Production of nitrogen-13-labeled ammonia by using 11MeV medical cyclotron: our experience

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Abstract

A method has been developed for the production of ^{13}N-labeled ammonia in usable quantities with negligible contamination. A system was developed and a process for the production of nitrogen-13 ammonium ions from a target material in the form of a dilute solution of ethanol in natural water, i.e. the bombardment of oxygen-16 with protons within the target material. The system includes a device for producing a proton beam which travels along a pre selected path and strikes the target material in a target chamber. This target chamber is positioned in the path of the proton beam such that subjection of the target material to the beam produces nitrogen-13 atoms and alpha particles. These nitrogen-13 atoms are converted in the aqueous solution to ammonium ions and oxides and are conducted from the target holder to a purification cartridge for collecting a purified product containing the ammonium ions.

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A brief history

As early as 1934, Joliot and Curie first produced ammonia-13 [^{13}N]-NH_3 by alpha particle irradiation and heating of boron nitride in sodium hydroxide [1]. Later, [^{13}N]-NH_3 was produced by deuteron irradiation of methane gas or metal carbides, which gave relatively low yields. A more efficient method is the proton irradiation of a natural water target [^{16}O (p, α) ^{13}N] [1, 2]. In this procedure, [^{13}N]-NH_3 is initially produced by hydrogen abstraction from the target water matrix. There is increasing production of oxo anions of nitrogen ($^{13}NO_3$- and $^{13}NO_2^-$) from radiolytic oxidation with increasing target dose. These oxo anions can be converted to [^{13}N]-NH_3 in aqueous solution by use of reducing reagents such as DeVarda's alloy in sodium hydroxide or titanium (III)-chloride/hydroxide [2, 3]. Ido et al. (1981) first described a fully automated synthesis method with titanium (III) chloride used as the reducing agent [4]. The radiochemical purity was >99.9% and the radiochemical yield was 87%-91% within 10min from the end of bombardment (EOB). [^{13}N]-NH_3 also can be produced directly in the target water (in-target production) by adding free radical scavengers (ethanol, acetic acid, or hydrogen) to prevent the formation of the oxo anions. Wieland et al. (1991) applied this method for [^{13}N]-NH_3 production with the use of pressurized, dilute aqueous solutions of acetic acid and ethanol [5]. Berridge et al. (1993) reported that the combination of hydrogen and ethanol was more effective than either alone at high beam doses [6]. One limiting factor of the [^{16}O (p, α) ^{13}N] nuclear reaction is that the relatively small cross-section of the reaction requires accelerators/ cyclotrons of energies >11MeV for production.

Introduction

Nitrogen-13 is a cyclotron produced radionuclide by a ^{16}O (p, α) ^{13}N irradiation reaction with 11MeV protons. This means bombardment of oxygen-16 with protons, emission of α-particles and production of nitrogen-13 as a final [7]. The physical properties of nitrogen-13 are half life of 10min, positron emission decay mode (100%), energy 511keV and abundance 200%. It is most commonly used as NH_3.

$$^{16}O + p = {}^{13}N + \alpha$$

Nitrogen-13- labeled ammonia is produced by reduction of nitrogen-13 labeled nitrates and nitrites. The major chemical species are nitrates, nitrites, ammonia and hydroxyl amine. Among them the nitrates have the highest yield. Nitrogen-13 is converted to NH_3 in aqueous medium. This is an exothermic reaction. The hydrogen evolved flushes out the ^{13}N- ammonia and dissolves in saline solution. It is aseptically filtered through 0.22μm filter before

use. Wieland et al. (1991) have used a pressurized target of aqueous ethanol, in which ethanol acts as a hydroxyl free radical scavenger to improve the yield of ^{13}N- ammonia [4]. The mixture is passed through an anion-exchange resin to remove all anionic impurities. Its pH should be between 4.5-7.5. Then, ^{13}N-labeled ammonia from the [^{13}N] NH_4^+ target appears in the desired chemical form. It needs to be filtered by passage through appropriate columns. Trapped and filtered before being mixed with the correct substrate for dispensing NH_3 in the form of NH_4^+ ions is used primarily for myocardial perfusion imaging by positron emission tomography (PET). The US Food and Drug Administration approved it for measurement of myocardial and cerebral perfusion. Ammonia is also used to label glutamine and asparagines for assessment of tissue viability [8].

Food and drug administration-production technique

Target basics

The aqueous ^{13}N-ammonia (NH_4^+) target system consists of one shielded and one unshielded target supporting units, associated cables and tubing and a cylindrical target body mounted in a target changer. A 0.001 inch thick titanium foil isolates the target material from the helium cooling space and provides the entrance for the beam. The 5 millimolar ethanol and water target material solution completely fill the entire target system.

In operation, the beam passes through the titanium foil and stops into the target material. Nitrogen-13 atoms are produced as the protons of the beam provoke displacement of alpha particles (having two protons and two neutrons) from oxygen-16 atoms in the target water.

Nitrogen-13-ammonia (NH_4^+) is produced in the target and the formation of other nitrogen compounds is inhibited through the action of the ethanol in the target material [9, 10].

Preparation of the target

Preparation of the target requires both daily preparation and target irradiation preparation.

Daily preparation

For the daily preparation we must have the following: a) Assure that the pre-initialization and post-initialization procedures of cyclotron have been completed and cyclotron is in standby mode. b) Prepare 5 millimolar ethanol and sterile water target material solution. c) Replace the target material container connected to the target support unit with a freshly prepared ethanol and water solution. d) Prime the pump. e) After priming, purge the line for 20min and collect it into a vial/beaker at delivery site as waste. f) Run fresh target material through the system. g) Turn off the pump. h) After target purging, disconnect and discard the vial from the delivery tube. Connect an ion exchange column, vent membrane filter and 18 gauge needle to the delivery tube. i) Do one target run for quality control (QC).

Target irradiation preparation

Insert a product delivery needle into a suitable sized sterile vial filled with a quality of USP grade saline solution sufficient to make the target product isotonic. Vent the vial with a second needle and a membrane filter. Empty the liquid from the target support unit and take care of the waste container to prevent from overflow. Determine the irradiation time necessary to produce the desired activity.

A 5 millimolar ethanol and water target material solution is prepared by injecting 0.28ml of USP grade ethyl alcohol in a one liter container of USP sterile water for injection.

The target material container is replaced connected to the target support unit with the freshly prepared ethanol and water target material solution. The pump is primed.

After that the line is purged for 20min and the waste is collected in a vial at the delivery site ("hot" cell).

Fresh target material through the system is run. Target pressure should rise to 300-350 psig.

One target run is done for QC for about 3min.

Production of ^{13}N-ammonia (NH_4^+)

A process for the production of nitrogen-13 ammonium ions in an aqueous solution are as given:

After preparation of the target and QC performance on one batch we can begin the next run. After completing the target preparation target, irradiation may be initiated. The target pressure, beam current, helium pressure and helium flow must be examined periodically for proper operation while the target is being irradiated.

The ^{13}N target system is automatically tested for leak before each run. If there is a leak indication, the run is aborted before the target is irradiated and the control system returns to the main menu.

The target pressure and the beam parameter are monitored until the requested target current has been achieved. The majority of the problem that occurs during a target irradiation is experienced during the first few minutes of the run. If unusual occurrence, abort the run by clicking the abort button [9].

At the end of bombardment the beam is turned off, the target system is tested for leaks and the target unloads. The total time for product delivery will take 200secs.

Materials required

The following items are required for use in preparing ^{13}N-labeled ammonia [8-10]:

Materials required	Amount/run
Sterile water for injection with 5 millimolar USP alcohol (95% ethyl alcohol)	50 ml
30 ml sterile empty vials	2
18 gauge needles	3
Sterile saline solution	As required
Vented 0.22μm membrane filters	2
20ml sterile syringe	1
Ion exchange column	1

Quality control

All radiopharmaceuticals must have QC procedures applied to be suitable for human use [6]: Appearance: clear.

The pH is determined by paper strip. This is a quick method to determine the pH value and this method gives a low radiation dose to the operator. The range should be 4.5-7.5.

Specific activity: No carrier added.

Radionuclide purity: Determined by T½ measurement or by gamma ray spectrum, not less than 99.5% correspond to 511keV, 1.022MeV or Compton scatter peak of ^{13}N, with no individuals impurity present more than 0.1%.

Chemical purity: It is determined by high performance liquid chromatography (HPLC) method. Aluminum and titanium are the common impurities determined by colometric methods.

Radiochemical purity: It is determined by the HPLC method. The radiochemical yield should be greater than 95%.

Bacterial endotoxin: It is determined by limulus ameobosite lysate (LAL) test. Sterility test: It is determined by tuberculosis skin test (TSB).

Daily preparation

We flush the target, whether or not a run will be performed that day, to inhibit bacterial growth in the parts of the target. We are doing first one run for about 3min for QC. After completions of the QC we assure that it fulfilled all parameters of the United States Pharmacopoeia. For the same day we need only the first run for QC and after that we can run multiple times for the patients. Run time of cyclotron is about 10min for patients. For 10min of cyclotron run we get about 3.33GBq of ^{13}N-ammonia (NH_4^+). After QC we do the next run for patients and dispense the dose for injection to the patient.

At present scenario in India we have eight cyclotron facilities. There are many more cyclotron and PET-CT centers under consideration and very soon India will be having sufficient numbers of PET- cyclotron facility to serve the patient even at the far end remote places.

Due to higher cost and maintenance, very few centers have cyclotrons in respect to PET/CT and they depend on nearby cyclotrons for PET radiopharmaceuticals. We are among those who regularly synthesize NH_3 being currently used for PET myocardial perfusion scan. In the near future almost all centers will be operational with the use of NH_3. Due to the very short half life of NH_3 (10min) the transportation of NH_3 is not routinely practiced.

We conclude that cyclotron has high production capabilities and allows enough flexibility for a clinical and research positron emission tomography center; furthermore, it can also be used for regional distribution of ^{18}F-FDG to satellite PET centers.

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