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Degradation of acetonitrile in eluent solutions for [^{18}F]fluoride PET chemistry: impact on radiosynthesis of [^{18}F]FACBC and [^{18}F]FDG

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In [^{18}F]fluoride chemistry, an eluent solution containing a weak aqueous base is used to release [^{18}F]fluoride after adsorption on an anion exchange resin. Traditionally, the eluent solution is freshly prepared, but modern PET tracer manufacturers may utilize the benefits of preparing bulk solutions or prefilled vials for storage. We discovered that typical eluent solutions containing kryptofix and K_2CO_3 in aqueous acetonitrile degraded upon storage. Acetonitrile will at alkaline pH hydrolyse to acetamide and ammonium acetate. Acetate may serve as a competing nucleophile to [^{18}F]fluoride. Eluent solutions used in the synthesis of [^{18}F]FACBC and [^{18}F]FDG generated mg/ml levels of acetamide and ammonium acetate during storage at room temperature or above. The synthesis of [^{18}F]FACBC was prone to eluent degradation, with gradual reduction of radiochemical yield (RCY) from 62.5% to 44.7% during 12 months of storage at 30 °C. The synthesis of [^{18}F]FDG was only affected when the eluent was stored at 50 °C, reducing the RCY from 86.8% to 66.7% after 3 months of storage. For degradation effects to be avoided, an alternative eluent solution with no acetonitrile was investigated in the synthesis of [^{18}F]FACBC. A methanol-based eluent was successfully made, showing no degradation and unchanged RCY after 6 months of storage at 50 °C.

Keywords: PET; [^{18}F]fluoride; eluent; degradation; acetate; methanol

Introduction

Today, nucleophilic substitution with [^{18}F]fluoride is by far the most important route in obtaining ^{18}F-labelled tracers for PET imaging.[1] The [^{18}F]fluoride is normally produced as an aqueous solution from the nuclear reaction ^{18}O(p,n)^{18}F by proton irradiation of [^{18}O]water.[2] The first step in radiochemistry is the removal of bulk [^{18}O]water to enhance the nucleophilicity of the [^{18}F]fluoride ion. Most commonly, [^{18}F]fluoride is adsorbed onto an ion exchange resin,[3] followed by elution with an aqueous acetonitrile solution containing a carbonate salt (K_2CO_3, $KHCO_3$) accompanied by a cryptand such as Kryptofix™ (K_{222}) or tetrabutyl ammonium.[4,5]

The eluent has typically been prepared manually on the day of synthesis, but more efficient centres and newer commercial synthesizers utilize the benefits of preparing bulk solutions or prefilled vials for storage. The use of prefilled vials allows more well-defined, reliable and reproducible synthesis processes.[6] In addition, prefilled vials can be made with a low bioburden and a documented shelf life, which serves as a better starting point for good manufacturing practice (GMP) quality manufacture compared with manually mixed solutions. An important requirement when using the advantage of prefilled vials is, however, that the stability of the solutions is investigated and that eventual issues are solved.

Our group discovered degradation of prefilled eluent solutions containing acetonitrile and K_2CO_3. It is well known from the literature that acetonitrile will hydrolyse at alkaline pH, forming acetamide and ammonium acetate in a two-step mechanism as illustrated in Figure 1.[7] Although the rate constants are relatively low, significant levels could be generated upon storage. It was hypothesized that the generated levels of acetate could work as a competing nucleophile to [^{18}F]fluoride, resulting in reduced radiochemical yield (RCY). Acetate alone is normally regarded as a weak nucleophile and should not possess a big threat. However, it has been shown that acetate solubilized in acetonitrile with an 18-crown-6 ether present reacts strongly with a wide range of organic substrates.[8] In our case, kryptofix could work in a similar fashion. Acetate has also been reported as a stronger inhibitor compared with other common anions such as chloride, nitrate, hydroxide and sulphate when labelling 3-FDG and fluoromethane.[9]

Acetamide should on the other hand not decrease the RCY, as it is a known [^{18}F]fluoride labelling solvent.[10–12] Acetamide is, however, a toxic carcinogen, and its formation is necessary to understand and control to an acceptable low level in the final product.

In this paper, we report how acetamide and acetate were generated during storage in two conventional acetonitrile-based eluents containing K_{222} and K_2CO_3. We measured what impact generated levels of acetate made on the RCY in the synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) and anti-1-amino-3-[^{18}F]fluorocyclobutyl-1-carboxylic acid ([^{18}F]FACBC).

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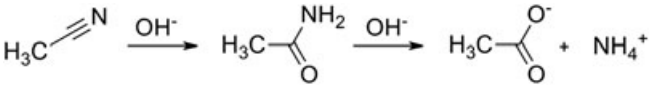

Figure 1. Base-catalysed hydrolysis of acetonitrile to acetamide (rate constant = $1.6 * 10^{-6}$ M^{-1} s^{-1}) and ammonium acetate (rate constant = $7.4 * 10^{-5}$ M^{-1} s^{-1}).

Furthermore, eluent solutions with no acetonitrile would avoid the formation of acetamide and ammonium acetate upon storage. We demonstrate how a methanol-based eluent was a better alternative for storage in the synthesis of [^{18}F]FACBC.

Results and discussion

Storage of prefilled eluent

The synthesis of [^{18}F]FACBC and [^{18}F]FDG can be performed by single-use cassettes on a FASTlab synthesizer module.[13] The cassette for each synthesis contains prefilled vials with all reagents and solvents used, including the eluent solution. Two similar eluent solutions optimized for either [^{18}F]FACBC or [^{18}F]FDG synthesis were made in 3-ml glass vials (Table 1). In both eluents, notable levels (mg/ml) of acetamide and acetate were generated during a 9-month period of storage as seen in Figures 2 and 3. Temperature was of major importance. The formation of acetamide developed very similarly in the two eluents, and the FACBC eluent generated higher levels of acetate compared with the FDG eluent. This indicated that the ratio K_{222} : K_2CO_3 might have influenced the degradation of acetonitrile, as this was the main difference between the eluent compositions.

It was observed that the acetamide level was 2–3 times higher than acetate both in the FACBC eluent and in the FDG eluent. This was a bit surprising as the second step of the hydrolysis is faster than the first one, and the reaction should proceed to the acetate salt rather than stopping at the amide stage (Figure 1).

Table 1. Eluent solutions for [^{18}F]FACBC and [^{18}F]FDG synthesis

Eluent composition	FACBC	FDG
K_{222}	53.0 mg/ml	53.0 mg/ml
K_2CO_3	7.3 mg/ml	9.5 mg/ml
MeCN : H_2O	79.5:20.5 (v/v)	79.5:20.5 (v/v)
Fill volume	1.105 ml	0.825 ml

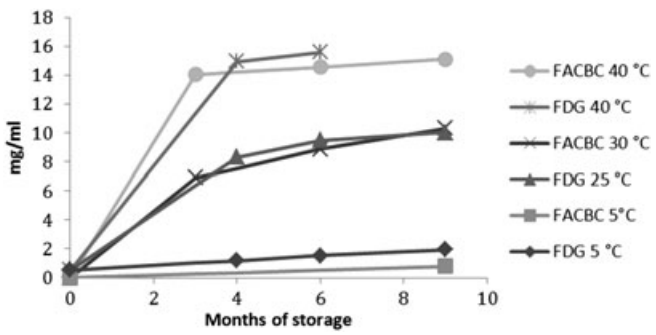

Figure 2. Acetamide generated in FACBC and FDG eluent vials during storage at 5, 25 and 40 °C. $n = 2–3$.

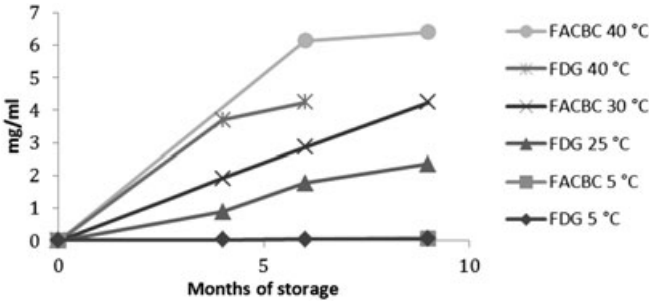

Figure 3. Acetate generated in FACBC and FDG eluent vials during storage at 5, 25 and 40 °C. $n = 2–3$.

Stored eluent versus radiochemical yield

The synthesis of [^{18}F]FACBC and [^{18}F]FDG was tested with both freshly prepared and stored eluents to investigate the impact of generated levels of acetamide and ammonium acetate on the RCY. With the use of freshly prepared eluents, the RCY of [^{18}F]FACBC and [^{18}F]FDG were 62.5% ± 1.93 (SD), $n = 4$ and 86.8% ± 1.25 (SD), $n = 9$, respectively.

When the FACBC eluent was stored at 30 or 40 °C, a decrease in the RCY with increasing storage time was observed as shown in Figure 4. The RCY of [^{18}F]FACBC dropped from 62.5% to 44.7% when the FACBC eluent was stored at 30 °C for 12 months and from 62.5% to 33.6% when stored at 40 °C for 6 months. We therefore observed a negative correlation between degradation of acetonitrile and reduction in the RCY of [^{18}F]FACBC.

The RCY for [^{18}F]FDG was not significantly affected when the FDG eluent was stored at 25 or 40 °C for 12 and 9 months, respectively. This was surprising as the hydrolysis of acetonitrile developed in a relatively similar fashion in the two eluent formulations. We, however, observed a reduction in the RCY from 86.8% to 66.7% for [^{18}F]FDG when the eluent solution was stored at 50 °C for 3 months ($n = 3$).

Acetamide and acetate tracking

In both syntheses, known levels of acetamide and acetate were tracked from the eluent to the end product to better understand how the RCY was affected. Fresh FACBC and FDG eluent vials were spiked with acetamide (8.7 mg/ml) and ammonium acetate (4.0 mg/ml) and then placed in their respective cassettes and run on the FASTlab as described earlier (no radioactivity present).

As seen in Table 2, concentration of acetate was three times higher during labelling of [^{18}F]FACBC versus [^{18}F]FDG. There

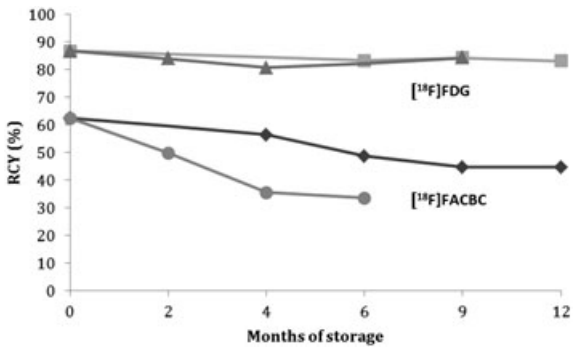

Figure 4. Radiochemical yield (RCY) of [^{18}F]FACBC after eluent stored at 30 (•) and 40 °C (♦) and RCY of [^{18}F]FDG after eluent stored at 25 °C (■) and 40 °C (▲).

Table 2. Tracking of acetamide and acetate

FASTlab process step	Volume (ml)	Acetamide (μg/ml)	Acetate (μg/ml)
[^{18}F]FACBC synthesis			
Eluent vial	1.105	8700	3100
Reactor before drying	0.682	7320	2530
Reactor during labelling	1.0	3495	1795
End product	26.0	0.2–0.5	n.m.
[^{18}F]FDG synthesis			
Eluent vial	0.825	8700	3100
Reactor before drying	0.377	6265	2120
Reactor during labeling	1.6	844	597
End product	15.0	0.2–0.4	n.m.

n.m. = not measured

were two factors contributing to this difference. First, the eluent volume reaching the reactor was almost twice as high in the synthesis of [^{18}F]FACBC. This was caused by the dead volume in the FASTlab eluent vial (375 μl) and retained eluent on the Sep-Pak quaternary methylammonium cartridge (QMA). Second, the differences in labelling volume (1.0 ml vs 1.6 ml) contributed to higher concentration of acetate in the synthesis of [^{18}F]FACBC. Therefore, on the basis of the hypothesis that the formation of ammonium acetate might have a detrimental effect on the RCY, it was logical that the synthesis of [^{18}F]FACBC was more prone towards eluent storage in this case.

Acetamide levels in both end products were within acceptable limits for genotoxic impurities (<120 μg/single dose).[14,15] Acetamide was removed during the drying step and most likely during washing of labelled intermediate trapped on the tC18 column.

Spiking studies and pH

The hypothesis that the RCY of [^{18}F]FACBC and [^{18}F]FDG was reduced because acetate would work as a competing nucleophile was investigated. Freshly made eluents were spiked with different levels of ammonium acetate and then tested. As seen in Figure 5, there was a clear correlation between added levels of ammonium acetate and reduction in the RCY for both syntheses. The effect on [^{18}F]FACBC corresponded well with the data in Figure 3, whereas the effect on [^{18}F]FDG was more pronounced with spiked eluent compared with stored eluent.

A reduction in pH was observed in both eluents upon storage. It could be argued that the reduction of pH could reduce the RCY as it is mandatory to have certain alkaline pH to avoid formation of unreactive H[^{18}F]fluoride.[1] Although limited data were collected, a few important observations were made. First, the pH of the FDG eluent was reduced from >13 to 10.7 after 6 months of storage at 40 °C. Fresh FDG eluent, spiked with 4.0 mg/ml ammonium acetate had a pH of 11.5. It was, however, only the spiked eluent that reduced the RCY of [^{18}F]FDG. Secondly, FACBC eluent that had been stored for 22 months at 30 °C had a pH of 10.7. If the fresh FACBC eluent was made with $KHCO_3$ rather than K_2CO_3 (no. of mol K^+ kept constant), the pH was reduced from >12.5 to 10.8, but the RCY was only reduced from 63% to 58% ($n = 2$). The reduction of pH might have contributed to lower RCY, but the main cause was the presence of acetate.

Eluent with methanol

The easiest approach to avoid degradation was to develop an eluent with no acetonitrile. An alternative organic phase was needed, and methanol was considered to be the best candidate for several reasons. Methanol is much more resistant towards alkaline pH and therefore more suited for storage. It has also been demonstrated that methanol-based eluents have excellent eluting properties, together with a potential of shorter evaporation time as eluents can be made with 100% methanol.[16–18]

FACBC eluent vials in which acetonitrile was replaced by methanol was stored for predetermined time points and tested in the synthesis of [^{18}F]FACBC as seen in Figure 6. Whereas the acetonitrile-based eluent resulted in a gradual decrease in the RCY with increasing storage time, the RCY remained unchanged with the methanol-based eluent even when stored at 50 °C for 6 months. Clearly, the methanol-based eluent was much more suitable for storage.

Although not shown here, there was no difference in the non-radioactive impurity profile between the eluent made with methanol or with acetonitrile (Aukland T, personal communication). A methanol-based eluent was not tested in the synthesis of [^{18}F]FDG because of the low impact of eluent degradation at standard storage temperature for the cassette.

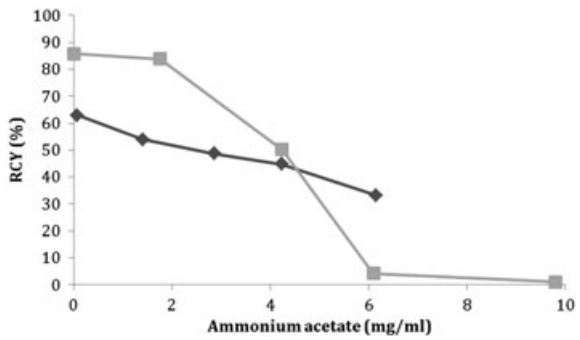

Figure 5. Radiochemical yield (RCY) of [^{18}F]FACBC (♦) and [^{18}F]FDG (■) after spiking the eluent solution with ammonium acetate.

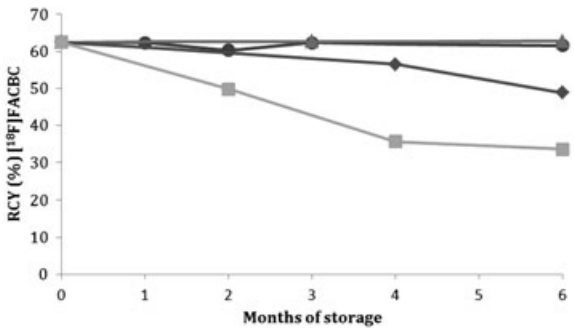

Figure 6. Radiochemical yield (RCY) of [^{18}F]FACBC by the use of methanol-based eluent stored at 30 (▲) and 50 °C (·) and RCY of [^{18}F]FACBC by the use of original acetonitrile-based eluent stored at 30 (♦) and 40 °C (■).

Experimental

General

All reagents and solvents were purchased from Merck (Darmstadt, Germany) and used without further purification. The FDG precursor 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-mannopyranose was purchased from ABX (Radeberg, Germany), whereas the FACBC precursor *syn*-1-(*N*-(*tert*-butoxycarbonyl)amino)-3-[[(trifluoromethyl)sulfonyl]oxy]-cyclobutane-1-carboxylic acid ethyl ester was obtained from GE Healthcare (Oslo, Norway). The Oasis hydrophilic lipophilic balanced (HLB) plus cartridge and the Sep-Pak cartridges QMA light Plus (K_2CO_3 form), tC18 light, Alumina N light were purchased from Waters (Milford, MA, USA). A NaI ion chamber was used for all radioactive measurements (Capintec, model CRC15R, Ramsey, NJ, USA). Radio-thin layer chromatography (radio-TLC) was performed on a Packard instant imager by using pre-coated plates of silica gel (Merck 60F_{254}). Acetamide was quantified by infrared spectroscopy by using a Perkin Elmer Spectrum 2000 Explorer fourier transform infrared (FT-IR) spectrometer with a deuterated triglycine sulphate (DTGS) detector and a single-reflection diamond attenuated total reflectance (ATR) (DuraSamplIR II from SensIR Technologies, Danbury, CT, USA). Acetate was quantified by liquid chromatography with UV detection (Agilent 1100 series).

Production of [^{18}F]fluoride

No-carrier-added [^{18}F]fluoride was produced via the ^{18}O(*p*,*n*)^{18}F nuclear reaction on a GE PETtrace 6 cyclotron (Norwegian Cyclotron Centre, Oslo, Norway). Irradiations were performed using a dual-beam, 30-μA current on two equal Ag targets with Havar foils by using 16.5-MeV protons. Each target contained 1.6 ml of $\geq$96% [^{18}O]water (Marshall Isotopes, Tel-Aviv, Israel). Subsequent to irradiation and delivery to a hot cell, each target was washed with 1.6 ml of [^{16}O]water (Merck; water for guaranteed reagent (GR) analysis), giving approximately 2–5 GBq in 3.2 ml of [^{16}O]water.

Synthesis module

All radiochemistry was performed on a commercially available GE FASTlab with single-use cassettes. The fully automated system is designed for single-step fluorinations with cyclotron-produced [^{18}F]fluoride (Figure 7). The FASTlab was programmed by the

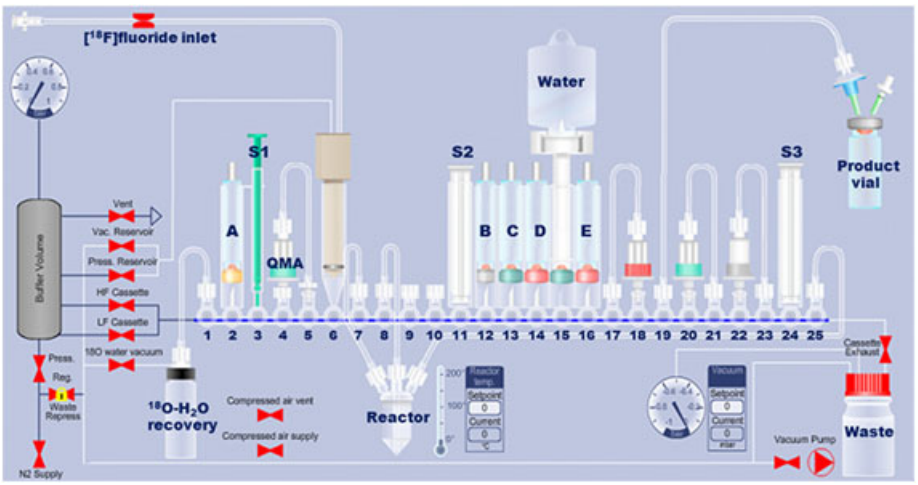

Figure 7. General diagram of the FASTlab synthesizer. The cassette is built around a one-piece-moulded manifold with 25 three-way stopcocks, all made of polypropylene. Briefly, the cassette includes a 5-ml reactor (cyclic olefin copolymer), one 1-ml syringe (S1) and two 5-ml syringes (S2 and S3), spikes for connection with five prefilled vials (A–E), one water bag (100 ml) as well as various solid phase extraction cartridges and filters. Fluid paths are controlled with nitrogen purging, vacuum and the three syringes.

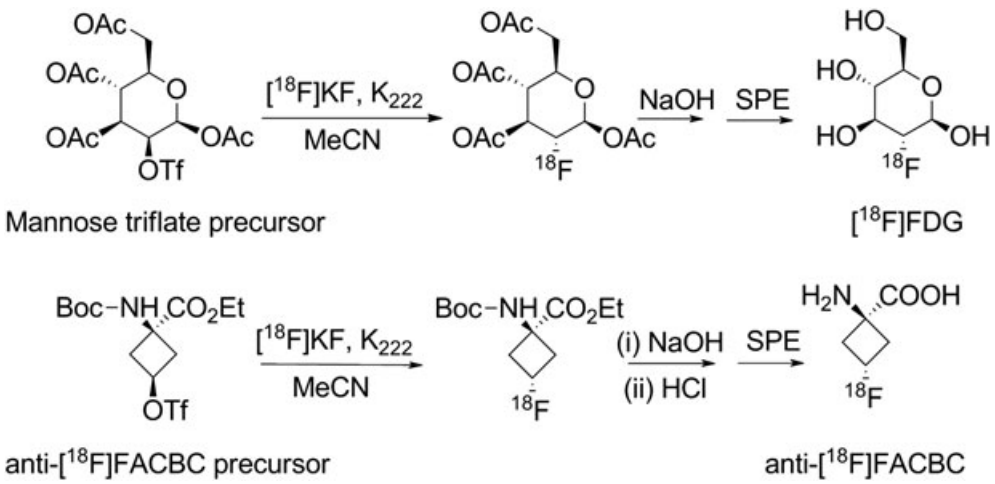

Figure 8. Automated syntheses of [^{18}F]FDG and [^{18}F]FACBC on GE FASTlab.

software package in a step-by-step time-dependent sequence of events such as moving the syringes, nitrogen purging, vacuum, and temperature regulation. Synthesis of [^{18}F]FDG and [^{18}F]FACBC were customized on separate cassettes, but both syntheses followed the three general steps: (a) [^{18}F]fluorination, (b) hydrolysis of protection groups and (c) solid phase extraction purification (Figure 8).

Eluent storage

The 3.0-ml FASTlab eluent vial consisted of type-1 borosilicate glass (FIOLAX, MGlas AG, Münnerstadt, Germany), capped with a chlorobutyl stopper coated with FluroTec® (West Pharmaceutical Services, Inc., Lionville, PA, USA) and sealed with an aluminium cap after filling the eluent solution. The vials were stored in darkness in an up-right position by using storage temperatures of 5, 25, 30, 40 and 50 °C.

Synthesis of [^{18}F]FDG

Vial A contained K_{222} (43.7 mg, 117 μmol), K_2CO_3 (7.8 mg, 56.7 μmol) in 79.5% (v/v) $MeCN_{(aq)}$ (825 μl). Vial B contained the precursor (39 mg, 81.2 μmol) in 2.0 ml of MeCN with 1700 μg/ml water. Vial C contained MeCN (4.1 ml). Vial D contained 2-M NaOH (4.1 ml). Vial E contained 2.3-M phosphoric acid (4.1 ml). Aqueous [^{18}F]fluoride (1 ml, 100–200 MBq) was passed through the QMA and into the ^{18}O-H_2O recovery vial. The trapped [^{18}F]fluoride was eluted into the reactor by using eluent from vial A (450 μl) and then concentrated to dryness by azeotropic distillation with acetonitrile (80 μl, vial C). Approximately 1.6 ml of precursor solution (corresponds to 31.2 mg; 65 μmol precursor) from vial B was added to the reactor and heated at 125 °C for 2 min. The reaction mixture was diluted with water and sent through the tC18 cartridge. Residual activity in the reactor was washed out with water and sent through the tC18 cartridge. The labelled intermediate, fixed on the tC18 cartridge, was first washed with water and then incubated with 2-M NaOH (2.0 ml) for 2 min. The crude mixture was mixed with water (1.5 ml) and 2.3-M phosphoric acid (1.5 ml) and passed through the HLB and Alumina cartridges into the product vial made of glass (30 ml). Water (9 ml) was then sent through the HLB and Alumina cartridges and into the product vial. The purified formulation of [^{18}F]FDG contained a final volume of 15 ml. Radiochemical purity was tested by radio-TLC by using a mixture of MeCN : H_2O (95:5) as the mobile phase. The RCY was expressed as the amount of radioactivity in the [^{18}F]FDG fraction divided by the total used [^{18}F]fluoride activity (decay corrected). The total synthesis time was 22 min.

Synthesis of [^{18}F]FACBC

Vial A contained K_{222} (58.8 mg, 156 μmol), K_2CO_3 (8.4 mg, 60.8 μmol) in 79.5% (v/v) $MeCN_{(aq)}$ (1105 μl). Vial B contained 4-M HCl (2.0 ml). Vial C contained MeCN (4.1 ml). Vial D contained the precursor (48.4 mg, 123.5 μmol) in its dry form (stored at −20 °C until cassette assembly). Vial E contained 2-M NaOH (4.1 ml). The 30-ml product collection glass vial was filled with 200-mM citrate buffer (10 ml). Aqueous [^{18}F]fluoride (1–1.5 ml, 100–200 MBq) was passed through the QMA and into the ^{18}O-H_2O recovery vial. The QMA was then flushed with MeCN and sent to waste. The trapped [^{18}F]fluoride was eluted into the reactor by using eluent from vial A (730 μl) and then concentrated to dryness by azeotropic distillation with acetonitrile (80 μl, vial C). Approximately 1.7 ml of MeCN was mixed with precursor in vial D from which 1.0 ml of the dissolved precursor (corresponds to 28.5 mg, 72.7 μmol precursor) was added to the reactor and heated for 3 min at 85 °C. The reaction mixture was diluted with water and sent through the tC18 cartridge. Residual activity in the reactor was washed out with water and sent through the tC18 cartridge. The labelled intermediate, fixed on the tC18 cartridge, was washed with water, and then incubated with 2-M NaOH (2.0 ml) for 5 min. The labelled intermediate (without the ester group) was eluted off the tC18 cartridge into the reactor by using water. The *tert*-butyloxycarbonyl (BOC) group was hydrolysed by adding 4-M HCl (1.4 ml) and heating the reactor for 5 min at 60 °C. The reactor content with the crude [^{18}F]FACBC was sent through the HLB and Alumina cartridges and into the 30-ml product vial. The HLB and Alumina cartridges were washed with water (9.1 ml total) and collected in the product vial. Finally, 2-M NaOH (0.9 ml) and water (2.1 ml) were added to the product vial, giving the purified formulation of [^{18}F]FACBC with a total volume of 26 ml. Radiochemical purity was measured by radio-TLC by using a mixture of MeCN : MeOH : H_2O : CH_3COOH (20:5:5:1) as the mobile phase. The RCY was expressed as the amount of radioactivity in the [^{18}F]FACBC fraction divided by the total used [^{18}F]fluoride activity (decay corrected). The total synthesis time was 43 min.

Conclusions

Eluent solutions containing K_2CO_3 and K_{222} in aqueous acetonitrile generated mg/ml levels of acetamide and ammonium acetate when stored at room temperature or above. Presence of ammonium acetate in the eluent solution reduced the RCY of [^{18}F]FACBC and [^{18}F]FDG. The synthesis of [^{18}F]FACBC was prone to eluent degradation, with gradual reduction of the RCY from 62.5% to 44.7% during 12 months of storage at 30 °C. The synthesis of [^{18}F]FDG was only affected when the eluent was stored at 50 °C, reducing the RCY from 86.8% to 66.7% after 3 months of storage. Coincidental factors like smaller volume of eluent and larger volume of labelling solvent made the synthesis of [^{18}F]FDG more resistant to eluent storage compared with the [^{18}F]FACBC reaction. [^{18}F]FDG synthesis set-ups elsewhere could therefore be more prone to eluent storage.

Eluent solutions based on methanol instead of acetonitrile prevent degradation upon storage. If the eluent solution for [^{18}F]FACBC synthesis was based on methanol, the RCY remained high and unchanged after 6 months of storage at 50 °C.

Conflict of Interest

The authors did not report any conflict of interest.

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