PRESENT STATUS OF YU-AMS SYSTEM

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ABSTRACT. A new compact accelerator mass spectrometry (AMS) system has been installed in the Kaminoyama Research Institute at Yamagata University (YU). The AMS system is based on a 0.5MV Pelletron accelerator developed by the National Electrostatics Corporation. An automated acid-alkali-acid (AAA) treatment system and an automated graphitization line were also installed in the same facility for sample preparation. Performance tests of the YU-AMS system were carried out by measuring the C-series standard samples (C1–C8) and HOxII provided by IAEA and NIST, respectively. We evaluated the YU-AMS system by comparing the radiocarbon ages of Japanese tree rings with dendrochronologically determined calendar ages with calibration data. We also carried out some performance tests using a control serum and a ^{14}C-labeled drug (oxaliplatin).

INTRODUCTION

Accelerator mass spectrometry (AMS) measurements have been widely utilized for radiocarbon dating in various fields, including archaeology, environmental science, geology, and space and Earth sciences (Tuniz et al. 1998; Burr and Jull 2009). In the medical and pharmaceutical areas, new interest in "microdosing" using AMS ^{14}C measurements has been attracting considerable attention for drug development (Lappin and Garner 2005). Microdosing studies have been proposed as a means of obtaining human pharmacokinetics information in the early stages of drug development. Since a microdose is defined as less than 1100th of the dose calculated to yield a pharmacological effect of the test substance with a maximum dose of <100 μg, a very sensitive analytical method using AMS is required to measure the distributions of drugs labeled with ^{14}C in samples of human blood, urine, feces, and tissue. AMS is capable of measuring ^{14}C-labeled drug concentration at very low radioactivity in various biological samples and high-performance liquid chromatography (HPLC) eluates. Microdosing studies in humans may reduce the failure rate and improve candidate selection in drug development and lead to a reduction in the use of laboratory animals in early drug development (Lappin and Stevens 2008). Hence, this type of study is expected to help accelerate drug development and reduce its cost. Following the guidance of the European Union (EMEA 2003) and the United States (FDA 2006), the Japanese Health Ministry issued a guidance on microdose clinical trials in 2008 (MHLW 2008). However, there are few AMS facilities in Japan for measuring samples obtained from microdosing studies.

Yamagata University (YU) installed an AMS (YU-AMS) system at the Kaminoyama Research Institute to meet the requirement of ^{14}C AMS for microdosing and medical studies as well as that of ^{14}C dating in the same facility. An automated graphitization line was also installed at the same research institute for sample preparation. This is the first AMS system installed at a university in north Japan (Tohoku-Hokkaido region). The facility also provides a ^{14}C dating service for samples from other universities, institutes, and public organizations. In this paper, we report the status of the YU-AMS system.

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GRAPHITE PREPARATION SYSTEM

In the ^{14}C measurement of an organic sample using the AMS system, the sample is physically and chemically treated to remove contaminants. After this treatment, it is combusted, chemically reduced to graphite, and compressed into an aluminum pellet that serves as a target for the cathode in the ion source.

An automated acid-alkali-acid (AAA) treatment system was installed to chemically remove contaminants from samples, such as wood, charcoal, peat, and other organic deposits. The system is based on a previous system developed by Sakamoto et al. (2004). This system can be used to simultaneously treat 10 samples using up to 4 types of solution (e.g. different concentrations of hydrochloric acid or sodium hydroxide solutions). After the AAA treatment, the samples are combusted to CO_2 using an automated system. A schematic diagram of the graphite preparation system is shown in Figure 1. The system consists of an elemental analyzer (EA; Vario MICRO Cube, Elementar), a stable isotope ratio mass spectrometer (IRMS; IsoPrime), and an automatic cryogenic CO_2 trapping system. Several institutes apply an EA for sample combustion and use its gaseous products in successive lines (Aerts-Bijma et al. 1997; Yuan et al. 2000; Wacker et al. 2010). Each sample is placed in a tin (or silver) capsule and placed in the EA system. The sample in the capsule is combusted in a quartz reactor at 1150 °C, yielding CO_2, N_2, and SO_2 gases after purification and H_2O removal. By this method, the amounts of carbon, nitrogen, and sulfur in the sample can be determined in addition to producing the amount of CO_2 required to prepare graphite. After carrying out the elemental analysis, the produced gases are transported to the IRMS and then to the cryogenic CO_2 trapping system by helium carrier gas. The gas flow of the He carrier gas is 200 mL/min. The flow is split into 2 pathways: one for the IRMS line with a flow rate of 20 mL/min and the other for the cryogenic CO_2 trapping system with a flow rate of 180 mL/min. The IRMS can precisely measure the $\delta^{13}C$, $\delta^{15}N$, and $\delta^{34}S$ of the sample.

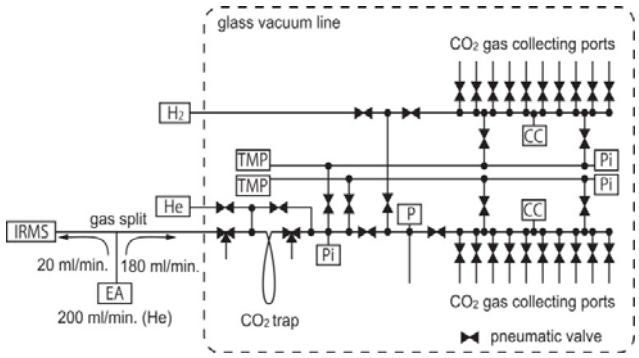


Figure 1 Schematic diagram of graphite preparation system employed in the YU-AMS. The system consists of an EA, an IRMS, and a CO_2 trapping system and can produce 20 graphite samples per day.

The cryogenic CO_2 trapping system consists of 20 identical glass lines. When CO_2 is released from the EA system, a trigger signal is sent to the cryogenic CO_2 trapping system. The collection of CO_2 and H_2 used for CO_2 reduction is automatically conducted by the following predetermined procedures: 1) the operation of valves; 2) the supply of liquid nitrogen to a cold trap; 3) the transfer of the Dewar vessel; 4) the measurement of the CO_2 gas pressure; and 5) the recording of the supplied H_2 pressure. These procedures are sequence-controlled by a programmable logic controller (PLC:

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Omron Corporation). The trapped CO_2 is finally reduced to graphite by the following reaction at 630 °C with hydrogen and an iron powder catalyst (Kitagawa et al. 1993):

$$CO_2 + 2H_2 \rightarrow C + 2H_2O$$

The quantity of CO_2 gas collected from the EA is measured as the final pressure at the CO_2 trapping line. The collection efficiency of CO_2 is approximately 95% for graphite preparation. The produced graphite powder is finally pressed into an aluminum target container under 150 psi using a manual press system. The standard sample of C1 and synthetic graphite powder (No.159-00425 Wako Pure Chemical Osaka, Japan) are used as chemical background (CB) samples. Figure 2 shows the measured ^{14}C concentration of the CB over 2.5 yr of operation. The average background level is 0.54 ± 0.07 percent modern carbon (pMC) for this system. Although "hot" samples of >1600 pMC were treated during the period, no memory effect on the following sample was observed.

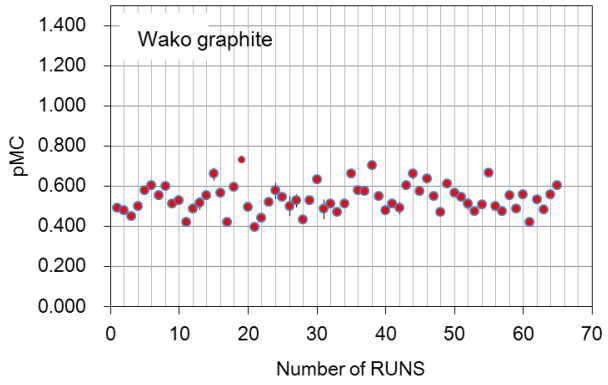


Figure 2 ^{14}C concentration (pMC) of Wako graphite prepared with graphite preparation system over 2.5 yr of operation obtained with YU-AMS system.

YU-AMS SYSTEM

The system is based on a conventional AMS instrument (Burr and Jull 2009). Figure 3 shows a schematic view of the AMS developed by the National Electrostatics Corporation (NEC). The system consists of 40 samples of a multicathode negative ion source by cesium sputtering (MC-SNICS) so as to convert the sample to negative carbon ions, a 45° electrostatic spherical analyzer (ESA), a 90° bending magnet with a biased chamber for sequential injection, an acceleration tube (NEC 1.5 SDH-1), a 90° analyzing magnet, offset Faraday cups for measuring ^{12}C and ^{13}C beam currents, a 90° ESA, and a solid-state detector for counting the ^{14}C beams. About 240 s was required for 1 measurement with a cycle repeat rate of 10 Hz. Since the 45° ESA is rotatable, it is possible to install a second ion source on a spare port at a position 90° from the first one. If there are multiple samples to be measured, the ion source can be made ready for the subsequent measurement by setting the samples in a chamber and evacuating it while the other source is being used for AMS measurement. This process could thus shorten the entire measurement time. Currently, we are planning to install a second new ion source by March 2013.

Performance Test of AMS System: Standard and Hot Samples

The performance tests of the YU-AMS system were periodically (every 3–4 months) carried out by measuring the C-series standard samples (C1–C8) and HOxII provided by IAEA and NIST, respec-

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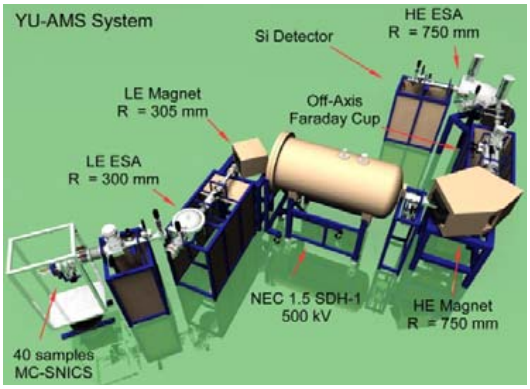


Figure 3 Schematic view of YU-AMS system. The ion source is placed at a 45° angle to allow possible future expansion with an additional ion source.

tively, similarly to those in previous studies (Nakamura et al. 2004; Kobayashi et al. 2007). Five cathodes were filled with graphite produced from HOxII. The graphite for each IAEA C-series standard sample was set into 2 cathodes. All the cathodes were loaded at random positions on a disk. The cathodes were each measured 8 times for 240 s. For the data analysis of unknown and standard samples, we use NEC's "abc ver.7" analysis software. The isotope ratio of ^{14}C to ^{12}C in each sample was calculated and then subtracted by that of C1 for background estimation. After $\delta^{13}C$ corrections, the final sample ratio is normalized to the simultaneously measured HOxII standard sample ratio. Finally, the measured values were combined into a weighted mean. Figure 4 shows an excellent linear relationship between the measured and consensus values. As listed in Table 1, the results obtained on 3 different dates in 32 months are in very good agreement with the consensus values. The relative deviations of most of the measured values from the consensus values are <0.5%.

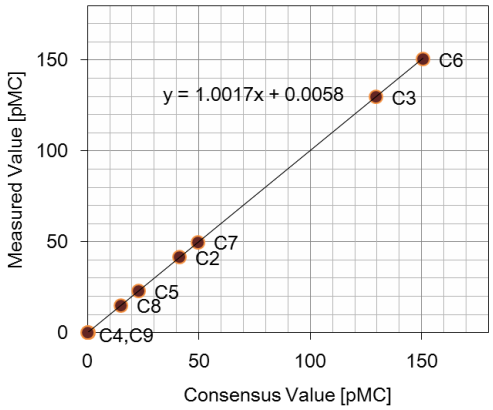


Figure 4 ^{14}C measurement results of YU-AMS for C-series provided by IAEA. The measured values of C2–C8 were obtained by subtracting the C1 value and normalizing against HOxII standards. The solid line is derived from the fit of a linear function to the measured values. The line is y = 1.0017x–0.0058 (pMC), where x represents the consensus values and y represents the measured values.

The long-term stability of the YU-AMS system including the graphite preparation system was assessed by producing and measuring a series of standard samples of IAEA C7. These standard samples have been measured routinely and periodically since the middle of October 2010. The measurement sequence was similar to that mentioned above. Figure 5 shows the long-term stabilities of the system for the standard samples of IAEA C7 over a 20-month period. The system was very stable

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over the 20-month period. The mean is 49.53 ± 0.14 pMC for the IAEA C7 standard samples, which is in excellent agreement with the consensus value of 49.53 ± 0.12 pMC.

Table 1 Percentages of modern carbon (pMC) from consensus values of C-series provided by IAEA and those obtained using YU-AMS system on 2 different dates. The measured values of C2–C8 were subtracted by that of C1 and normalized against HOxII standards.

Sample type	Consensus value IAEA standard (pMC)	Measured value 24 Mar 2010 (pMC)	Measured value 31 Jan 2011 (pMC)	Measured value 31 Jan 2013 (pMC)
IAEA-C2	41.14 ± 0.03	41.06 ± 0.25	41.88 ± 0.13	41.36 ± 0.10
IAEA-C3	129.41 ± 0.06	130.13 ± 0.24	129.20 ± 0.24	129.57 ± 0.27
IAEA-C4	0.20 ± 0.44	0.04 ± 0.03	0.11 ± 0.05	0.18 ± 0.04
IAEA-C5	23.05 ± 0.02	22.98 ± 0.07	22.99 ± 0.09	23.11 ± 0.08
IAEA-C6	150.61 ± 0.11	150.09 ± 1.14	150.51 ± 0.23	150.12 ± 0.23
IAEA-C7	49.53 ± 0.12	49.77 ± 0.29	49.70 ± 0.13	49.43 ± 0.11
IAEA-C8	15.01 ± 0.17	15.09 ± 0.06	15.05 ± 0.01	15.00 ± 0.07

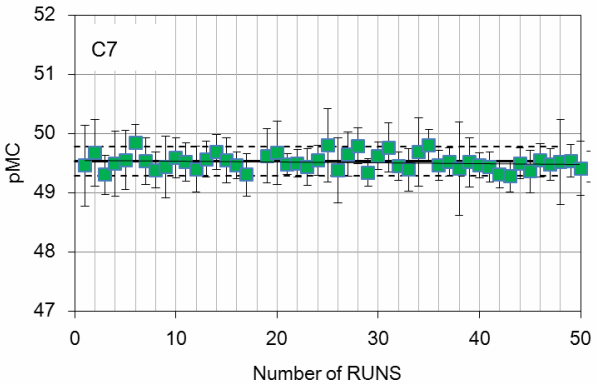


Figure 5 Long-term stability of YU-AMS system obtained over 20 months of ^{14}C concentration measurements for IAEA C7. Each solid line denotes the certified value of 49.54 pMC for IAEA C7. The dashed lines indicate an accuracy of 0.5% for the certified values.

We investigate the background property of the YU-AMS system with particular emphasis on possible cross-contamination from "hot" samples similar to the procedure developed by Zoppi et al. (2007). Two "hot" samples with fractions of modern carbon (Fm) of approximately 6 and 16 were prepared. Each of the 2 hot samples (HOT) was preceded by 2 HOxII samples (NIST) and followed by 2 machine background (MB) and 2 chemical background (CB) samples. The MB samples were synthetic graphite powder (Wako graphite) and the CB samples were the graphite sample produced from the Wako graphite with the graphite preparation system described above. Each cathode was measured 8 times in the sequence of NIST, HOT, MB, and CB samples. Figure 6 shows the measured ^{14}C concentrations of the samples. The machine background (MB) and chemical background (CB) were 0.20 ± 0.09 and 0.42 ± 0.09 pMC, respectively. There were no significant differences of the ^{14}C concentrations during the eighth AMS measurement for both MB and CB samples. This result indicates that the memory effect is negligible for the "hot" sample with Fm = 16 in the AMS measurement.

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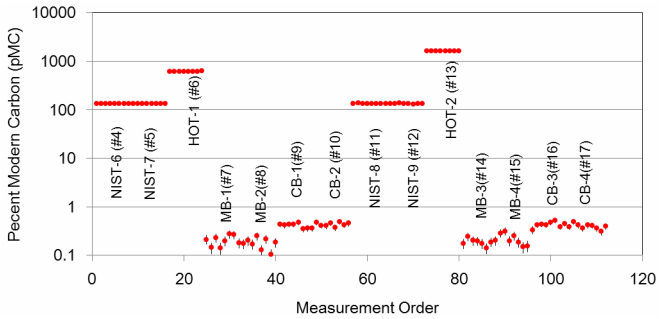


Figure 6 ^{14}C concentration (pMC) for 2 "hot" samples with Fm values of approximately 6 and 16. ^{14}C concentrations were indicated for the HOxII samples, and 2 each of machine background (MB) and chemical background (CB) samples before and after measuring each hot sample.

Performance Test of YU-AMS System: Dendrochronology Sample

The YU-AMS system was evaluated by comparing the ^{14}C ages of 2 Japanese cedar trees with dendrochronologically determined calendar ages using calibration data. The trees grew in the Tohoku area in Japan. The first tree is a Choukai Jindai cedar in the time range from 965–511 BC taken at Nikaho, Akita Prefecture (39°05′N, 140°03′E). The other is a Sendai castle cedar in the time range from AD 1662–1965 taken at Sendai, Miyagi Prefecture (38°30′N, 140°85′E). Each tree was cut into 5-yr tree-ring specimens with intervals from 10 to 55 yr. We selected 12 and 15 samples with 5 yr of tree rings for the Choukai Jindai and Sendai castle cedars, respectively. After AAA chemical treatment, the samples were graphitized individually using the described graphitization system.

Figures 7a and b show a comparison between the IntCal09 calibration curves (Reimer et al. 2009) and ^{14}C concentrations of the samples of the Choukai Jindai and Sendai castle cedars, respectively. The ^{14}C concentrations of the Choukai Jindai cedar are consistent with the IntCal09 calibration curve in the time range from 965 to 560 BC. In the time range from AD 1665 to 1945, the ^{14}C concentrations of the Sendai castle cedar are consistent with the IntCal09 calibration curve except for the period AD 1725–1765. In this range, the maximum difference is 65 yr and the average difference is 42 yr. These discrepancies will be further investigated in order to clarify whether this offset is caused by the "island effect," which is the release of ^{14}C-depleted CO_2 from surface ocean water (Nakamura et al. 2007). In particular, since the time range of the Sendai castle cedar includes the Maunder minimum (AD 1617–1745), we plan to carry out ^{14}C measurement with an annual time resolution to investigate the relationship between solar activity and ^{14}C concentration in northern Japan.

Performance Test of YU-AMS System: Medical Application

To evaluate a human sample by AMS measurement, we analyze a ^{14}C-labeled compound (oxaliplatin; Moravek Biochemicals, Inc.) in a control serum. The specific radioactivity was 2.0 GBq/mmol. Oxaliplatin was diluted with water from Sekisui Medical Co., Ltd. The radioactivity of the diluted oxaliplatin used as the stock solution was 3.7 kBq/mL. The solution was diluted at various concentrations from 50 to 5000 pg/mL with a Lyphochek drug-free serum (BIO-RAD, Lot 19680). A blank serum diluted with pure water by 100-fold was also measured as a background sample. Some 20 µL of each diluted sample was placed in a tin cup in the EA with about 2 mg of sodium benzoate (Sigma-Aldrich), which was used as the carrier carbon for the AMS measurement (Miyaji et al. 2009). After drying at room temperature, the samples were combusted and chemically reduced to graphite using the system mentioned above. Three cathode targets were prepared for each sample.

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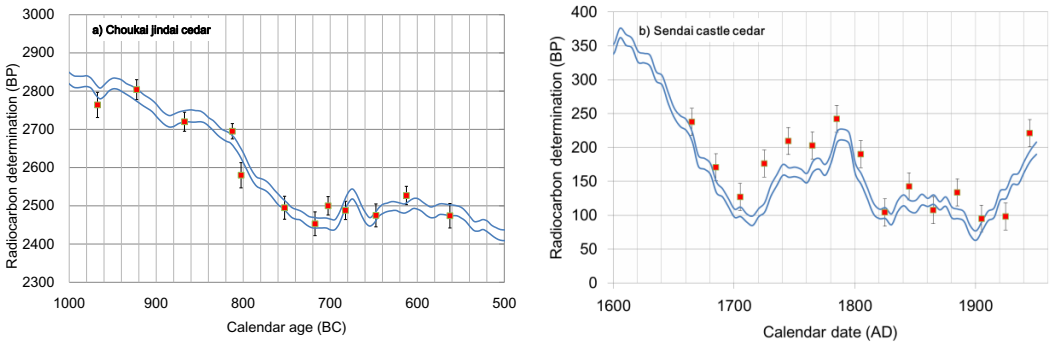


Figure 7 Comparison of ^{14}C concentrations of Tohoku-Japan trees with IntCal09 calibration curves. a) Choukai Jindai cedar in time range from BC 965 to 560 and b) Sendai castle cedar in time range from AD 1662 to 1965.

Table 2 and Figure 8 show the relationship between the ^{14}C concentration obtained by the AMS measurement and the concentration of ^{14}C-labeled oxaliplatin in the serum. The AMS results are expressed as pMC and the coefficient of correlation is 0.999 for this measurement. We are planning to compare these results with those obtained by liquid scintillation counting (LSC) to conduct a microdosing test using the YU-AMS system.

Table 2 Relationship between concentration of ^{14}C-labeled oxaliplatin in serum and ^{14}C concentration obtained by AMS measurement.

Serum oxaliplatin concentration (pg/mL)	0	50	250	500	1000	2000	5000
^{14}C concentration (pMC)	1.34 ± 0.01	17.79 ± 0.05	81.68 ± 0.13	148.20 ± 0.20	322.97 ± 0.36	635.10 ± 0.78	1667.52 ± 1.96

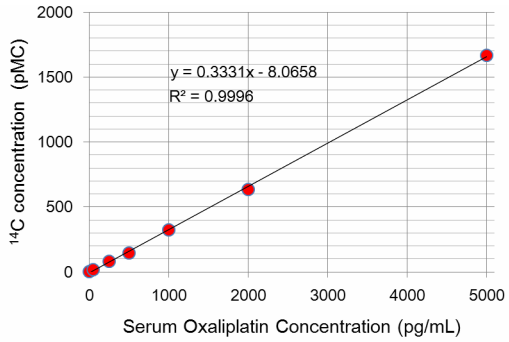


Figure 8 Relationship between concentration of ^{14}C-labeled oxaliplatin in serum and ^{14}C-concentration (pMC) obtained by AMS measurement.

The ^{14}C concentration in the control serum of X pMC can be expressed in dpm/L (decays per minute per liter) units using the following equation (Miyaji et al. 2009):

$$^{14}C \text{ concentration (dpm/L)} = X \text{ pMC} \times 0.1356 \text{ (dpm } ^{14}C/\text{g C)} \times \text{carbon content (g C/g)}.$$

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The value of 100 pMC is defined as 100 pMC = 13.56 dpm (decays per minute) $^{14}C/g$ C (g of carbon) in 1950. The carbon content of the sample was calculated from the amount of CO_2 gas measured with the EA for graphite preparation. The contribution of the carrier (sodium benzoate) was independently measured and subtracted from the sample. The carbon content and pMC for sodium benzoate (carrier) were 0.58 and 0.22 ± 0.01, respectively. The pMC for the fold-100 control serum was 1.34 ± 0.01 pMC. The ^{14}C concentration was determined to be 0.975 ± 0.006 dpm/mL by subtracting the contribution of the carrier and taking the dilution factor of 100 into account. This result is consistent with the ^{14}C concentration of human blood (1.613 ± 0.114 dpm/mL) and plasma (0.648 ± 0.049 dpm/mL) obtained by Minamimoto et al. (2008).

SUMMARY

A system with fully automated 20-reactor graphite lines and a new compact AMS system were installed at the Kaminoyama Research Institute at Yamagata University (YU). An automated acid-alkali-acid (AAA) system was also installed to reduce the working time and prevent contamination by people unfamiliar with the required levels of caution. The graphitization system has been automated by employing an elemental analyzer (EA), a stable isotope ratio mass spectrometer (IRMS), and an automatic cryogenic CO_2 trapping system. This system is capable of producing 20 graphite samples per day. The performance tests of the YU-AMS system were carried out by measuring standard, dendrochronology, and human samples. The results show that the YU-AMS system achieves precise measurements of ^{14}C concentration of these samples. The long-term stability of the YU-AMS system with a graphite preparation system was demonstrated by carrying out periodical measurements of the standard IAEA C7 samples. The final goal of this project is to apply the system in the medical and pharmaceutical fields, particularly in microdosing studies to predict the pharmacokinetics of new drugs by labeling them with ^{14}C and administrating them to human volunteers.

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