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Optimized Treatment and Recovery of Irradiated [^{18}O]-Water in the Production of [^{18}F]-Fluoride

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Abstract: Enriched [^{18}O]-water is the target material for [^{18}F]-fluoride production. Due to its high price and scarce availability, an increased interest and necessity has arisen to recycle the used water, in order to use it multiple times as a target material for [^{18}F]-fluoride production. This paper presents an efficient treatment and reprocessing procedure giving rise to high chemical quality [^{18}O]-water, thereby maintaining its enrichment grade. The reprocessing is subdivided into two main steps. In the first step, the [^{18}F]-FDG (fluorodeoxyglucose) synthesis preparation was modified to preserve the enrichment grade. Anhydrous acetonitrile is used to dry tubing systems and cartridges in the synthesis module. Applying this procedure, the loss in the enrichment throughout the reprocessing is <1%. The second step involves a fractional distillation in which the major part of the [^{18}O]-water was recycled. Impurities such as solvents, ions, and radioactive nuclides were almost completely separated. Due to the modified synthesis preparation using acetonitrile, the first distillation fraction contains a larger amount of an azeotropic [^{18}O]-water/acetonitrile mixture. This fraction is not further distillable. Contents of the remaining [^{18}O]-water were separated from the azeotropic mixture by using a molecular sieve desiccant. This process represents a fast, easy, and inexpensive method for reprocessing used [^{18}O]-water into new [^{18}O]-water quality for further application.

Keywords: recycling of [^{18}O]-water; enrichment grade; fractional distillation; azeotropic mixtures; molecular sieve desiccant

1. Introduction

The [^{18}O]-water recovered from the synthesis of [^{18}F]-based radiopharmaceuticals could in principle be reused for further irradiation. During synthesis and irradiation, the [^{18}O]-water gets contaminated with solvents and ions from the synthesis module and the target [1,2]. The synthesis of [^{18}F]-based radiopharmaceuticals involves an [^{18}F]-fluoride separation step, in which the irradiated [^{18}O]-water is eluted through an anion exchange cartridge, which is commonly preconditioned with [^{16}O]-water [3]. Most of the end users also rinse the target and the [^{18}F]-fluoride transfer line with [^{16}O]-water [4]. Hence, the degree of enrichment drops through intermixing with [^{16}O]-water. For a further irradiation, the recycled [^{18}O]-water has to be of high chemical quality, and of the highest possible enrichment grade. A method for recycling the [^{18}O]-water must also be able to separate all impurities [5]. The recycling processes using condensation and/or UV-irradiation did not lead to good [^{18}O]-water quality, sufficient quantity, or a stable enrichment grade [6–8]. Most of the end users collect the irradiated [^{18}O]-water samples and return them to the manufacturers for recycling. The aim of this work was to develop a cost-effective, coherent reprocessing concept for [^{18}O]-water suitable for routine production. The desired goal was to recycle >90% of the [^{18}O]-water, while maintaining the enrichment grade with the prescribed method. For further radiation, the [^{18}O]-water quality needs to possess a high chemical quality, thereby attaining the release specifications [9].

2. Materials and Methods

2.1. Overview of the Optimized Recovery Method

For use in the target, the [^{18}O]-water has to be present with high chemical and microbiological purity, as well as sufficient enrichment grade. After the bombardment, the irradiated [^{18}O]-water is usually transferred via [^{18}F]-transfer lines into the synthesis modules. For a meaningful recovery, an additional rinse of the transfer lines and target was conducted exclusively with [^{18}O]-water. During the synthesis of [^{18}F]-radiopharmaceutical, the irradiated [^{18}O]-water was passed through an anion exchange cartridge to separate the [^{18}F]-fluoride from the [^{18}O]-water, which was collected separately. Residues of [^{16}O]-water on the cartridge and in the tubing system of the module would lead to a significant contamination of the [^{18}O]-water with [^{16}O]-water. Therefore, an improved synthesis module preparation ensures the maintenance of the enrichment grade of the [^{18}O]-water. A fractional distillation was performed for the purification of the [^{18}O]-water. The first collected fraction contained an azeotropic [^{18}O]-water/acetonitrile mixture (10–15% of the preparation). The [^{18}O]-water was separated from this azeotropic mixture via an optimized molecular sieve procedure. Microbiological contaminants were removed via UV-irradiation before the final distillation, followed by a quality control of the recycled [^{18}O]-water before its release for the next irradiation. A schematic overview of the whole recovery method is shown below in Figure 1.

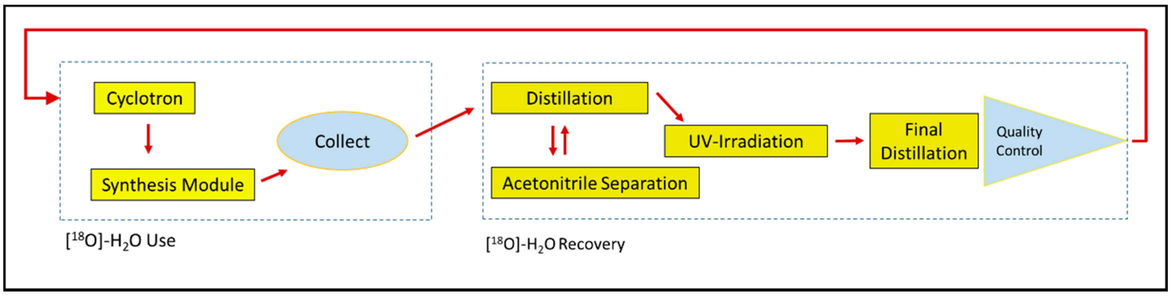

Figure 1. Overview of the optimized recovery method.

2.2. Improved Synthesis Preparation for Maintaining the Enrichment Grade

The use of [^{16}O]-water to rinse the transfer lines during the cleaning process and the preparation of the synthesis modules resulted in a significant loss of the enrichment grade in the collected [^{18}O]-water. During the synthesis, [^{18}O]-water was recovered by trapping [^{18}F]-fluoride on an anion exchange cartridge (Chromafix 30-PS-HCO$_3$ by Macherey-Nagel) and subsequent elution with an aqueous potassium carbonate solution [10]. The cartridge itself was also preconditioned with 5 mL of [^{16}O]-water. Residues of the [^{16}O]-water reduce the enrichment grade of the recollected [^{18}O]-water. First attempts to remove the water residues from the cartridge with a stream of helium gas still revealed a significant loss of the enrichment grade (Table 1). A clear improvement in the retention of the enrichment grade was achieved by an additional flushing of the red tubing system in Figure 2 with anhydrous acetonitrile [11]. Additionally, the anion exchange cartridge was rinsed with 1 mL of anhydrous acetonitrile after conditioning. After performing the above-mentioned steps, the synthesis module was prepared according to common literature procedures [12]. A flow chart representing the tubing system is shown in Figure 2.

Table 1. Influence of the synthesis preparation on the enrichment grade.

Enrichment Grade	Common Synthesis Preparation	Drying Module + Cartridge with Helium Flow	Drying Module + Cartridge with Acetonitrile
[%]	74.0–80.0	84.0–88.0	95.0–96.5

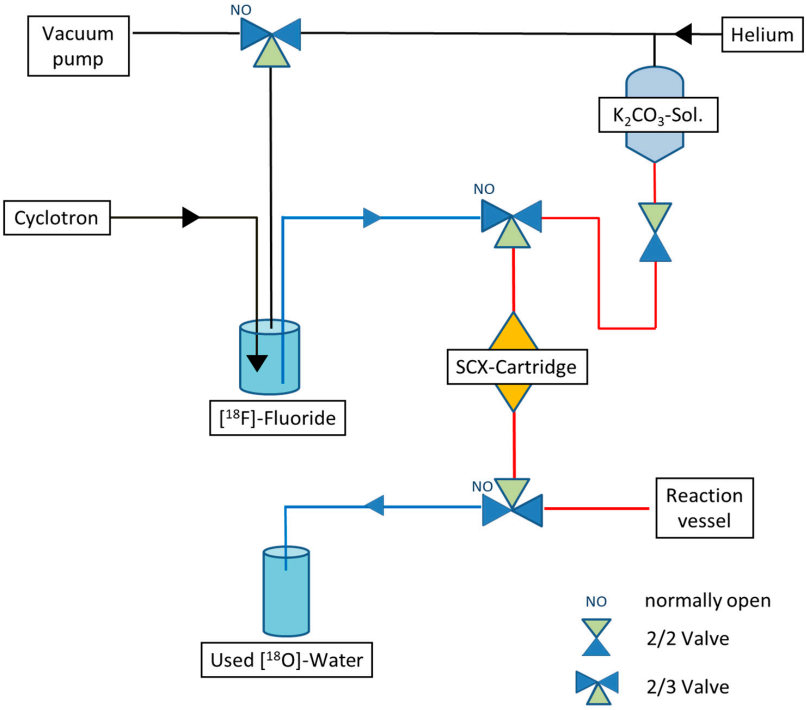

Figure 2. Schematic partial representation of the tubing system.

2.3. Purification by Fractional Distillation

The distillation is a simple separation process that can be used for the cleaning and separation of liquids with boiling points below 150 °C. A fractionated distillation in commercial glassware is used for the purification of the collected $[^{18}O]$-water [13]. The distillation unit (Figure 3a) consists of a heating jacket, a 500 mL flask (a 1–2 mL flask can also be used), a 30 cm vacuum-coated Vigreux column, a thermometer (20–150 °C), a 100 mL distillate receiver with vent stopcock, and a special distillation cooling attachment (Figure 3b). This special semi-micro scale apparatus allows an improved separation of the fractions, thereby obtaining a lower volume loss.

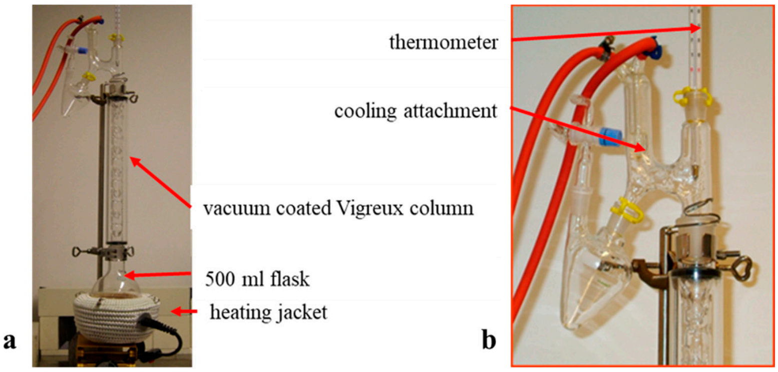

Figure 3. (**a**) Distillation unit; (**b**) special distillation cooling attachment.

2.4. Separation of the [^{18}O]-Water from the Azeotropic Mixtures by Means of a Molecular Sieve

The idea of the separation of [^{18}O]-water from organic solvents using a desiccant (including molecular sieves) has already been described in the literature [14]. We adapted this method for the purification of the first distilled fractions, which contain an [^{18}O]-water/acetonitrile mixture with an acetonitrile content of 50–80% (10–15% of the preparation). Separation of the [^{18}O]-water by further distillation is not possible [15]. A simple and suitable routine method for an almost complete recovery of the [^{18}O]-water from azeotropic mixtures using molecular sieve 3Å is briefly described below [16]. Special attention had been paid to the preservation of the [^{18}O]-enrichment grade.

A condensation unit (Figure 4) consisting of a three-necked flask with a thermometer, a stopcock, an inlet pipe with a diameter of 10 mm, and a heating jacket has been constructed. A cooling trap with ice cooling was connected to the diaphragm vacuum pump via PTFE tubing connections with a piston and a three-way stopcock.

The use of a molecular sieve containing [^{16}O]-substitute groups led to a significant loss of enrichment grade. Therefore, the molecular sieve has to be pretreated before use. Dust and breakage from the molecular sieve 3Å was removed by washing with double distilled water. For activation, the molecular sieve was dried under argon flow in the condensation unit at a maximum temperature of 300 °C. Subsequently, the molecular sieve was mixed with [^{18}O]-water of about 50% enrichment grade, and dried again at about 200 °C. Further handling and storage was carried out under argon.

For the separation of the [^{18}O]-water from the azeotropic [^{18}O]-water/acetonitrile mixture, 150 g of the preconditioned 3Å molecular sieve was added to 150 g of the mixture, and allowed to stand under argon for 24 h. After 24 h, most of the [^{18}O]-water molecules had been absorbed by the molecular sieve. After decantation of the acetonitrile, the residual amount of acetonitrile was removed by drying for 1 h at 40 °C under a membrane pump vacuum, and subsequently under a weak argon stream for another 5 min. Following this, the cold trap was cleaned and placed in ice water. For the recovery of the [^{18}O]-water, the molecular sieve was heated for 3 h under atmospheric pressure in a weak stream of argon at a maximum temperature of 200 °C. The pure [^{18}O]-water was collected in the cold trap. The solvent content of the recollected [^{18}O]-water is usually >1%, and can be returned to the distillation.

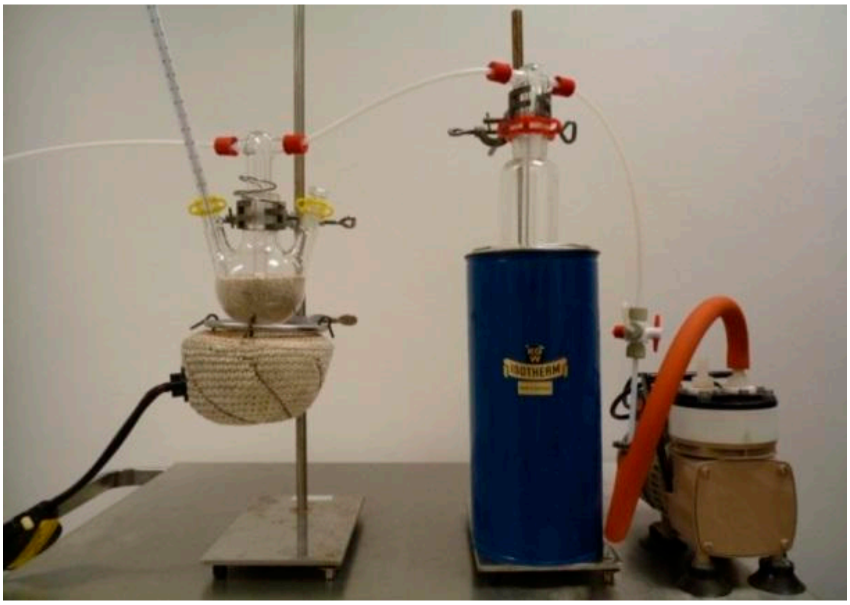

Figure 4. Condensation unit for the recovery of [^{18}O]-water from azeotropic mixtures.

2.5. Determination of the Degree of Enrichment via Pycnometry

The effects on the enrichment grade of the individual process steps were examined via pycnometry [17,18]. With an increased amount of [^{18}O] in [^{16}O]-water, an increase of the density of the [^{18}O]-water mixture is observed. The increase of the density is dependent on the increase of the amount of [^{18}O] present in the [^{18}O]-water.

$$\rho[^{18}\text{O}]\text{-water}(T) = \rho[^{16}\text{O}]\text{-water}(T) \times (20.0153/18.0153)\ [\text{g/mL}] \text{ for pure } [^{18}\text{O}]\text{-water} \quad ()$$

(20.0153/18.0153) is the molecular weight ratio of [^{18}O]-water to [^{16}O]-water.

Since the number of atoms is proportional to the volume, the enrichment grade is dependent on the density (ρ = m/V) at constant temperature.

$$\rho_{\text{ sample}} = (w[^{18}\text{O}]\text{water} \times \rho[^{18}\text{O}]\text{water}) + (w[^{16}\text{O}]\text{water} \times \rho[^{16}\text{O}]\text{water}) \quad ()$$

At a constant volume measurement (using the same pipette), the enrichment grade can be determined by the mass ratio of [^{18}O]-water to [^{16}O]-water. The density of the [^{18}O]-water can be determined experimentally, and the enrichment grade can be calculated using the following formula:

$$w_{\text{sample}}\left[^{18}\text{O}\right] = 9 \times \frac{m\left[^{18}\text{O}\right]\text{water}}{m\left[^{16}\text{O}\right]\text{water}} - 9[\%]$$

m [^{16}O]-water (T) = mass of [^{16}O]-water at certain temperature and pipette
m [^{18}O]-water (T) = mass of [^{18}O]-water sample at certain temperature and pipette
w: enrichment grade in %
9 = 1/K, K = (20.0153/18.0153) − 1;
K: constant from the difference of the molecular weights.

Hence, the enrichment grade is determined by simple weighing in combination with volume measurement, whereas the density is temperature dependent.

3. Results

For the validation of the purification procedures and the quality control of the purified [^{18}O]-water, the following parameters (Table 2) have been investigated.

Table 2. Examination parameters for the quality control of [^{18}O]-water.

Parameter	Method	Device
[^{18}O]-Enrichment grade	Relative pycnometry	Libra, pipette
Solvent content	Gas chromatography	Trace 1310 Thermo Fischer, FID
Aromatic compounds	UV-Spectroscopy	Genesys 10 S Thermo Fisher
Ions	Conductivity measurement	Vario Cond, WTW, 0.001-200 µS/cm
Radioactive nuclide	Gamma measurement, multi-channel-analyzer	Germanium Detector GC 1200-7500 SL Canberra

Using fractionated distillation, a separation of the [^{18}O]-water from the solvent mixture in the first step was possible, in both good quantity and sufficient quality (Table 3). About 80% of the used [^{18}O]-water can be recycled in the first step. The process was established in common laboratory scales of 1 to 2 L. No differences in the yields of activity during [^{18}F]-fluoride production and the radiochemical yields of [^{18}F]-FDG in the following radiosynthesis were observed, comparing the use of recycled

[^{18}O]-water to fresh [^{18}O]-water. After more than 10 times of use and purification, no accumulation of any impurity, in particular of radionuclides, has been detected. Furthermore, during irradiation in the cyclotron, the recycled [^{18}O]-water showed no pressure increase in the target, normally observed when additional solvent residues are present. It has also been found that purification by fractional distillation does not diminish the enrichment grade. In summary, following the above-mentioned recycling process, used [^{18}O]-water can be recovered without any loss in the enrichment grade.

Table 3. Quality of the recovered [^{18}O]-water.

Parameter	Unit	Collected-[^{18}O]-H_2O	Main Fraction	First Fraction	Residue	Specification
Volume	%	100	80	15	5	-
Conductivity	µS/cm	1200	0.9	133	3000	<10
Acetonitrile	%	8–10	<0.00001	40–80	<0.1	<0.0001
Ethanol	µg/mL	126	<0.1	1600	<0.1	<100
Acetone	µg/mL	19.2	<0.1	260	<0.1	<100
UV-Spectrum	220 nm	0.120	0.0005	0.052	2.095	<0.2
	280 nm	0.040	0.0014	0.010	0.400	<0.1
MCA	keV	810; 846; 1238; 1460; 1770	not detectable	136; 1460	122; 320; 744; 810; 846; 1037; 1238; 1770	not detectable
[^{18}O]-Enrichment	%	100	<0.1	0.3	99.6	-
	%	95.0	94.5	-	-	95.5

Gamma spectroscopy, in particular a multi channel analyzer (MCA) was used to determine the radionuclidic purity of the recovered [^{18}O]-water fractions. Specifications for [^{18}O]-water request no detectable energy lines. Aliquots of the different [^{18}O]-water fractions, comprising the same volume and geometry, were examined in regards to their relative nuclidic purity (Table 3).

During the development of an improved synthesis procedure, the effects on the enrichment grade were investigated. Conventional cleaning of the synthesis module reduces the enrichment grade of the [^{18}O]-water by about 25% per use. As part of the further optimization, with [^{16}O]-water-contaminated collection vessels, tubing and cartridges were identified as the origin of the contaminations. By excluding these contaminants, the loss in the enrichment grade was reduced to 15%. Further helium drying reduced the enrichment loss to 10%. However, a constant enrichment grade (98.3% to 98.8%) could be obtained by further rising of the whole system with acetonitrile. The results of the optimization steps in the improved preparation and handling protocol that preserve the enrichment grade of the [^{18}O]-water are summarized in Table 1.

The synthesis preparation with acetonitrile drying increased the acetonitrile content in the used [^{18}O]-water from approximately 1% to 8–10%. As a result, a volume increase of the first distillation fraction from around 10% to 25% was obtained. The [^{18}O]-water in this azeotropic mixture can be separated by the molecular sieve process, without any loss in the enrichment grade (Table 4).

Table 4. Influence of the recovery on the enrichment grade.

Enrichment Grade	[^{18}O]-Water Original	[^{18}O]-Water after Distillation	[^{18}O]-Water after Molecular Sieve
[%]	97.0	96.5	96.5

The use of a new molecular sieve could possibly lead to a reduction in the enrichment grade of the [^{18}O]-water, due to [^{16}O] substituted groups in the resin. Therefore, the molecular sieve has to be preconditioned before use. The quantitative determination of [^{16}O]-substituted groups was conducted by isotope dilution analysis (Tables 5 and 6).

Table 5. Parameters of the molecular sieve separation method.

Molecular Sieve	**Amount**	**Equates to X mL H_2O**
	150 g	200 mL
Absorbed water	0.2 mL/g	30 mL
Substituted O-Functions	3.3 mmol/g	7.6 mL

Table 6. Temperature range of the separation method using a molecular sieve.

Separation Temp. for Acetonitrile	**40 °C**	**Desorption Temp. $[^{18}O]$-H_2O**	**200 °C**
Recovery rate	>95%	**time**	30 min

The untreated molecular sieve contains 3.3 mmol/g substitutable O-functions, which reduces the enrichment grade, when occupied by $[^{16}O]$. In our case, that correlates to 7.6 mL of water per 150 g, which would reduce the enrichment grade from 90% to 72%. After conditioning and multiple uses of the molecular sieve, the separation of the $[^{18}O]$-water was achieved without detectable reduction of the enrichment grade.

The molecular sieve was left in the apparatus under argon, and can be reused several times. Therefore, the disadvantages of using a molecular sieve are negligible, or at least more than offset by the considerable robustness of the process.

4. Discussion

The developed recycling concept allows the repetitive recovery of >90% of the $[^{18}O]$-water, while retaining the enrichment grade and the required chemical quality, which corresponds to the release specifications, and allows for reuse without any loss in performance of the overall process. The purification procedure can be performed in conventional glassware in usual laboratory scale, and is both time-saving and cost-effective. The recycling process also allows the desired rinsing of the $[^{18}F]$-fluoride transfer line with $[^{18}O]$-water, since the optimized treatment of the $[^{18}O]$-water-circuit has been adjusted to maintain the enrichment grade. Additionally, the optimization of the cleaning and preparation of the synthesis module enabled a recovery of the $[^{18}O]$-water without any loss of the enrichment grade.

Further use of the recovered $[^{18}O]$-water did not reveal any interfering effects during $[^{18}F]$-fluoride production and subsequent syntheses. Compared to the use of fresh $[^{18}F]$-water, no difference in the yields of $[^{18}F]$-fluoride production and the radiochemical yields of subsequent radiosyntheses were observed.

The developed optimization steps can be easily established in the routine process, and thus allow for considerable cost savings.

Author Contributions: A.U. participated in the design of the study, did the majority of the chemical experiments, designed and composed most of the draft manuscript and participated in its finalization. H.H. was involved in the initial investigations of the study and experiments. W.B. supervised the study. V.H. participated in the design of the manuscript and finalized it. All authors read and approved the final manuscript.

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