-photon), convenient availability from ^{99}Mo/^{99m}Tc generator, versatile coordination chemistry of ^{99m}Tc for preparation of wide variety of radiopharmaceuticals and commercial availability of lyophilized 'cold' kits which offer a cost-effective route for preparation of these radiopharmaceuticals suitable for human administration. The column chromatographic ^{99m}Tc/^{99}Mo generator using a bed of acidic alumina has emerged as the most popular choice for availing ^{99m}Tc in nuclear medicine departments worldwide [3]. However, the capacity of bulk alumina for taking up molybdate ions is limited (2–20 mg Mo per gram of alumina), necessitating the use of NCA ^{99}Mo produced through fission route [3]. Owing to the inherent complexities in production of fission ^{99}Mo and the vulnerability of irradiation services from 5 old research reactors which are currently in use for fission ^{99}Mo production, there is an increasing consensus to use low specific activity ^{99}Mo produced through the neutron activation route [(n,γ)^{99}Mo] for preparation of clinically useful ^{99}Mo/^{99m}Tc generators [3, 11]. However, the specific activity of (n,γ) ^{99}Mo is at least 1000-fold lesser than that of fission ^{99}Mo and is therefore not suitable for preparation of bulk alumina based column chromatographic generators [3].

In order to reduce reliance on fission ^{99}Mo, our group demonstrated for the first time the utility of electrochemical separation approach for preparation of clinical scale ^{99}Mo/^{99m}Tc generator [12]. This is primarily based on the selective electrodeposition of ^{99m}Tc on a platinum electrode by taking advantage of the difference in formal electrode potentials of MoO_4^{2-} and TcO_4^- ions in alkaline media. The preferential electodeposition of ^{99m}Tc relies on applying a potential of 5 V in 0.1 M NaOH medium for 45 min. With a view to recover the ^{99m}Tc deposit on the cathode, electrolysis was carried out in saline solution by reversing the polarity of the electrode and application of a high positive potential for a few seconds. In this process, the ^{99m}Tc deposit could be quantitatively brought into saline solution, wherein ^{99m}Tc existed as $^{99m}TcO_4^-$. It was demonstrated that the process was suitable for the separation of clinically useful ^{99m}Tc, even from very low specific activity (<1.85 GBq/mg) ^{99}Mo.

Our group also demonstrated for the first time, the utility of nanosorbents such as TiP, t-ZrO_2, (γAl_2O_3 and MA for preparation of clinical scale ^{99}Mo/^{99m}Tc generators [10, 13-15]. Recently, a comparative evaluation of the performance of the different nanosorbents reported was carried out to identify the best choice for preparation of ^{99}Mo/^{99m}Tc generators using (n,γ)^{99}Mo [16]. Though, ^{99}Mo/^{99m}Tc generators prepared using any of the nanosorbents met the requirements for use in preparation of radiopharmaceuticals, MA and γ-Al_2O_3 were identified as the best choices in view of their higher sorption capacities (~ 160 mg Mo/g) which could be used for preparation of clinical-scale ^{99}Mo/^{99m}Tc generator even while using (n,γ) ^{99}Mo produced in medium flux reactors.

The performances of the ^{99}Mo/^{99m}Tc generators prepared by both the approaches remained consistent over a period of 2 weeks, which is comparable to the shelf life of the commercially available (fission ^{99}Mo based) ^{99}Mo/^{99m}Tc generators. ^{99m}Tc could be obtained with >99.99 % radionuclidic purity and the compatibility of the product in the preparation of ^{99m}Tc-labeled formulations were found to be satisfactory.

^{68}Ge/^{68}Ga generator

The ^{68}Ge/^{68}Ga generator is an excellent source for availing ^{68}Ga ($t_{½}$ = 68 min), which is a positron emitter, with 89% positron branching accompanied by low photon emission (1,077 keV, 3.22%) [1, 5]. The cyclotron-independent availability of ^{68}Ga from this generator in an ionic form has led to the development of a wide variety of ^{68}Ga-based radiopharmaceuticals, which have opened new horizons for molecular diagnostics using PET. Despite excellent attributes of ^{68}Ga-radiopharmacy, the low radioactive concentration, high acidity, unacceptable ^{68}Ge breakthrough, and the presence of potential metal ion impurities in the generator eluate have emerged as the major deterrents towards preparation of ^{68}Ga-based radiopharmaceuticals using ^{68}Ga eluted from most of the ^{68}Ge/^{68}Ga generators available in the market [5]. Also, most of these generator systems demonstrate deteriorating performance in terms of increased ^{68}Ge breakthrough and reduced ^{68}Ga elution yield on repeated elutions over a prolonged period of time [5]. These limitations could be circumvented with the availability of 'state-of-the-art' automated modules for post-elution processing of ^{68}Ga eluate and subsequent radiopharmaceutical preparation [5]. However, these automated modules are highly expensive and increases the production cost of ^{68}Ga-based radiopharmaceuticals.

The development of ^{68}Ge/^{68}Ga generators which could directly be used for preparation of radiopharmaceuticals without the need for post-elution processing of ^{68}Ga was first reported by our group. CeO_2-PAN and t-ZrO_2 was used as sorbent matrices in these generators [6, 17]. Gallium-68 could be regularly eluted from these generators with > 70% elution yield with high radionuclidic purity (<1 × 10^{-5} % of ^{68}Ge impurity), chemical purity (<0.1 ppm of Ce, Ti, Ni, Fe and Mn ions) and was directly amenable for the preparation of ^{68}Ga-labeled radiopharmaceuticals. The performances of the generators were evaluated for a period of 1 year. The generators gave consistent performance with respect to the elution yield and purity of ^{68}Ga throughout the period of investigation. The CeO_2-PAN based ^{68}Ge/^{68}Ga generator (named as 'BARC' ^{68}Ge/^{68}Ga generator) was deployed in Tata Memorial Hospital (TMH), Mumbai (**Figure 5**), where it was successfully used for preparation of clinically relevant doses of ^{68}Ga-based radiopharmaceuticals for cancer diagnosis

using PET.

Figure 5: 'BARC' $^{68}Ge/^{68}Ga$ generator supplied to TMH, Mumbai for clinical studies.

$^{90}Sr/^{90}Y$ generator

Yttrium-90 is a therapeutic radioisotope of enormous interest and radiopharmaceuticals based on ^{90}Y are widely used for the treatment of cancer as well as in radiation synoviorthesis [4]. The broad interest in the use of ^{90}Y in therapeutic nuclear medicine is due to its suitable nuclear characteristics ($t_{½}$ = 64.1 h, $E_{\beta max}$ = 2.28 MeV, no γ emission) and M (+3) coordination chemistry suitable for complexation with various ligands and biomolecules. A radionuclide generator system based on the secular equilibrium of ^{90}Sr decaying to ^{90}Y is a convenient method for the production of high specific activity ^{90}Y [4].

Over the past three decades, several separation techniques were reported for the development of $^{90}Sr/^{90}Y$ generators [4]. Most of these separation techniques involve multiple steps employing conventional separation approaches such as solvent extraction, ion exchange or extraction chromatography either alone or in combination. However, none of these procedures are amenable for regular use in a hospital radiopharmacy or in a centralized radiopharmacy. This is primarily because the level of ^{90}Sr impurity in ^{90}Y obtained from these systems does not meet the requirements prescribed in the pharmacopoeias for clinical use [4]. In view of the necessity to achieve a satisfactory degree of separation of ^{90}Y from ^{90}Sr, resorting to two-step electrochemical separation procedure was found to be effective [18]. The separation of Y from a mixture of Sr and Y is based on the selective electrodeposition of Y on a platinum electrode attributed to the difference in formal electrode potential of Sr^{2+} and Y^{3+} ions in acidic media. This enabled extraordinarily high decontamination factors ($^{90}Sr/^{90}Y$ activity ratio $<10^{-5}$) to be achieved and ^{90}Y was obtained in a form suitable for preparation of radiopharmaceuticals.

Figure 6: Automated electrochemical $^{90}Sr/^{90}Y$ generator (Kamadhenu)

Adopting the process chemistry developed by our group, a fully automated electrochemical module for the electrochemical $^{90}Sr/^{90}Y$ generator (named as 'Kamadhenu') was developed (**Figure 6**) and is commercially available from Isotope Technologies Dresden (ITD), Germany. The automated module is already in operation in some countries. The above module is designed for the production of up to 37 GBq (1 Ci) of ^{90}Y per day.

$^{188}W/^{188}Re$ generator

The $^{188}W/^{188}Re$ generator is an excellent source for availing NCA grade ^{188}Re, which has immense potential for use in therapeutic nuclear medicine [2,19]. The pre-eminence of this radioisotope is primarily due its excellent nuclear decay characteristics [reasonable half-life (16.9 h), high-energy beta radiation ($E_{\beta max}$ = 2.118MeV), 155 keV (15.8% abundance) suitable for scintigraphic imaging and dosimetry] and convenient on-site availability from $^{188}W/^{188}Re$ generators [2]. The chemistry of Re is similar to that of Tc since they belong to the same group in the periodic table, and this is an additional advantage towards preparing therapeutic analogues with molecules that have shown promising results in diagnosis as ^{99m}Tc-radiopharmaceuticals. Most of the separation methodologies which have been reported for $^{99}Mo/^{99m}Tc$ generators have also been exploited for preparation of $^{188}W/^{188}Re$ generators [2]. Out of these procedures, the alumina based column chromatographic approach wherein ^{188}W is absorbed on bulk alumina matrix and ^{188}Re is selectively eluted using saline solution at regular intervals, has been identified as the most reliable method for the preparation of $^{188}W/^{188}Re$ generator [19]. Owing to the limited sorption capacity of bulk alumina (~50 mg W/g), clinical-scale $^{188}W/^{188}Re$ generator can only be prepared using high specific activity (150-190 GBq/g) ^{188}W that can be produced in only very few high flux (~10^{15} $n.cm^{-2}.s^{-1}$) reactors available in the world [2]. Even while using high specific activity ^{188}W produced in these reactors, the $^{188}W/^{188}Re$ generators currently available yield low specific volume (activity/mL) of ^{188}Re and require post-elution concentration procedures prior to radiopharmaceutical preparation which is not always very convenient to perform in hospital radiopharmacies [2]. From this perspective, it is desirable to develop $^{188}W/^{188}Re$ generators where the

concentration step can be avoided to simplify the operational procedure for their widespread clinical utility.

Our group has exploited the utility of electrochemical separation approach for preparation of $^{188}W/^{188}Re$ generator [20]. Electrolysis was carried out in oxalic acid medium by applying a potential of 7 V for 45 min, using platinum electrodes. The presence of oxalate ions in the electrolyte helps in enhancing the reduction of ReO_4^- ions through formation of a 1:1 rhenium"oxalato complex. The ^{188}Re deposit on the electrode was dissolved in 0.1 M HCl to yield perrhennic acid, which was neutralized and passed through an alumina column for further purification. The recovered ^{188}Re had high radiochemical (>97%) and radionuclidic purity (>99.99%) and was suitable for radiolabeling various biomolecules. Repeated electrochemical separation of ^{188}Re from the same stock solution of ^{188}W could be demonstrated for a period of 6 months and reproducible results were obtained.

The feasibility of developing clinical scale $^{188}W/^{188}Re$ column chromatographic generators using nanosorbents such as TiP, nano-ZrO_2 and γ-Al_2O_3 was also explored in our laboratory [1, 21]. A comparative evaluation of the nanosorbents was carried out and γ-Al_2O_3 was identified as the best choice for preparation of $^{188}W/^{188}Re$ generator since this material exhibited highest sorption capacity for ^{188}W ions (300 mg W/g) [1, 22]. Leaving aside the difference in sorption capacity, all the generators developed using nanosorbents yielded ^{188}Re with high radiochemical (>99%) and radionuclidic purity (>99.99%) and were suitable for use in clinical context without post-elution concentration and purification procedures.

Conclusions

In summary, emerging concepts in radionuclide generator technology has been described, which are expected to make captivating advances in the field of nuclear medicine. The electrochemical separation approach was demonstrated as an innovative strategy for the development of clinically useful $^{90}Sr/^{90}Y$, $^{188}W/^{188}Re$ and $^{99}Mo/^{99m}Tc$ radionuclide generators. Compared with conventional methods, the electrochemical method provides higher yields as well as higher radioactive concentration of the daughter product, good reproducibility and acceptable product purity. Also, the recent advances in material science have paved the way for synthesis of a wide variety of nanosorbents through different routes to obtain tailored sizes, shapes and distributions. These nanosorbents have been used for preparation of clinically useful $^{68}Ge/^{68}Ga$, $^{188}W/^{188}Re$ and $^{99}Mo/^{99m}Tc$ radionuclide generators. The utility of $^{68}Ge/^{68}Ga$ generator prepared using nanosorbents has actually been demonstrated for cancer imaging at Tata Memorial Hospital, Mumbai.

While the advances made so far are exciting and efforts to develop new generation of radionuclide generators are evolving persistently, we still have a long way to go in terms of regular utilization of these novel generator systems in clinical context. Completing the technology development as well as establishing the economics of the approach is the cornerstone for the survival and strength of such new approaches. Nevertheless, with sustained efforts of all stakeholders, including, radiopharmacists, radiochemists, system designers, automation engineers, nuclear medicine physicians and regulators, the technological and regulatory barriers can be surmounted and the potential rewards at the end are expected to be substantial.

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Table 1: Potentially useful separation methodologies for radionuclide generators

Separation method	**Physical/ chemical property for parent daughter separation**	**Basis**	**Typical examples of radionuclide generators**
Column chromatography	Charge	Difference in adsorption on an adsorbent.	^{99}Mo/^{99m}Tc, ^{68}Ge/^{68}Ga, ^{188}W/^{188}Re, ^{90}Sr/^{90}Y
Solvent extraction	Hydrophobicity	Difference in solubility in two phases.	^{99}Mo/^{99m}Tc, ^{90}Sr/^{90}Y
Sublimation	Vapor pressure	Difference in vapor pressure.	^{99}Mo/^{99m}Tc
Thermochromatography	Vapor pressure	Difference in relative volatility.	^{99}Mo/^{99m}Tc
Precipitation	Solubility	Difference in solubility product.	^{90}Sr/^{90}Y
Solid-phase column extraction	Hydrophobicity	Difference in affinity.	^{99}Mo/^{99m}Tc
Electrochemical	Standard electrode potential (E^o)	Difference in standard or formal electrode potential.	^{99}Mo/^{99m}Tc, ^{188}W/^{188}Re, ^{90}Sr/^{90}Y
Extraction chromatography	Specific chemical interaction	Difference in affinity of solutes dissolved in a liquid for an extractant immobilized in solid.	^{99}Mo/^{99m}Tc, ^{90}Sr/^{90}Y
Supported liquid membrane (SLM)	Chemical energy	Difference in solubility on the liquid membrane.	^{99}Mo/^{99m}Tc, ^{90}Sr/^{90}Y

Table 2: The radionuclide generator systems developed by the electrochemical separation approach

Generator system	**^{90}Sr/^{90}Y**	**^{188}W/^{188}Re**	**^{99}Mo/^{99m}Tc**
Parent production	^{235}U(n,f)^{90}Sr	^{186}W(n,γ)^{187}W(n,γ)^{188}W	^{98}Mo(n,γ)^{99}Mo
Electrochemical reactions	$Sr^{2+} + 2e \rightarrow Sr$ $E^o = -2.89$ V $Y^{3+} + 3e \rightarrow Y$ $E^o = -2.27$ V	$WO_3 + 6H^+ + 6e \rightarrow W + 3H_2O$ $E^o = -0.090$ V $ReO_4^- + 8H^+ + 7e \rightarrow Re + 4H_2O$ $E^o = +0.362$ V	$MoO_4^{2-} + 4H_2O + 6e \rightarrow Mo + 8OH^-$ $E^o = -1.05$ V $TcO_4^- + 4H^+ + 3e \rightarrow TcO_2 + 2H_2O$ $E^o = +0.738$ V
	Daughter is selectively electrodeposited by careful control of applied potential		

Table 3: Synthesis and structural characterization of nanosorbents reported for preparation of column chromatographic radionuclide generators

Nanosorbent	Synthesis method	Structural characteristics	Radionuclide generators reported using this material
TiP	Controlled hydrolysis of $TiCl_4$ in isopropyl alcohol medium	Nanocrystalline, rutile phase, 5 nm crystallite size, surface area ~ 30 m^2/g	$^{99}Mo/^{99m}Tc$, $^{188}W/^{188}Re$
nano-ZrO_2	Controlled hydrolysis of $ZrOCl_2.8H_2O$ in isopropyl alcohol medium	Nanocrystalline, biphasic with monoclinic phase as major, 15 nm crystallite size, surface area ~ 45 m^2/g	$^{188}W/^{188}Re$
t-ZrO_2	Controlled hydrolysis of $ZrOCl_2.8H_2O$ in ammonical medium	Nanocrystalline, tetragonal phase, 7 nm crystallite size, surface area ~ 340 m^2/g	$^{99}Mo/^{99m}Tc$, $^{68}Ge/^{68}Ga$
γ-Al_2O_3	Mechanochemical reaction of aluminum nitrate with ammonium carbonate	Nanocrystalline, γ-phase, 2 nm crystallite size, surface area ~ 250 m^2/g	$^{99}Mo/^{99m}Tc$, $^{188}W/^{188}Re$
MA	Controlled hydrolysis of aluminum isopropoxide using glucose template	Nanocrystalline, γ-phase, 2-3 nm crystallite size, surface area ~ 230 m^2/g	$^{99}Mo/^{99m}Tc$
CeO_2-PAN	Decomposition of cerium oxalate precursor followed by incorporation in polyacrylonitrile matrix	Nanocrystalline, 10 nm crystallite size, surface area ~ 70 m^2/g	$^{68}Ge/^{68}Ga$

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