

## Enriched water-H<sub>2</sub><sup>18</sup>O purification to be used in routine <sup>18</sup>F-DG production

Abdul H. Al Rayyes

**Abstract.** <sup>18</sup>O-water obtained from an 2-deoxy-2-[<sup>18</sup>F]-fluoro-D-glucose (<sup>18</sup>F-DG, Synthra) synthesis unit is used for purification. The purification process consists of ultraviolet (UV) irradiation followed by a distillation in a preevacuated system. After purification, the loss of enriched water was about only 5%. Organic compounds, radioisotopes, trace metals and gases are eliminated efficiently. Results show that there is no significant difference in the production yield of 2-deoxy-2-[<sup>18</sup>F]-fluoro-D-glucose ([<sup>18</sup>F]FDG) whether using purified enriched water by the proposed method of purification or using the new enriched water. This method offers the necessary precaution from contamination by tritium during the purification process. The obtained <sup>18</sup>F-DG or Na-<sup>18</sup>F using the purified <sup>18</sup>O-water is of tritium free.

**Key words:** H<sub>2</sub><sup>18</sup>O • purification • <sup>18</sup>F-DG • radiopharmaceuticals

### Introduction

<sup>18</sup>F<sup>-</sup> is one of the most important isotopes used in nuclear medicine and large quantities are produced for the sake of diagnostic, especially for the production of <sup>18</sup>F-DG radiopharmaceutical. Due to the high consumption of water-H<sub>2</sub><sup>18</sup>O in PET centers, the necessity to purify the enriched water from impurities in order to be reused in <sup>18</sup>F-DG production has been a high priority task. It is well known that good manufacturing practices (GMP) guidelines impose the use of well established and validated method to purify and recycle the enriched water.

The irradiated enriched water cannot be re-irradiated by proton beam in the presence of organic impurities due to the formation of high pressure in target. Also this water will be contaminated by ions sputtered from the target foil, usually Havar and target body manufactured from titanium or niobium [2, 4, 6, 8]. Tritium is another radioactive by-product produced by the nuclear reaction <sup>18</sup>O(p,t)<sup>16</sup>O [5]. The presence of the impurities affects the reaction yield of the <sup>18</sup>F-DG production (giving lower yield).

Different methods have been used for the purification of recovered enriched water from FDG synthesis units. Ozonolysis has been used to remove organic impurities from the used enriched water [1]. UV, ozone and solid-phase extraction methods were also used as purification methods [7].

The aim of this work was the evaluation of a purification method for water-H<sub>2</sub><sup>18</sup>O using UV treatment followed by distillation, in a preevacuated system, in order to be reused for <sup>18</sup>F-DG production.

A. H. Al Rayyes  
Cyclotron Division,  
Chemistry Department,  
Atomic Energy Commission of Syria,  
P. O. Box 6091, Damascus, Syria,  
Tel.: +963 11 2132580, Fax: +963 11 6112289,  
E-mail: cscientific@aec.org.sy

Received: 25 February 2010

Accepted: 21 June 2010

## Experimental

The production of  $^{18}\text{F}^-$  was performed through the  $^{18}\text{O}(p,n)^{18}\text{F}$  reaction using a 17.5 MeV proton beam energy from a cyclone-30 cyclotron. 97% enriched water  $\text{H}_2^{18}\text{O}$  purchased from Isoflex (Russia) was used. The titanium target body with a 25  $\mu\text{m}$  Havar window (from Goodfellow) has a volume of 2 ml. The target is water-cooled and the window is helium cooled, no filter is mounted between the target and water recovery system. The bombardment beam current is fixed on 30  $\mu\text{A}$  giving a target pressure of 34 bars. The bombardment time is 90 min. The average activity of  $^{18}\text{F}^-$  under these conditions is  $2565 \pm 140$  mCi at the end of bombardment. Activities are measured using a calibrated Capintec CRC 15 dose calibrator.

$^{18}\text{F}^-$  with enriched water  $\text{H}_2^{18}\text{O}$  is transferred to a FDG synthesis module (Synthera, obtained from Ion Beam Applications).  $^{18}\text{F}^-$  is trapped in the quaternary methyl ammonium (QMA) cartridge anion ex-change purchased from (Waters). The enriched water is recovered to a separate vial and  $^{18}\text{F}^-$  is eluted to a reactor with 300  $\mu\text{l}$  of  $\text{K}_2\text{CO}_3$  and 22.6 mg of Kryptofix 222 dissolved in 300  $\mu\text{l}$  of acetonitrile obtained from advanced biochemical compounds (ABX, Germany).

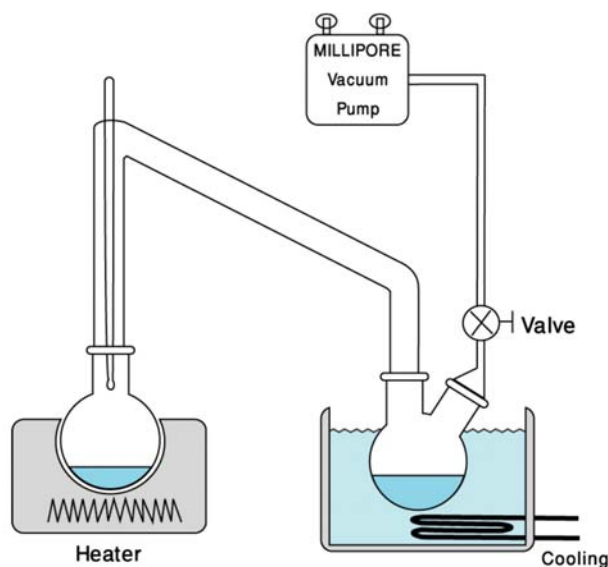


Fig. 1. Schematic representation of the distillation system.

$^{18}\text{F}$ FDG is prepared based on the nucleophilic substitution reaction, described by Hamacher [3] using the automated (Synthera) module.

The purification of  $^{18}\text{O}$ -water recovered from the Synthera- $^{18}\text{F}$ FDG synthesis system has been performed in three steps: 1) irradiation with UV; 2) centrifuging, if necessary; 3) distillation in preevacuated atmosphere.

UV irradiation of recovered enriched water was performed by a 705 UV digester system from Metrohm. This system comprises a wet part and control unit. The wet part contains a UV high pressure mercury lamp, a cooling system and a sample holder for 12 quartz glass tubes, each can containing 12 ml. The polytetrafluoroethylene (PTFE) stoppers act as cooling fingers and prevent atmospheric contamination. After UV treatment, the enriched water was distilled in a preevacuated and closed system equipped with a membrane vacuum pump. Figure 1 shows the arrangement of the closed distillation system. A 50 ml batch of treated enriched water by UV is used for distillation. The sterilized apparatus is closed and the air is evacuated by the membrane vacuum pump. The purified enriched water is received in a second cooled flask.

Several types of analysis were performed in order to qualify the purified enriched water.

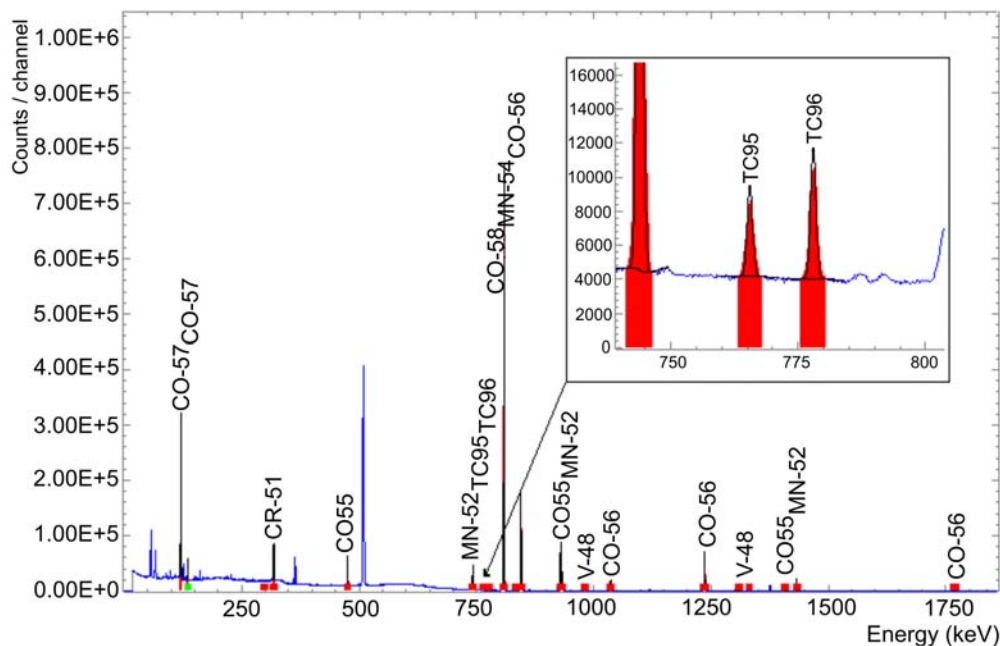
The by-product radioisotopes were counted by gamma spectrometry using a high purity germanium (HPGe) detector with 25% efficiency, where the amplifier output of the detector was processed by a 4096 channel, multi channel analyzer (MCA) system. The detection of organic materials in the purified water was carried out using a gas chromatograph from Shimadzu equipped with a flame ionization detector (FID) and a capillary column, CBP20-M25-025 (25 m  $\times$  0.22 mm), filled with polyethylene glycol. A programmed temperature from 50°C to 165°C and a nitrogen gas carrier were used.

A developed anodic stripping voltammetry system from Metrohm (VA processor 693 with VA stand 694) was used for trace metals analysis.

The determination of tritium was performed using a liquid scintillation counter (LSC – Wallac Gardian, from PerkinElmer). Samples of 500  $\mu\text{l}$  of enriched water were mixed with 10 ml of a scintillation cocktail (Hi Safe 3) and beta activity was measured and compared with standard water.

Table 1. Activities of the radionuclides detected before and after purification

Isotope	$T_{1/2}$ (h)	$E$ (keV)	Gamma (%)	Activity in the enriched water before purification (Bq/ml) $\pm$ uncertainty	Activity measured in QMA (Bq) $\pm$ uncertainty	Activity in the enriched water after purification (Bq/ml) $\pm$ uncertainty
$^{57}\text{Co}$	6522.48	122.06	85.6	$52.0 \pm 2$	$665.6 \pm 7.9$	$0.2 \pm 0.01$
$^{51}\text{Cr}$	664.87	320.08	9.8	–	$1925.0 \pm 111.7$	$0.1 \pm 0.3$
$^{95}\text{Tc}$	20.0	765.64	94.3	$2.5 \pm 1.5$	$39.7 \pm 13.9$	–
$^{96}\text{Tc}$	104.4	778.1	100	–	$18.8 \pm 6.2$	–
$^{58}\text{Co}$	1698.72	810.67	99.4	$53.2 \pm 3.6$	$2773.6 \pm 22.2$	$0.30 \pm 0.01$
$^{54}\text{Mn}$	7488.0	835.0	99.9	$0.4 \pm 0.8$	$20.2 \pm 4.8$	$0.12 \pm 0.01$
$^{56}\text{Co}$	1850.88	846.7	99.92	$14.0 \pm 2$	$661.9 \pm 11.9$	$0.16 \pm 0.01$
$^{55}\text{Co}$	17.54	931.2	75	$11.5 \pm 2.7$	$8914.4 \pm 115.9$	–
$^{48}\text{V}$	383.4	983.4	100	$0.4 \pm 0.8$	$16.3 \pm 5.7$	–
$^{52}\text{Mn}$	136.8	1433.9	100	$46.7 \pm 2.4$	$1018.3 \pm 31.5$	–



**Fig. 2.**  $\gamma$ -Spectrum of recovered water from the recovery system, peaks of <sup>95</sup>Tc and <sup>96</sup>Tc are shown in a separate spectrum.

**Results**

**Radioisotopes and trace metals concentration in the enriched water before and after its purification**

Due to proton irradiation of the target body and target window, radioisotopes are formed. Some of them can pass from the irradiated surface to the enriched water. 10 radioisotopes have been detected in the recovered enriched water from the <sup>18</sup>F<sup>18</sup>FDG synthesis system. The activities of these radioisotopes are shown in Table 1. The gamma ray spectrum of this water is shown in Fig. 2.

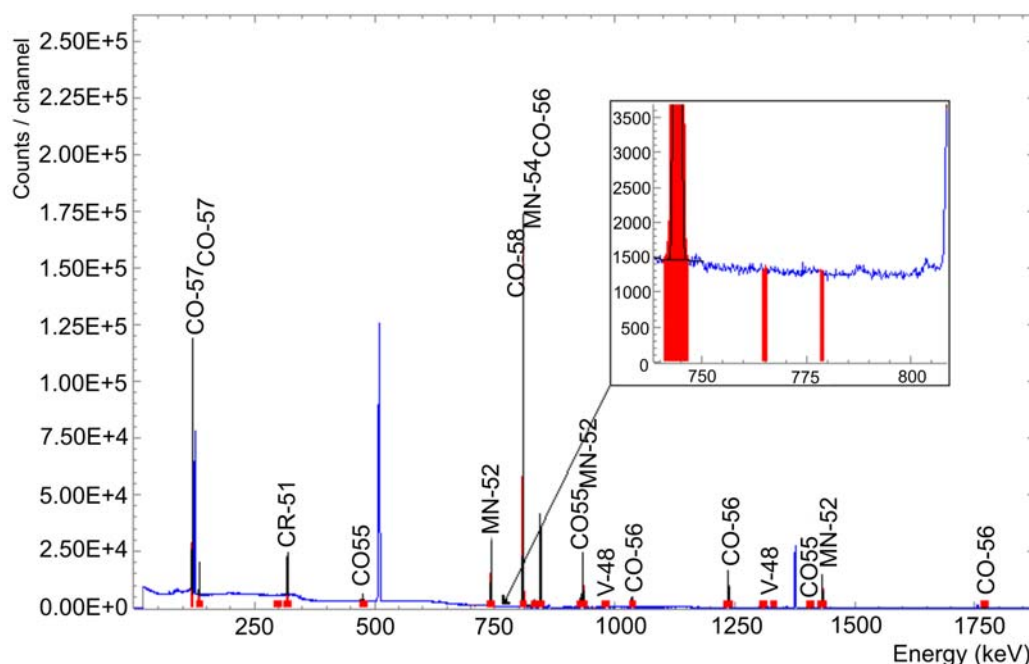
As can be seen from Table 1, the activities of different radioisotopes measured in the QMA cartridge confirm that, depending on radioisotopes identity, QMA can retained from 25 to 90% metallic radioisotopes.

The gamma ray spectrum of radioisotopes present in the QMA cartridge is shown in Fig. 3.

Trace metals, Ti, Cr and Co in the enriched water before purification, coming from the target body and target window were analyzed. The concentration of Ti, Cr and Co were found to be  $2.7 \pm 0.04$  mg/l for Ti and below of detection limit for Cr and Co.

Also Table 1 shows the activities of different radioisotopes in the purified enriched water calculated in Bq/ml. As can be seen from these results a very low traces of different radioisotopes are measured in the purified enriched water confirming the feasibility of using the applied method of purification.

The concentrations of trace metals were below the detection limit in the purified enriched water obtained by our method of purification. The detection limits of Ti, Cr and Co were 0.4, 0.3 and 0.4  $\mu$ g/l, respectively.



**Fig. 3.**  $\gamma$ -Spectrum of the QMA cartridge.

**Table 2.** Tritium activities in different samples

Sample	Activity of tritium
Purified irradiated enriched water	113 ± 2 (kBq/ml)
Enriched water after irradiation and passing QMA	115 ± 2 (kBq/ml)
Prepared <sup>18</sup> FDG 5 days old	0.02 ± 0.01 (Bq/ml)
Prepared <sup>18</sup> NaF 5 days old	0.04 ± 0.01 (Bq/ml)
Standard water	0.10 ± 0.03 (Bq/ml)

Table 2 shows the results of tritium activities in different extracted samples. Taking into account the radioactive properties of tritium (beta emitter,  $T_{1/2} = 12.3$  y), our method of distillation in a closed atmosphere offers necessary precaution for a possible contamination during the open distillation used in many centers.

#### Organic impurities in the enriched water before and after its purification

The organic substances detected by gas chromatography in the irradiated enriched water are mainly acetonitrile and ethanol; their concentrations are  $0.70 \pm 0.01$  and  $0.02 \pm 0.01$  mg/ml, respectively. Also, due to the synthesis process of <sup>18</sup>FDG and <sup>18</sup>FNa, nonmeasurable quantities of organic substances can pass from the QMA to the enriched water.

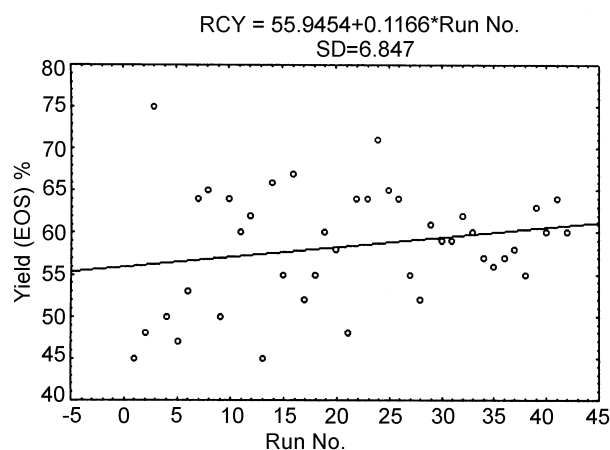
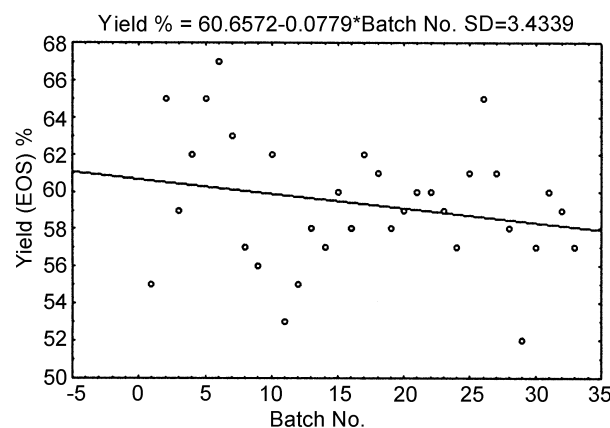
We noticed that the treatment of enriched water by our UV system for 12 h caused, in the first purified batches, a slight increase in target pressure during irradiation which we attribute to the remaining of some traces of organic materials and gases that we could not measure by gas chromatography. This anomaly was solved by increasing the treatment duration by UV to 20 h. After this treatment time, no more cases of pressure increase was observed and the target pressure, during irradiation, was identical whether using purified enriched water or fresh, new enriched water.

#### <sup>18</sup>FDG production yield using purified and fresh, enriched water

33 <sup>18</sup>FDG production runs have been carried out using the recycled purified enriched water and 42 <sup>18</sup>FDG production runs using the new enriched water. The mean radiochemical yield of <sup>18</sup>FDG using purified enriched water was  $60 \pm 4\%$ , while the mean of this yield was  $59 \pm 8\%$  when using fresh, new enriched water. These results confirm that no significant difference in the <sup>18</sup>FDG production yield occurred whether using purified enriched water by this method of purification, or fresh new enriched water. Figures 4 and 5 show the <sup>18</sup>FDG production yields using fresh, new and purified enriched water, respectively. In addition, no radionuclides impurities were detected in all the produced <sup>18</sup>FDG batches.

#### Conclusion

The proposed purification method of enriched water obtained from an FDG synthesis system shows that

**Fig. 4.** <sup>18</sup>FDG production yield using fresh, new enriched water.**Fig. 5.** <sup>18</sup>FDG production yield using purified enriched water.

about 95% of <sup>18</sup>O-water is recovered after the purification. Organic compounds, radioisotopes and trace metals are eliminated efficiently by this method. The results show that no significant difference in the <sup>18</sup>FDG production yield is occurring whether using purified water by the proposed method or new enriched water. Our method of purification offers necessary precautions to avoid any contamination of laboratory surfaces by tritium. Tritium was not detected in the produced <sup>18</sup>FDG or Na-<sup>18</sup>F when using the recycled enriched water.

**Acknowledgment.** The author is grateful to the IAEA for supporting this research through CRP 13484, and thankful to Dr M. Haji-Saeid head of Ind. Applications and Chemistry Section at the IAEA. Thanks to Prof. I. Othman (GD of AECS) for the encouragement and support. Thanks to Y. Ailouti, A. Abdelziz and N. Zakkar for their technical support.

#### References

1. Asti M, Grassi, E, Sghedoni R *et al.* (2007) Purification by ozonolysis of <sup>18</sup>O enriched water after cyclotron and the utilization of the purified water for the production of [<sup>18</sup>F]FDG (2-deoxy-2-[<sup>18</sup>F]-fluoro-D-glucose). *Appl Radiat Isot* 65:831–835
2. Gillies JM, Najim N, Zweit J (2006) Analysis of metal radioisotope impurities generated in [<sup>18</sup>O]H<sub>2</sub>O during

- the cyclotron production of fluorine-18. *Appl Radiat Isot* 64:431–434
3. Hamacher K, Coenen HH, Stocklin G (1986) Efficient stereospecific synthesis of no-carrier-added 2-[<sup>18</sup>F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. *J Nucl Med* 27:235–238
  4. Ito S, Sakane H, Deji S, Saze T, Nishizawa K (2006) Radioactive by-products in [<sup>18</sup>O]H<sub>2</sub>O used to produce <sup>18</sup>F for [<sup>18</sup>F]FDG synthesis. *Appl Radiat Isot* 64:298–305
  5. Ito S, Saze T, Sakane H, Ito S, Ito S, Nishizawa K (2004) Tritium in [<sup>18</sup>O] water containing [<sup>18</sup>F] fluoride for [<sup>18</sup>F] FDG synthesis. *Appl Radiat Isot* 61:1179–1183
  6. Marengo M, Lodi F, Magi S, Cicoria G, Pancaldi D, Boschi S (2008) Assessment of radionuclidic impurities in 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose([<sup>18</sup>F]FDG) routine production. *Appl Radiat Isot* 66:295–302
  7. Moon WY, Oh SJ, Cheon JH *et al.* (2007) Simple purification of recovered [<sup>18</sup>O]H<sub>2</sub>O by UV, ozone and solid-phase extraction methods. *Appl Radiat Isot* 65:635–640
  8. Wilson JS, Avila-Rodriguez MA, Johnson RR, Zyuzin A, McQuarrie SA (2008) Niobium sputtered Havar foils for the high-power production of reactive [<sup>18</sup>F] fluoride by proton irradiation of [<sup>18</sup>O]H<sub>2</sub>O targets. *Appl Radiat Isot* 66:565–570