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

Yamazaki S., Nakagawa H., Tanaka M., Kusumoto K., 
Iwata R.*, Ido T.*

Engineering Research Center, Division of Nuclear Plant, NKK Corp. 
CYRIC, Tohoku University*

Introduction

Since $^{13}$N-ammonia is currently one of the most frequently used 
radiopharmaceuticals for myocardial PET studies, a simple method suitable for routine 
preparation of $[^{13}]$NH$_3$ has been extensively sought. The direct production of $[^{13}]$NH$_3$
by deuteron irradiation of a flowing CH$_4$ target via the $^{12}$C(d,n)$^{13}$N reaction was first 
developed$^1$. However, this method was soon substituted for the synthetic method using
$[^{13}]$NH$_3$ produced by proton irradiation of water via the $^{16}$O(p,$\alpha$)$^{13}$N reaction$^{2,3}$, and this
procedure was automated for routine clinical use$^4$.

Meanwhile another approach to direct production has been sought. The second
notable nonsynthetic method is the on-line conversion of $[^{13}]$NH$_3$ from $[^{13}]$N$_2$ and H$_2$
with microwave discharge$^5$. $[^{13}]$N-nitrogen was converted to $[^{13}]$NH$_3$ in an approximate
65% radiochemical yield within 10 min discharge. An alternate method for direct $[^{13}]$NH$_3$
production using a slurry of $[^{13}$C carbon powder in water was also developed$^6$, and over
50% of the $^{13}$N produced by the $^{13}$C(p,$\alpha$)$^{13}$N reaction was $[^{13}]$NH$_3$ with 15 $\mu$A-20 min
irradiations.

A new and more convenient method for this approach has recently been reported$^7$.
More than 95% of the $^{13}$N produced by proton irradiation of water under H$_2$ pressure was
found as $[^{13}]$NH$_3$ at a proton current of 20 $\mu$A. The present automated system for
$[^{13}]$NH$_3$ production has been developed based on this excellent method, which enables the
in-target product of $[^{13}]$NH$_3$ 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
senors 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 $[^{18}\text{F}]$fluoride production previously reported$^9$. 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 $\mu$m 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 controller$^9$. 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 $[^{13}\text{N}]$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
derector.

Performance Results and Discussion

Nucleogenic $^{13}$N atoms produced in water can take various chemical forms of $^{13}$NH$_3$,
$^{13}$NO, $^{13}$NO$_2^-$ and $^{13}$NO$_3^-$ $^{10,11}$. However, under intense irradiation radiation-induced
oxidation overcomes the other radiolytic reactions involved in low dose irradiations, and
$^{13}$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 $[^{13}\text{N}]$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 $[^{13}\text{N}]$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 $^{48}\text{V}$ 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.

References

Table 1. Production yields of $^{13}$N$\text{H}_3$ vs beam currents with a circulating target.

<table>
<thead>
<tr>
<th>Proton energy (MeV)</th>
<th>Beam current (μA)</th>
<th>Production yield (mCi)</th>
<th>Saturation yield (mCi/μA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>1.8</td>
<td>13.3</td>
<td>14.8</td>
</tr>
<tr>
<td>12</td>
<td>16.1</td>
<td>115.6</td>
<td>14.3</td>
</tr>
<tr>
<td>18</td>
<td>1.0</td>
<td>22.0</td>
<td>43.9</td>
</tr>
<tr>
<td>18</td>
<td>15.0</td>
<td>283.3</td>
<td>37.7</td>
</tr>
</tbody>
</table>

Irradiation time : 10 min  
Target volume : 4 mL  
$\text{H}_2$ 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 $\mu$A.

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