PRODUCTION AND DEVELOPMENT OF RADIOISOTOPES IN HANARO

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1. INTRODUCTION

Radioisotopes (RIs) are extensively used in numerous ways for medical, scientific, agricultural, and industrial purposes. The global demand for RIs is increasing rapidly. Nowadays, utilizing radioisotopes in such application fields is considered one of the key technologies in the radiation-related industry.

Commercial applications are persistently extended with the industrial development. Approximately 3800 organizations use radioisotopes for their businesses in Korea. As a sole organization equipped with a research reactor, Korea Atomic Energy Research Institute (KAERI) is the main manufacture of radioisotopes. The nation-wide demand of RI in 2008 was approximately 395 kCi. Such consumed RIs are mostly for industrial usages when it is estimated by radioactivity basis, but it is for medical usages by cost basis.

The history of the production of radioisotopes in Korea started in 1962 when the first research reactor, TRIGA Mark II, went into operation. After only few years of the operation of the reactor, KAERI could successfully produce iodine-131. The second landmark in the history of Korea’s radioisotope production is the operation of Korea’s second research reactor, TRIGA Mark III, in 1972. With this reactor, KAERI could produce several radioisotopes on a practical scale to meet domestic demands. Based on such accumulated technologies and experiences, the production of radioisotopes in Korea became flourishing right after the construction of the multi-purpose high performance reactor, HANARO (30 MW) and a new radioisotope production facility in 1997. Both HANARO and the other related facilities have been actively utilized to meet the local demand of radioisotopes in medicine, industry, and other research areas. In addition, such a successful local production capability has promoted the development of radiolabelled compounds and new medical applications. Also, such activities at KAERI stabilize the local prices of the radioisotope products.

The goal of this paper is to review the current activities at HANARO for the radioisotope production and related research activities in Korea, Also, the future directions in radioisotope production and its applications are described.

2. RI PRODUCTION AND RESEARCH INFRASTRUCTURE

2.1. Reactor and tools for neutron irradiation

At present, a significant amount of radioisotopes are produced from HANARO at KAERI. HANARO has a full power of 30 MW thermal capacity and a high neutron flux up to 5×10^{14} $cm^{-2}s^{-1}$. This reactor is designed to meet the various research needs and requirements including radioisotope production. After the initial criticality in 1995, much instrumentation around HANARO has been completed, and it is still being equipped for various research works in addition to the production of radioisotopes. The successful operation of HANARO could be possible upon KAERI’s human power build-up from the operation of TRIGA Mark-II (250 kW_t) and TRIGA Mark-III (2 MW_t) for 30 years. These two previous reactors were shutdown in 1996 and under the decontamination and decommissioning stages.

HANARO is an open tank type reactor cooled with light water. There are 28 irradiation holes for radioisotope production (Table 1). Since the neutron fluxes in the IR and OR holes are high, these holes are employed for the production of radioisotopes at high specific activities. A hydraulic transfer system and a LH (large hole) irradiation hole for an on-power irradiation have been installed and are used to produce short-lived radioisotopes.

TABLE 1. IRRADIATION HOLES IN HANARO FOR RI PRODUCTION

Region	Symbol	Number of holes	Thermal neutron flux ($cm^{-2}s^{-1}$)
Inner-core	CT	1	~4.0×10^{14}
	IR	2	3.0~4.0×10^{14}
Outer-core	OR	4	2.2~3.0×10^{14}
Reflector	HTS	1	8.0×10^{13}
	IP	17	2.5×10^{13}~1.5×10^{14}
	LH	1	8.5×10^{13}

Many devices and tools required for the target irradiation have also been developed. Capsules and rigs for irradiation holes were designed specifically to fit HANARO. All safety cautions were considered and verified in the development of the IR and OR rigs. Various transportation containers for the irradiated targets and the final products have been developed. Other tools for handling targets, capsules, and radioactive materials in the hot cells and in the water pool of the reactor have developed for an easy operation, safety, and minimal radiation doses.

2.1.1. Radioisotope production facilities

The radioisotope production facilities (RIPF) were installed in a three story building next to the HANARO reactor building in 1997. Total space of this building is about 9000 m^2, which accommodates the hot cells, a storage pool, clean rooms, laboratories, etc.

Hot cells are installed in four banks depending on the characteristics of radioisotopes that are handled in the banks. The first bank has 4 hot cells with 1.2 m thick heavy concrete walls and a water pool 5.7 m deep for ^{60}Co storage. These hot cells are employed in the production of the industrial sealed sources such as ^{192}Ir and ^{60}Co. Bank II has 11 lead hot cells each equipped with two manipulators. These hot cells are employed for the production of radioisotopes such as ^{32}P, ^{166}Ho, ^{51}Cr, etc. and other research works. The shielding thicknesses of these hot cells are from 10 to 15 cm. In Bank III, there are 6 lead hot cells for the production of medical radioisotopes. These hot cells are employed for the production of the ^{131}I, ^{125}I solution and labeled compounds such as ^{131}I-mIBG. Bank IV is in commercial operation for the production of ^{99m}Tc generators. One hundred twenty radionuclides are selected to be handled in the facility. More than 400 kCi/yr of the radioisotopes can be treated at this facility. At the second floor of RIPF, research laboratories and a production line of labeled compounds and ^{99m}Tc cold kits are installed.

2.2. Production of radioisotopes

KAERI have supplied radioisotopes and cold kits since 1967. Series of radioisotopes have now been produced on a regular basis by utilizing the HANARO reactor, and they are supplied to domestic users. Such radioisotopes are ^{131}I, ^{99m}Tc, ^{166}Ho, ^{192}Ir, ^{60}Co, ^{32}P, and ^{51}Cr. Also various cold kits for ^{99m}Tc and labeling compounds have been produced. In 2009, the total amounts of supplied radioisotopes and cold kits to domestic users were approximately 177 kCi (Table 2) and 6,400 vials (Table 3), respectively.

To produce a high quality ^{131}I, a dry distillation process for TeO_2 targets was developed in 1992. Approximately 60 Ci/batch of high quality ^{131}I solution can be produced. The ^{131}I solutions are distributed to the users in small solution packs and therapeutic capsules in activities from 30 to 200 mCi. Currently, KAERI supplies more than 20 Ci of ^{131}I capsules and solutions every week, covering about 60% of domestic demand.

To supply ^{99m}Tc generators, a generator loading facility (GLF) was installed at KAERI in 2003. The facility is being administered by a private company, Samyoung Unitec. Co. It is in the operation for the commercial supply of ^{99}Mo/^{99m}Tc generators at 200 to 1500 mCi activities using the fission ^{99}Mo imported from South Africa (NTP). Recently, the production from this facility covers about 80% of the domestic needs. Also, some of generators are supplied to other countries. Alternatively, KAERI is maintaining a solvent extraction method to produce ^{99m}Tc from the ^{99}Mo produced from HANARO by the activation method. The purpose of maintaining this method is to secure the supply ^{99m}Tc to the domestic market when the foreign supply of ^{99}Mo is stopped. The production capacity by this method is about 10 Ci ^{99}Mo equivalent.

For the non-destructive testing (NDT) applications, routine production system of the ^{192}Ir sealed sources was established in 2001. The activity of this NDT sources ranges from 50 to 100 Ci. Total produced activity in 2009 was 172 kCi which covered more than 90% of the domestic demand and also exported. As another sealed source, several ^{60}Co gauge sources were produced and supplied for process and quality control in the industrial sector.

The medical labeled compounds including the ^{99m}Tc cold kits are regularly produced. Various ^{131}I labeled compounds, ^{32}P, and ^{51}Cr are also supplied for research purposes. The ^{166}Ho compounds for cancer therapy were supplied to several hospitals for clinical trials. For the quality assurance of the final products, the ISO 9001:2000 certificate was achieved and has been applied to radioisotope production.

TABLE 2. PRODUCTION OF RIDIOISOTOPES AT KAERI [1]

Radioisotope	Chemical Form or Shape	Activity (mCi)
^{131}I	NaI solution	97 323
	NaI capsule	873 960
^{99m}Tc	$NaTcO_4$	43 300
^{192}Ir	Seed (for brachtheraphy)	34 630
^{192}Ir	Disc (for NDT)	172 231 580
^{60}Co	Metal (for gauge)	4 310
^{32}P	H_3PO_4	2
^{51}Cr	Na_2CrO_4	8
^{198}Au	Seed (for brachtheraphy)	4864
Total		177 617 871

TABLE 3. PRODUCTION OF LABELED/LABELING COMPOUNDS AT KAERI [1]

Radioisotopes		Quantity
Radionuclides	Chemical form	
^{131}I	m I B G	6574 mCi
^{166}Ho	CHICO	100 mCi
^{99m}Tc	MDP	1620 vials
	DMSA	15 vials
	Mebropenin	4765 vials
Total		6674 mCi 6400 vials

2.3. Research activities

During last few years, the research topics were the development of the production technologies for therapeutic beta emitters, generator systems, and industrial gauge sources. Also, research activities to expand the applications of medical sealed sources were being actively undertaken such as the use of a ^{32}P sealed source as an ophthalmic applicator.

Current research interests are on the development of ^{99m}Tc generator which uses activated molybdenum and applying the technologies developed during last years for the production of therapeutic radioisotopes at a real scale. [2]

2.3.1. Medical radioisotopes

2.3.1.1. $^{188}W/^{188}Re$ generator [3]

A novel adsorbent is developed specifically for the chromatographic generators, such as $^{188}W/^{188}Re$ and $^{99}Mo/^{99m}Tc$ generators. In this research, the adsorbent is successfully applied to $^{188}W/^{188}Re$ generator and demonstrated for the possibility of commercial production. Synthesis of the adsorbent is performed by a sol-gel processing to produce an alumina with sulfate functional groups on the pore surface. The sulfate groups are exchanged when the groups react with tungstate ions in an aqueous solution. Through this chemical mechanism, this adsorbent can adsorb more than 500 mg of tungsten on a gram of the adsorbent. This adsorption capacity is exceptionally high to produce 30 times smaller generator columns than that produced by ever available technology. The performance of this adsorbent is demonstrated for one Ci of $^{188}W/^{188}Re$ generator. The quality of the ^{188}Re from the reactor is better than any other available generators. Several application research works by using the developed generator are reported by a radiopharmaceutical group at KAERI.

This technology is patented in the nation and pending in the USA. Also, this achievement is nominated as one of the hundred outstanding research results in the nation. Currently, this technology is transferred to a private company for commercialization.

2.3.1.2. $^{90}Sr/^{90}Y$ generator system

Development of $^{90}Sr/^{90}Y$ generator system is attempted for the first time in the nation, even though the importance of ^{90}Y has been well known for several years. This research aimed to develop such generator system that can produce a radiopharmaceutical grade ^{90}Y. The developed separation materials for ^{90}Sr and ^{90}Y are organo-ceramic hybrid materials functionalized by organophosphrus groups. Current technology level of KAERI can be represented by 70% separation yield of ^{90}Y from ^{90}Sr/^{90}Y solution with the impurity ratio (^{90}Sr/^{90}Y ratio in ^{90}Y product) of 10^{-10}. This impurity ratio is at least 10 000 times less than radiopharmaceutical grade (2×10^{-6} or less). By using such purer ^{90}Y, one can minimize the toxicity of ^{90}Sr when ^{90}Y is applied to the patients.

A pilot generator system is developed in a capacity of 500 mCi of ^{90}Sr/^{90}Y. It is expected to construct a production plant for the regular supply of ^{90}Y at a extended quantity in near future. The developed technology is protected by two domestic patents and one international PCT patent applications.

2.3.1.3. Carrier free ^{177}Lu production

Among the radiolanthanides, ^{177}Lu have received special interest as it has appropriate beta energy for the targeted therapy. In this regard, the development of separation technology including adsorbents to produce ^{177}Lu is attempted. Main research activities for this topic are the development of the selective and efficient adsorbents for ^{177}Lu from Yb/Lu ionic solutions, the optimization of the separation process, and the construction of a remote production system at a laboratory scale. Through these activities, a currie quantity of ^{177}Lu is successfully produced from a tenth milligram of ytterbium target.

By using the developed adsorbent with an optimized process, the yield of ^{177}Lu is as high as 80% after 11 hours of the process. The yield of ^{177}Lu from this study is higher than that by commercially available chemical process. The quality of the produced ^{177}Lu is compatible with a commercially available one.

2.3.1.4. ^{99m}Tc generator using activated ^{99}Mo

As one of the alternative options to secure the supply of ^{99m}Tc, a research project to develop a ^{99m}Tc generator using activated ^{99}Mo is undergoing. This project is not aiming to replace the conventional ^{99m}Tc generator. However, it is proposed to develop an alternative generator technology when ^{99m}Tc supply becomes critical. Based on the availability of the irradiation holes at HANARO and the generator column material, it is estimated that the production of 500 mCi ^{99m}Tc generator with a 6 day reference is possible. The column material for ^{99m}Tc generator is the same material that is employed for ^{188}W/^{188}Re generator. By using this material, one can simply apply the same loading scheme that is normally applied for the conventional generator production by using the fission molybdenum. This research project is just about demonstrated at a real scale, such as at a level of few hundreds mCis. The research results will be published in near future.

2.3.2. Sealed sources

2.3.2.1. β ray sealed sources for thickness measurement and brachytherapy

β ray sealed sources have been used widely in the industries of paper, pulp, plastics, steel, environment, etc. However, all such sources have never been developed domestically but relied on the import. Hence, such sources are designed and developed to localize the production. The source frame is stainless steel at a specific geometry that provides strong refinement of the active source. The windows are micro-thin stainless steel sheet through which β-rays are emitted. The radiation core is made of a ceramic plate, which is fabricated by forming a zirconia. The radioactive source is produced by absorption of ^{90}Sr or ^{32}P solutions to the core plate.

These β ray sealed sources are tested by ISO 2919:1999(E) and 9978:1999(E) standards at the conditions of low temperature, heating, low and high pressures, impact, leaching, and vibration. Through these tests, the mechanical safety of the sources is proven, and KOLAS certificate is received. Specially, the thickness gauge source will be installed to the KAERI's measurement system, which is recently developed for the fabric thickness measurement.

Similar to the thickness gauge source, a medical beta source for the postoperative β irradiation after pterygium excision is designed. Recently, it was reported that β irradiation substantially reduced the risk of surgical failure after glaucoma surgery. Pure β irradiation using a $^{90}Sr/^{90}Y$ applicator has been almost exclusively used for this purpose. As an alternative to $^{90}Sr/^{90}Y$-irradiation, it is proposed to uses a ^{32}P source. While ^{32}P has a lower maximum energy [1.71 MeV] than $^{90}Sr/^{90}Y$ [2.27 MeV], it has an average energy comparable to that of $^{90}Sr/^{90}Y$. Hence, the potential use of ^{32}P source is evaluated by using Monte Carlo simulation and then the source is designed and produced. The results show that the ^{32}P ophthalmic applicator can be used to treat eye diseases such as pterygium and glaucoma.

2.3.2.2. Small focal γ ray source for radiography

A ^{192}Ir small-focal source has been developed. The small-focal source with the dimension of 1.5 mm in diameter and 0.5~1.0 mm in length was fabricated as an aluminium-encapsulated form. For the estimation of the radioactivity, neuron self-shielding and γ ray self-absorption effects on the measured activity were considered. From this estimation, it is realized that ^{192}Ir small-focal sources over 7 Ci activities can be produced from the HANARO. Field performance tests were performed to compare the image quality by a conventional ^{192}Ir NDT source and the developed source for a carbon steel. The small focal source showed better penetration sensitivity and geometrical sharpness than the conventional source does. It is concluded from the tests that the focal dimension of this source is small enough to maximize geometrical sharpness in the image taking for close proximity shots, pipeline crawler applications, and contact radiography. The key technology for small-focal ^{192}Ir source was transferred to a private company for the commercial production. Twenty sources were provided to domestic users in 2009.

2.3.3. ^{60}Co industrial irradiation source

^{60}Co is one of the most commonly used radioisotopes for a long term storage of agricultural goods and the sterilization of medical devices. The worldwide demand on ^{60}Co has gradually grown by 5∼10% every year. KAERI currently is carrying out a feasibility study for the mass production using a commercial pressurized heavy water reactor (PHWR, CANDU type). Since four units of PHWRs operated by the Korea Hydro & Nuclear Power Company (KHNP) and the Radioisotope Production Facilities at KAERI are available as the infrastructure, there is enough possibility to localize the production of the ^{60}Co sources. The decision will be made whether to start the project at the end of this year after the feasibility study is completed.

3. CONCLUSION

On the basis of a good infrastructure, the high performance reactor, HANARO, and the well equipped radioisotope production facility, KAERI have made a great effort to develop high quality radioisotope products and the relevant mass production technologies. As the results of these efforts, a large portion of radioisotopes could be produced domestically and even exported to other countries. Currently, KAERI is considering a capacity expansion and cooperation with private companies for the distribution of radioisotopes. In addition, a feasibility study is going on to construct a new research reactor to meet the increasing needs for medical applications. It is fully intended for a mass production and the backup supply of radioisotopes while HANARO is serving as the main nuclear research tool.

4. ACKNOWLEDGEMENTS

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5. REFERENCES

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