RESEARCH AND DEVELOPMENT FOR THE APPLICATION OF RADIOISOTOPE TECHNOLOGY IN SINR

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ABSTRACT

A brief systematic account on the research and development for the application of radioisotope technology in Shanghai Institute of Nuclear Research (SINR) is presented. It comprehensively covers the following categories: 1. Radioisotopes produced by cyclotron; 2. Radioisotope-labeiled compounds; 3. Radioisotope as source of energy converter; 4. Induced-radioisotope generation as a means for elemental analysis--the activation analysis; 5. Radioisotope equipped with electronic instrument for various application, and 6. Special usage of some radioisotopes.

I. INTRODUCTION

Shanghai Institute of Nuclear Research, Academia Sinica was founded in 1959, locating at east suburb of Jiading county, about 40 kilometers northwest of Shanghai municipality. The main goal of research activity is dedicated to, in parallel with the basic research in nuclear physics, the research and development for the application of nuclear technology to various fields in scientific and technical research and the related national economy. In nuclear technology, among the three major branches: nuclear energy, radiation and radioisotope, SINR had selected radioisotope technology as first priority at the very beginning with radiation technology and nuclear energy technology being followed up in later years. In early 1960's, radioisotope for clinical liver imaging was rather common in large hospitals. Physicians occasionally complained about the delayed delivery and deteriorated quality of the imported colloidal ^{198}Au and were looking for domestic supply of this radiopharmaceutical. In view of this fact, SINR took the task of colloidal ^{198}Au preparation. As this was the first radioisotope work for medical use, colleagues in SINR engaged in this project studied every step very carefully, established the correct process to control gold particles homogeneous in size. The final product met the strict specification set for clinical application and within a short period the whole producing process had been transferred to a chemical work for routine production.

By the year 1964, the installation of the main facility--the cyclotron in SINR was completed, providing a means to produce radioisotopes artificially. In the meantime, other work in connection with radioisotope technology was underway. Due to the disturbance by "Cultural Revolution", the progress of SINR had been interfered severely but has regained its vitality in the recent decade. In this short article, it is intended to give a general view and present status on works in connection with the assigned title. Materials have been grouped into six categories just for simplicity of description. Technical details are usually referred to original papers mostly appeared in Chinese journal "Nuclear Techniques".

II. RADIOISOTOPES PRODUCED BY CYCLOTRON

It is well known, radioisotopes produce by cyclotron constitute a complementary counterpart to those produced nuclear reactor. Although in China, the first reactor and the first cyclotron had simultaneously come into beings in the late 1950's, the cyclotron however had been quite busy in nuclear experiments and unavailable for radioisotope production. The successful installation of the domestic made cyclotron in SINR at the end of sprin 1964 provided a chance putting this project into reality. Since then colleague in this field have consecutively performed studies on a number of radioisotopes produced by cyclotron, namely:

^{24}Na, ^{42}K, ^{74}As, ^{56}Co, ^{57}Co, ^{61}Cu, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{85}Sr, ^{54}Mn, ^{7}Be, ^{11}C, ^{59}Fe, ^{64}Cu, ^{197}Hg, ^{199}Te, ^{200}Te, ^{201}Te, ^{203}Pb, ^{123}I... etc. Among them, efforts have been emphasized on prospective radioisotopes for clinical application, such as:

^{67}Ga, ^{11}C, ^{123}I, ^{201}Te etc. As professor Li Yongjian of SINR will give a separate article on this subject for the conference , it is not necessary to go into detail about this work here, However, it is worth while to mention some technical measures being taken to improve the quality of the radioisotope preparation work. Comprehensive elucidation are given as follow:

A. The Remodelling of Cyclotron

The original cyclotron in SINR is of the definite energy type with the accelerated beam energy: 6.8 MeV for proton; 13.6 MeV for deuteron and 27.2 MeV for α particle. Obviously, it is no way to generate radioisotope under optimum nuclear reaction condition by such cyclotron. Further more the energy of proton is too low. In order to remedy this defficiency, scientists and engineers of the cyclotron laboratory had successively taken steps to upgrade cyclotron's intrinsic property. The first step was to raise the beam energy by increasing the magnetic field strength and the corresponding Y-f resonance frequency. Thus beam energy of 8 MeV for proton; 16 MeV for deuteron and 32 MeV for α particle had been achieved. This remodelling was realized in the late 1970's. The second step was to rebuild the cyclotron, forming an isochronous, sector-focus, changeable energy type, providing variable beam energy: 10--30 MeV for proton, 5--16 MeV for deuteron and 10--32 for α particle. To attain this goal, the cyclotron's original magnetic poles were replaced by a newly manufactured pair with triple spiral-ridge face and the twin Dees were substituted by a mono Dee. Actually the entire accelerating system of the cyclotron had been redesigned and rebuilt. Including the preliminary study and preparation it took more than four years to complete the whole reconstruction but the cyclotron being actually shut down just 18 months. By the end of 1983, the remodelled cyclotron was ready for operation. The proton beam current at target chamber versus beam energy E_p is shown as follow[2]

E_p (in MeV)	9	12	15	20	25	30
I_p (in uA)	110	50	33	50	40	66

The time spent for changing energy is less than two hours. The performence of the new machine is much better than former one and is a great merit to radioisotope preparation, such as using 30 MeV proton to produce ^{201}Tl under the reaction $^{203}Tl(p,3n)\ ^{201}Pb$, and $^{201}Pb \xrightarrow{\beta} {}^{201}Tl$ with satisfactory result.

B. Auxiliary Device for Short Half-life Radioisotope Preparation

In the case of short half-life radioisotope preparation, time economy is an important factor to be considered in the whole handling process. The conventional, time-consuming method of radioactive material transportation from cyclotron building to radiochemistry building should be avoided. A pneumatic rabbit conveying system connecting between the target chamber of the cyclotron and the radiochemical room has been installed. Employing this system together with other intermadiate product transfering device, the total time spent in the preparation of ^{11}C labelled compounds from disengaging the B_2O_3 target at cyclotron target chamber to the final product obtained (such as ^{11}C-carboxyl-labelled amino acids) is around one hour[3]. This pneumatic rabbit system is not only good for short half-life radioisotope preparation, but also very useful for ion beam activation analysis.

III. RADIOISOTOPE LABELLED COMPOUNDS

Radioisotope labelled compounds is a very big category, covering more than thousand items, and is extensively used as tracer in biological, medical, agricultural research, etc. SINR at the very beginning of founding era had paid much attention to the establishment of this work. Research program on the preparation of new radioisotope labelled compounds has been proceeded successively and has made a significant contribution to the growing of this technology in China. SINR has been specialized in the preparation of tritium labelled compounds, but this does not mean that compounds labelled with other radioisotopes should not be developed in SINR. For example, radioisotopes produced by cyclotron are usually studied thoroughly as well as their final form of labelled compounds, thus as ^{67}Ga in ^{67}Ga-citrate, ^{123}I in $Na^{123}I$, ^{11}C in ^{11}C-carboxyl-labelled amino acids. In recent years, SINR has an agreement with Shanghai Nuclear Technique Development Corporation (SNTDC) which acts as an agency to distribute the radioisotope labelled compounds to client for SINR. The number of radioisotope labelled compounds appeared in the catalog of SNTDC is around 70 items, covering most commonly used tritium labelled compounds, and new items will be added to the list in the coming years.

It may be worth while to mention some achievement in the course of proceeding of this research and development work.
Namely:

A. Preparation of High Activity $NaBT_4$

Sodium borohydride-T is a very useful reducing agent in the preparation of certain tritium labelled compounds. Radiochemists of SINR have succeeded in synthesis sodium borotritonide, $NaBT_4$ with specific activity of 56

Ci/mmol (theoretical max activity 116 Ci/mmol), comparable with the best value reported in the literature[4] (30-60 Ci/mmol). Using this product as reducing agent and prostaglandin, PGE_2 as precursor, the tritium labelled prostaglandin [9-^{3}H] $PGF_{2\alpha}$ has been prepared with specific activity of 15 Ci/mmol.

B. Study in Connection with the Storage Life

Radioisotope labelled compounds are usually subjected to quality deterioration during storage time. In most cases, the part of labelled compound decomposes or degenerates into some contaminant. In order to assure a good quality of the product, SINR has emphasized the study of investigating a better way to preserve the quality of the product during storage time such that the degree of deterioration could be reduced to a minimum. The result of the study shows that there is no universal method good to all products and for one specific product different method of preservation will yield different result. For example: in the preservation of DL- [7-^{3}H]-nor-Adrenaline tartrate (6.8Ci/mmol; in aqueous solution 1mCi/ml), one sample added 2% ethyl alcohol, store under -196^{o}C condition, the second sample added 1% ascorbic acid and store under -196^{o}C condition. It turns out that the first sample after one half month decomposes quickly; the second sample at eight month. only 3% decomposes.

C. The Methodology Development

In the preparation of a new radioisotope labelled compound, it is frequently to try some new method differed from those reported in the literature. In so doing, the result attained is frequently better than expected. For example, the method of preparing [α ^{35}S] dATP, which is adopted to extract ^{35}S from neutron irradiated KCl target and to convert into $H_2{}^{35}S$ and finally to label into [α ^{35}S] dATP is quite different to formerly reported by others. However, the specific activity achieved is about 1000 Ci/mmol in the same best level as reported in literature (the theoretical maximum value will be 1492 Ci/mmol for ^{35}S labelled compound). A second example is in the preparation of tritium labelled concanavalin A, mercury light excitation method being used the first time. The specific activity of the product ~10 Ci/mmol. better than 1/3 of the maximum possible value.

III. RADIOISOTOPE AS SOURCE OF ENERGY CONVERTER

It is well known that radioisotope, used as energy source possesses the typical property either of very long life-time (such as ^{226}Ra) or of very high specific power (in watt/gram, such as ^{210}Po). In practice, radioisotope having its property in compromise of these two is more preferential. Unfortunately energy provided by radioisotope is in the form of hazardous α, β, or γ radiations. It is necessary to convert the radiation energy into other form of energy when one uses radioisotope as energy source. In doing so the problem of safety shielding should be carefully studied.

In the past years, SINR had performed three R and D project in this field. All of them are well developed techniques in advanced countries. They are nothing new but to fill the blank in Chinese radioisotope technology.

A. Permanent Luminous Phosphor

Permanent luminous phosphor has been extensively used as marker or indicator in various types of meters, especially those installed in dim light or dark evironment. China has continued to import this material even in the early 1960's. In order to establish a domestic supply SINR in co-operation with industry carried out a series of studies on this matter. A number of radioisotopes and phosphors such as ^{226}Ra, ^{90}Sr, ^{147}Pm, ^{3}H and ZnS had been investigated and different types of permanent luminous phosphors prepared. Evaluation based on safety consideration, particularly the handling and treatment of the out-of-use phosphor, the best choice product should be ^{147}Pm activated phosphors.

B. ^{85}Kr Light Bulb

This is a variety of permanent luminous phosphors. The phosphor is coated on the inner surface of a sealed bulb activated by the filled ^{85}Kr. In dark place, it works like light bulb and is particularly useful in places where electrical light is unsafe or unreliable. SINR did this development project for a factory.

C. Radioisotope Power Generator

In the beginning of 1960s, programme on the artificial satellite was underway. Various kinds of long life-time power supply for the space instrument were needed to develop urgently. SINR shouldered the development project of radioisotope power generator. It was understood that nuclear power had been considered as an alternative candidate, to be used only when other power supply (such as solar cell) fails to be available in time. Due to sanitary and economical consideration, radioisotope power generator was not adopted in satellite orbit. SINR, however, after years strenuous research had succeeded in constructing a proto-type radioisotope power generator for space use which was loaded with 1100 curies of ^{210}Po (the designed

capacity was 2200 Ci), showing an output power of 1.4 watt and 4.2% efficiency[5]. This cell is of spherical shape with 150 mm in diameter and weight about 2 kg.

As a by-product of this research program, model of radioisotope power generator for terrestrial use has been designed, constructed and tested[6].

IV. INDUCED-RADIOISOTOPE GENERATION AS A MEANS FOR ELEMENTAL ANALYSIS-THE ACTIVATION ANALYSIS

When a thin tested sample is exposed to neutron flux or accelerated ion beam, induced-radioisotopes used to be generated. By measuring the intensity of certain particular radio-nuclide, the elemental content relating to this nuclide could be determimed directly. The number of the specific induced-nuclide, N_S, at the end of time, T irradiation is given by the expression

$$N_S=\sigma\Phi\frac{\theta M}{A} \times 6.023 \times 10^{23} (1-e^{-\lambda T})/\lambda$$

or its decay rate, R_S by

$$R_S=\lambda N_S=\sigma\Phi\frac{\theta M}{A} \times 6.023 \times 10^{23}(1-e^{-\lambda T})\ldots(1)$$

Where M is mass of the element to be determined in the sample; θ, A and σ are respectively the percentege abundance, mass number and reaction cross-section (in $10^{-24}cm^2$) of the pertaining isotope which generate N_S; Φ is the flux of inducing particles (in number of particles/cm^2. sec). The decay rate of the induced nuclide is measured by a detector at time t^* after the end of irradiation, the counting rate, C is related to Rs by

$$C=\epsilon Rs=\epsilon\sigma\Phi\frac{\theta M}{A} \times 6.023 \times 10^{23}(1-e^{-\lambda T})e^{-\lambda t^*}$$

where ϵ is the total detection efficiency of the detector. In practice, instead of counting rate, the total number, n of net counts in time, t is used which is expressed by

$$n=\int_o^t Cdt=\epsilon\sigma\Phi\frac{\theta M}{A} \times 6.023 \times 10^{23} (1- e^{-\lambda T})$$

$e^{-\lambda t^*}(1-e^{-\lambda t})/\lambda$. Thus

$$M=nA[\epsilon\sigma\Phi A \times 6.023 \times 10^{23}(1- e^{-\lambda T})e^{-\lambda t^*}$$
$$(1- e^{-\lambda t})/\lambda]^{-1}\ldots(2)$$

This relation is also good for on-line analysis. In this case, the approximation:

$e^{-\lambda T}\simeq 0$, $e^{-\lambda T^*}\simeq 1$, $(1- e^{-\lambda T})/\lambda \simeq t$ maybe useful, and

$$M=nA[\epsilon\sigma\Phi\theta \times 6.023 \times 10^{23}t]^{-1}\ldots(3)$$

Since nA ~10^2- 10^3, ϵ~10^{-2}- 10^{-1}, σ~10^{-26}- 10^{-23}, Φ~10^9- 10^{14}, θ~10^{-1}- 10^0, t~10^1- 10^3, the value of M determined by this method is in the range 10^{-3}g to 10^{-10}g. accordingly. The percentage content of the tested element will be M/W, where W is the weight of the sample. From the expression of (2) or (3), in order to get a better sensitivity of M, Larger values of ϵ, σ, Φ and θ seem to be preferable, but in practice this will not be always true. For the sake of lowering interference, and increasing reliability one or two of these parameters with smaller value may be used. For example, in the determination of oxygen content in copper with proton activation first done by SINR, the less abundant isotope ^{18}O (θ=0.204%). instead of ^{16}O (θ=99.759) was used as precursor and ^{18}F, an induced radioisotope by the reaction $^{18}O(p,n)^{18}F$ with 6.8 MeV proton, was chosen for measurment. In this way, the interference of that part of ^{18}F induced from $^{17}O(p,\gamma)^{18}F$ is negligible because of ^{17}O being the least abundant isotope (θ=0.038%) and the cross-section of (p,γ) reaction is smaller than(p,n) reaction, After a simple chemical separation to get rid of ^{63}Zn, ^{65}Zn, etc the induced radio-nuclides from copper, micro oxygen content as low as 0.5 ppm in copper was satisfactorily determimed[7]. SINR has performed a lot of work on the activation analysis study with charged particle accelerated by cyclotron, It may be helpful to mention some of them, such as using proton to determime trace oxygen in high purity germanium, nitrogen in tantalum and niobium; using deuteron to determime trace nitrogen in high purity copper, boron, carbon and nitrogen in silicon; using α particle to determine trace oxygen in germanium, calcium in yttrium oxide[8].

Besides cyclotron, SINR possesses a 200 kV set for 14 MeV fast neutron generation. It has also been employed for activation analysis, such as to measure major elements content in a meteorite sample, to determine protein content in various kind of grains. In case of some analysis has to be activated with thermal neutron, samples must be sent to Beijing for reactor thermal neutron flux irradiation, such as to determine noble metals content in high purity copper, trace content of arsenic, selenium, copper and zinc in biological samples.

V. RADIOISOTOPE EQUIPPED WITH ELECTRONIC INSTRUMENT

This category covers many branches of electronic instrument using radioisotope as source of radiation interacting with some physical quantity to achieve certain measuring purpose. The typical, non-contact radioisotope gauging instruments such as level gauge, thickness gauge and density gauge have been used and well known in chemical work, paper making and metal sheet rolling factories for many years. SINR has engaged in the research and development work in this field for more than twenty years. Besides the typical gauging instruments, many types of special usage instrument have been developed. Some of them will be described in the following:

A. Alpha-Particle Thickness Gauge by Air Equivalent Method[9]

This thickness gauge for measuring ultrathin foil (0--4 mg/cm^2) is based on the principle of diminishing of α particle range in air, ΔR, due to inserting of the foil sample in between the α source and detector. With a fine-screw structure to vary the range distance, ΔR can be measured precisely, and the mass of air in ΔR per unit area is equivalent to mass per unit area of the foil, after correction being made for the different stopping power of α particle in the two materials. This instrument is very useful to experimental nuclear physicists who need a meter to measure the thickness of ultrathin foil target.

B. Under-ground Oil Pipe Leak Detector

This is a robust and rigid detector structure fixed on a frame steadily together with a tape recorder and power supply inside a tightly sealed shell in the shape of sphere on ellipsoid. When this device is used to detect oil pipe leakage, a column of oil containing homogeneously certain radioisotope (e.g. ^{77}Br, ^{131}I) is sent to flow under pressure followed by a long column of non-radioactive oil and then the said detector of proper size is put into the pipe and let flow with the non-radioactive oil. In the same time, the detection and the recording tape are both going to work all through pipe, the device traveled. At normal section of the pipe, the tape recorder registers only background radiation, however at the location of leakage, a higher radiation intensity will be recorded, due to the fact that the radioactive oil leaked outside the pipe could not be wiped away by the clean oil flowing behind the radioactive oil. Upon scanning the registered tape, the location of leakage can be determined precisely.

C. Thickness Gauge to Measure the Plating Layer of Watch Parts[10]

By means of the X ray fluorescence technique the thickness of a plating layer can be measured relatively. With the aid of a microprocessor, the value of the measured thickness can be printed out directly. The sample for measurement can be cobalt-nickel plating layer on the base of steel, or brass and gold plating layer on the base of nickel, white copper. The measuring range of thickness is usually 1--6 μm with an error of less than $\pm$ 0.3μm and the area for the measurement is usually to less than 2 mm in diameter.

VI. SPECIAL USAGE OF CERTAIN RADIOISOTOPES

There are a number of radioisotopes, each one with its typical application not included in the above categories. So it is better to group them together under this heading.

A. ^{57}Co and Mössbauer Effect; ^{22}Na and β^+ annihilation; ^{111}In and Perturbed Angular Correlation

In mid 1970's, SINR had developed a set of instruments for Mossbauer effect study, positron annihilation experiment in materisl science and perturbed angular correlation study in life science[11]. These work had been usually performed in co-operation with other institution in the specific field and produced an incentive effect for them to adopt these nuclear techniques in their laboratorial study. SINR has kept a strong group up to present.

B. ^{241}Am, ^{238}Pu and RXF analysis

Energy dispersive X ray fluorescence analysis excited by radioisotope source such as ^{241}Am, ^{238}Pu (RXF) is very popular in recent years. SINR has developed several sets of such instruments and used extensively for elemental analysis on herbal medicine study, environmental pollution study and topics on life science research. A book on treatise of "Radioisotope X ray Fluorescence Analysis" has been published for promulgation of this knowledge[12]. For high "Z" sample analysis, the radiation energy of either ^{238}Pu or ^{241}Am are not big enough to excite K-X rays. Under such condition, ^{109}Cd and ^{57}Co radioisotope sources have been employed.

C. ^{90}Sr Applicator for Clinical Use

Beta ray irradiation for the treatment of certain skin disease has brought satisfactory release to the patient. About 15 years ago, SINR had engaged in the study of ceramic ^{90}Sr applicator preparation and achieved in producing a batch of more than 50 pieces applicator with each one containing 10 millicurie of ^{90}Sr, for clinical application in various hospitals over the country.

D. ^{125}I and Radioimmunoassay Kit

Radioimmunoassay has been used very extensively in hospital circle these years. SINR has'nt done much on the development of this technology in the past, but recently has a remarkable start on the preparation of ^{125}I labelled cortisol RIA Kat[13]. It is expected that the work in this field will become more attractive in future.

E. ^{3}H Content in Water and the Method of Measurement with a Cyclotron

Tritium as a naturally occurred nuclide exists generally in water with a constent ratio to hydrogen (about 1:10^{16} by atom). Once a source of water is isolated and stopped to be replenished with rain-water, the content of

tritium in this water source will decrease as a result of radioactive decay, while the free water has some way of obtaining newly generated ^{3}H to ballance its decay loss. Therefore, by determining the ^{3}H content in the isolated water and comparing it with that of fresh water, the time of isolation could be calculated. For this purpose, SINR has developed a method to measure ^{3}H content in water sample with a cyclotron successfully[14].

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