

Automated System for Direct Production of [N-13]Ammonia with a Circulating Water-Hydrogen Target

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III. 3. Automated System for Direct Production of [N-13]Ammonia with a Circulating Water-Hydrogen Target

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Introduction

Since [¹³N]ammonia is currently one of the most frequently used radiopharmaceuticals for myocardial PET studies, a simple method suitable for routine preparation of [¹³N]NH₃ has been extensively sought. The direct production of [¹³N]NH₃ by deuteron irradiation of a flowing CH₄ target via the ¹²C(d,n)¹³N reaction was first developed¹⁾. However, this method was soon substituted for the synthetic method using [¹³N]NO₃- produced by proton irradiation of water via the ¹⁶O(p,α)¹³N reaction^{2,3)}, and this procedure was automated for routine clinical use⁴⁾.

Meanwhile another approach to direct production has been sought. The second notable nonsynthetic method is the on-line conversion of [¹³N]NH₃ from [¹³N]N₂ and H₂ with microwave discharge⁵⁾. [¹³N]nitrogen was converted to [¹³N]NH₃ in an approximate 65% radiochemical yield within 10 min discharge. An alternate method for direct [¹³N]NH₃ production using a slurry of [¹³C]carbon powder in water was also developed⁶⁾, and over 50% of the ¹³N produced by the ¹³C(p,n)¹³N reaction was [¹³N]NH₃ with 15 μA-20 min irradiations.

A new and more convenient method for this approach has recently been reported⁷⁾. More than 95% of the ¹³N produced by proton irradiation of water under H₂ pressure was found as [¹³N]NH₃ at a proton current of 20 μA. The present automated system for [¹³N]NH₃ production has been developed based on this excellent method, which enables the in-target product of [¹³N]NH₃ to be easily purified by passing through an ion exchange column and rapidly supplied for subsequent clinical PET studies.

Automated system

The present system consists of the main and target units. It is entirely automated with

feedback control by combined use of a personal computer (NEC PC-9801 RX, Japan) and sensors of radiation, flow and pressure. Figure 1 shows a flow chart of the whole system.

The target unit is an assembled irradiation system and practically the same with the system for [^{18}F]fluoride production previously reported⁸). A water target is circulated with a small geared pump while it is irradiated by a 12 or 18 MeV proton beam under H_2 pressure, which is monitored with a pressure sensor attached to the vessel, for separating radiolytic gaseous products from the circulating water. The irradiation vessel is made of silver and has a 30 μm thick titanium window.

The main unit supplies a water target to the target unit through polyethylene tubing. Four mL of water is injected into a line with a syringe pump and then transferred with a H_2 flow to automate this procedure with a thermal mass flow controller⁹). The irradiated target is also recovered to this unit in the same way. It is first collected in a glass vessel and then passed through a disposable column packed with cation exchange resin (Na^+ form; Sep Cartridge IC-H or AG50W-X8, 100-200 mesh) which has been washed with saline in advance. The column is washed with 2.5 mL of sterile water and then [^{13}N] NH_3 retained by the resin is recovered in a vial with 10 mL of saline through a membrane filter. All 3-way valves, tubes and syringes are disposable, sterile and apyrogenic for easy maintenance, and valves and syringes are pneumatically actuated.

Radiochemical purity was determined by HPLC on a NOVA-PAK C18 column (RCM8 \times 10, Waters) with a PIC B-8 reagent (Waters), and radionuclidic purity with a pure Ge detector.

Performance Results and Discussion

Nucleogenic ^{13}N atoms produced in water can take various chemical forms of $^{13}\text{NH}_3$, ^{13}NO , $^{13}\text{NO}_2^-$ and $^{13}\text{NO}_3^-$ (10,11). However, under intense irradiation radiation-induced oxidation overcomes the other radiolytic reactions involved in low dose irradiations, and $^{13}\text{NO}_3^-$ is finally produced as a major product. Contrary to pure water system, H_2 dissolved in water scavenges oxidative species and then predominant radiation-induced reduction results in the production of [^{13}N] NH_3 . Figure 2 clearly demonstrates the very drastic effects of H_2 added in the target. Over 99 % of the ^{13}N produced can be brought into a chemical form of [^{13}N] NH_3 with a H_2 pressure of more than 1 kg/cm^2 , independently of the beam current. This marked change in chemical form was also observed for a static target at higher H_2 pressures although it was not reproducible. The effects of the H_2 pressure can be accounted for by the increase in the H_2 solubility. It seems that circulation of the target facilitates the dissolution of H_2 into the target.

It is generally observed that with increasing a beam current the yield of ^{13}N decreases mainly due to evolution of radiolytic gaseous products or vaporized water by deposit of heat in a small volume of water. Circulation of the target finds its successful way in efficient

suppression of this effect as clearly shown in Table 1.

In practical productions, the recovery yield of ^{13}N from the target unit is 70-80%, probably owing to a relatively large dead volume in the geared pump, and pure $[^{13}\text{N}]\text{NH}_3$ is recovered with 10 mL of saline in a 60% yield from a Sep Cartridge IC-H or in a 80% yield from a AG50W-X8 column. As purification procedure is usually completed within 2 min after irradiations, more than 40 mCi of $[^{13}\text{N}]\text{NH}_3$ can be supplied for PET use with 10 min irradiations. This production can be repeated every 15 min without any change except for an injection vial. Radiochemical purity of directly produced $[^{13}\text{N}]\text{NH}_3$ is high enough without further purification. However, purification with cation exchange resin is also an important procedure for replacing a water target with saline for injection. It should be also noted that a radioactive contaminant, which was identified as ^{48}V derived from a beam window, can be removed by this purification procedure as shown in Fig.3.

In conclusion, the present system, which is totally automated from a target loading in the irradiation vessel to collection of a final product in a vial, can supply a sufficient amount of readily injectable $[^{13}\text{N}]\text{NH}_3$ in high radiochemical purity at 20 min intervals. Circulation of a target increases reliability and production yield with less H_2 pressure than a static target.

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Table 1. Production yields of [¹³N]H₃ vs beam currents with a circulating target.

Proton energy (MeV)	Beam current (1A)	Production yield (mCi)	Saturation yield (mCi/1A)
12	1.8	13.3	14.8
12	16.1	115.6	14.3
18	1.0	22.0	43.9
18	15.0	283.3	37.7

Irradiation time : 10 min
 Target volume : 4 mL
 H₂ pressure : 2.5 kg/cm²

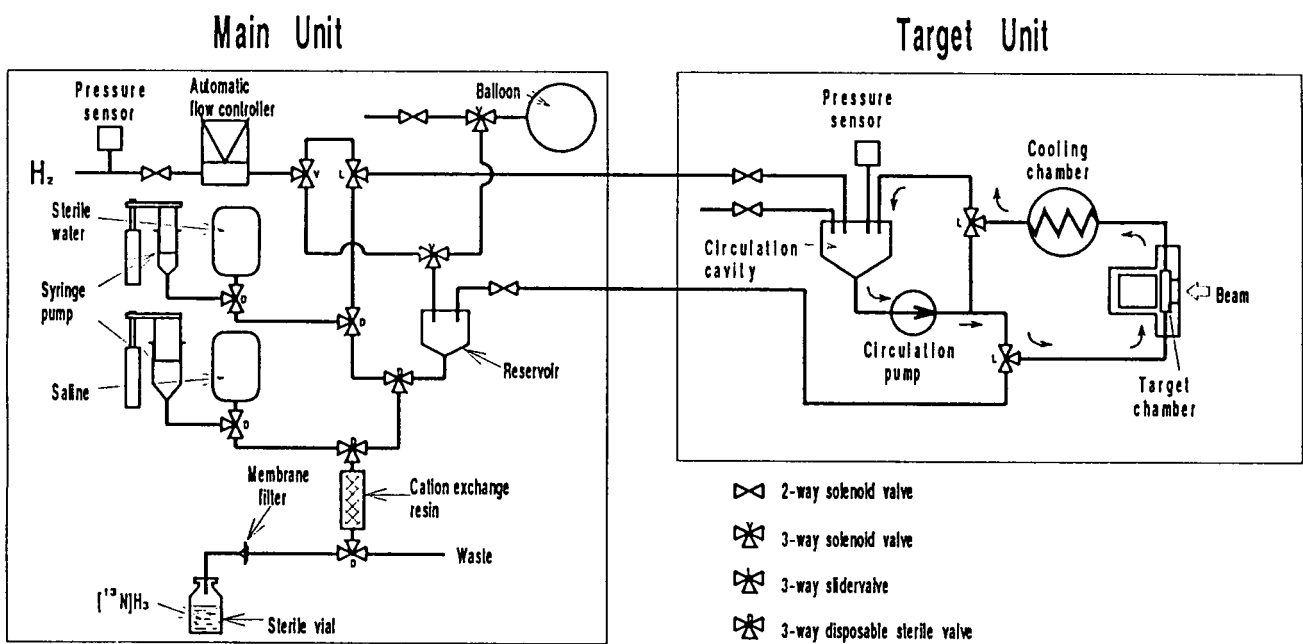


Fig. 1 A flow chart of the automated system.

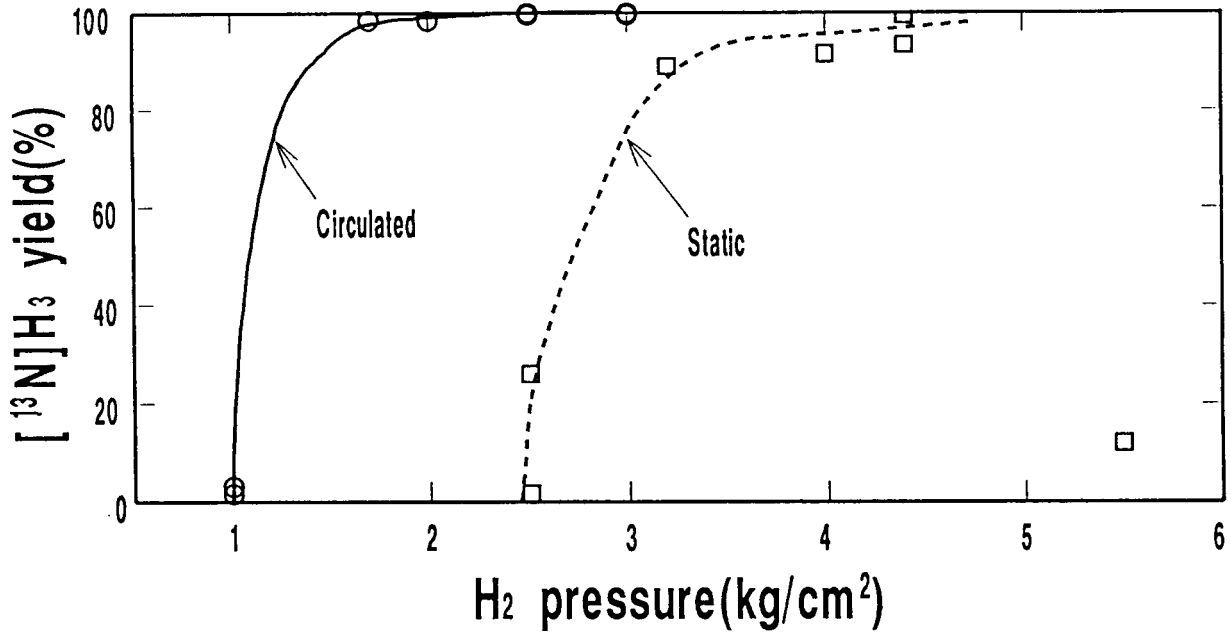


Fig. 2 Correlation curves between the %production yield of $[^{13}\text{N}]\text{H}_3$ and the H_2 pressure. A beam current: 14-18 μA .

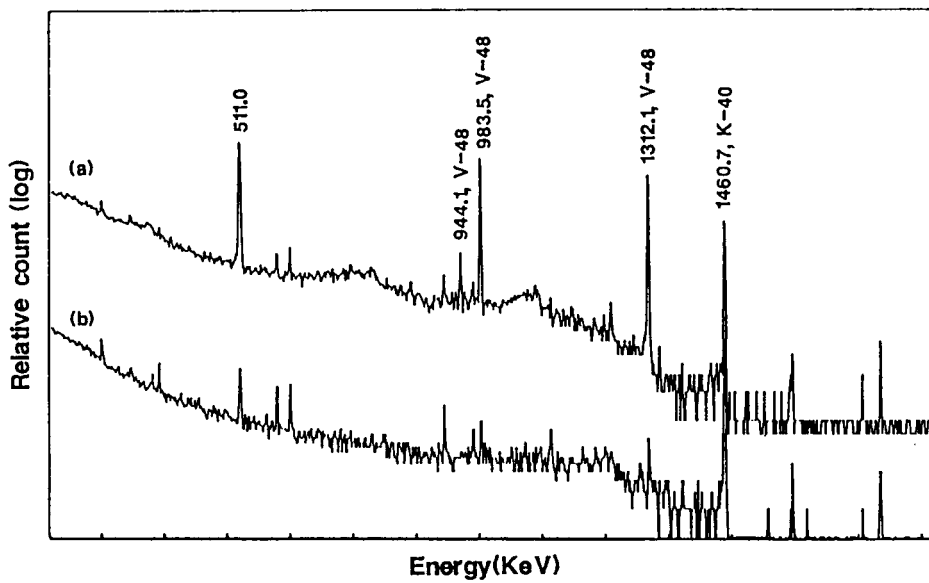


Fig. 3 Gamma-ray spectra of (a) irradiated water target and (b) purified $[^{13}\text{N}]\text{ammonia}$ saline solution. Measured with a pure Ge a week after irradiation.