JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2002; **45**: 435–447.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.572

Research Article

Fast [^{18}F]FDG synthesis by alkaline hydrolysis on a low polarity solid phase support†

C. Lemaire*[,1], Ph. Damhaut[2], B. Lauricella[1], C. Mosdzianowski[3], J-L. Morelle[3], M. Monclus[2] J. Van Naemen[2], E. Mulleneers[2], J. Aerts[1], A. Plenevaux[1], C. Brihaye[1] and A. Luxen[1]

[1] *Cyclotron Research Center, Liège University, Sart Tilman B.30, B-4000 Liège, Belgium*

[2] *PET/Biomedical Cyclotron Unit, Hôpital Erasme, ULB, B-1070 Bruxelles, Belgium*

[3] *Coincidence S.A., c/o ULg B30, B-4000 Liège, Belgium*

Summary

The synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) has been simplified by the use of a ^{t}C18 Sep Pak cartridge to effect purification and hydrolysis of the tetraacetylated [^{18}F]fluoro-glucose compound ([^{18}F]TAG). After radiolabelling, this derivative was trapped on a solid phase extraction (SPE) cartridge and the residual reaction solvent (CH_3CN), reagents (K222, K_2CO_3,...) and by-products removed by washing the support with water. After this cleaning step, the acetyl groups were cleaved on the same $^{t}C_{18}$ column using 2N sodium hydroxide. This fast reaction proceeded near quantitatively (>98%) at room temperature in less than 2 min. The [^{18}F]FDG was then recovered with a small amount of water, neutralized with a slight excess of 2N hydrochloric acid, buffered for pH with a citrate solution and finally purified on a neutral alumina oxide and a second ^{t}C18 column. After filtration, the

*Correspondence to: C. Lemaire, Cyclotron Research Center, Liège University, Sart Tilman B.30, B-4000 Liège, Belgium. E-mail: christian.lemaire@ulg.ac.be

†Parts of this work was presented at the XIIth International Symposium on Radiopharmaceutical Chemistry Uppsala, Sweden, June 15–19, 1997

Contract/grant sponsor: Fonds National de la Recherche Scientifique; Contract/grant number: 1.5.08699

Received 26 June 2001
Revised 3 January 2002
Accepted 5 January 2002

radiochemical yield of this [^{18}F]FDG isotonic solution after more than 100 production runs was found to be very reliable and reproducible (70 ± 6% decay corrected). The synthesis time was about 22 min. Quality controls showed that the radiochemical purity was higher than 98% and in any case no [^{18}F]FDM was detected. Only traces of 2-chloro-2-deoxy-glucose (ClDG) were found in the final sample (64 ± 9 μg/ batch of 16 ml). [^{18}F]FDG specific activity averaged between 1 and 20 Ci/μmol (EOS). No evaporation and use of ion retardation resin (AG11A8) are required. Moreover, this new approach is suitable for complete remote operation using available single use medical components.

Key Words: [^{18}F]FDG; solid phase extraction; hydrolysis; CIDG; fluorine; [^{18}F]FDM

Introduction

2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) being the most frequently used radiopharmaceutical for PET investigation, a great deal of effort has been devoted to the development of reliable methods for its preparation. After labelling, the removal of the acetyl groups of the tetraacetylated [^{18}F]fluoro-glucose compound ([^{18}F]TAG) is generally performed by a time consuming acid hydrolysis step using either aqueous hydrochloric acid or Dowex 50 sulfonic acid resin and heating.[1,2] Generally all these methods require after the labelling, a first purification of the peracetylated 2-[^{18}F]fluoro-2-deoxy-D-glucose on an adequate support (C18, SiO_2,. . .) which implies an additional solvent elimination step. Thereafter, the acetylated carbohydrate protective groups are removed by heating (15 min).

Deprotection using sodium hydroxide as alkaline hydrolysis agent has been more recently proposed by Füchtner *et al.*[3] In this case, after evaporation of the acetonitrile, the alkaline hydrolysis is conducted in the same radiofluorination vessel. Although this approach presents some advantages in terms of hydrolysis time, in case of low radiolabelling yield the final purification is undoubtedly more problematic since unreacted [^{18}F]fluoride, highly soluble in such a mixture, can only be removed by the final alumina Sep pak cartridge. Moreover, the risk of epimerization of FDG to FDM exists in the case or the heater is not cooled down to sufficiently low temperature before the beginning of the hydrolysis.[4,5]

This paper reports a novel alternative to overcome the disadvantages given by the commonly acid and basic aqueous hydrolysis steps. In this

case, the acetyl groups of the 2-[^{18}F]fluoro-1,3,4,6-tetraacetylated labeled compound are removed by basic hydrolysis on the solid phase support previously used for trapping the [^{18}F]TAG compound.

Experimental

[^{18}F]fluoride was produced by ^{18}O(p, n)^{18}F reaction on ^{18}O-enriched water (95–97% enrichment, Rotem) as previously described.[6] All reagents, unless otherwise specified, were commercially available and were used without further purification. 1,3,4,6-tetra-*O*-acetyl-2-trifluoromethane-sulphonyl-β-D-manno-pyranose (mannose triflate) as well as methyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-*O*-(trifluoromethanesulfonyl)-β-D-glucopyranoside and 2-deoxy-2-fluoro-D-mannose (FDM) were synthesised in our laboratory and purified by recristallization according to the known methods.[1,7,8] 2-deoxy-2-fluoro-D-glucose (FDG) and 2-chloro-2-deoxy-glucose (ClDG) were purchased from Toronto Research Chemical (Canada). FDM can now also be purchased from this supplier. [^{18}F]FDM was synthesized by improving a literature method.[9] Melting points were measured in open capillaries on a Buchi B545 apparatus and are uncorrected. Radiochemical yields of [^{18}F]FDG and measurement of associated synthesis components were performed in a shielded gamma ionization chamber (Capintec model CRC 120).

First synthesis was conducted on our Zymate robotic system (Zymark Corp).[10] Routine productions were realized in a module developed by Coincidence Technologies.[11]

[^{18}F]FDG synthesis

After the irradiation, the enriched water was transferred from the target through a small Accel Plus QMA Sep Pak light cartridge (Waters) previously treated with 0.5 *M* K_2CO_3 (10 ml) and water (20 ml). Enriched ^{18}O-enriched water was then recovered. The [^{18}F]F^- trapped on the column was eluted with 400 µl of a solution previously prepared by mixing of an equal volume of potassium carbonate in water (35 mg/ml) and kryptofix 2.2.2 in acetonitrile (110 mg/ml).

A small stream of nitrogen was introduced above the solution. At the end of the water evaporation (120°C), the mixture was azeotropically dried with three successive 0,1 ml portions of CH_3CN. A solution of 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulphonyl-β-D-manno-pyra-

nose (30 mg) in 1.5 ml of CH_3CN was added to the dry [^{18}F]residue, the vial capped and the solution was refluxed at a temperature of 85°C for 4 min.

The solution of [^{18}F]TAG) was then diluted with 30 ml of water and passed through a $^{t}C_{18}$ Sep Pak column that had been pretreated with ethanol (10 ml) and water (10 ml).

The cartridge was washed with water (2×10 ml) and dried with nitrogen. At this time, the residual amount of water on the support was lowered to 50 µl and negligible dilution of NaOH occured when the support was wetted with 800 µl of 2M sodium hydroxide. The hydrolysis was then conducted for 2 min at room temperature. The [^{18}F]FDG was eluted from the column with sterile water (5 ml) and pulled into a buffer volume containing 2N HCl (900 µl) and for isotonic adjustment, a calculated amount of citrate buffer (6 ml). The resulting homogenised solution was then pushed successively through a dry neutral alumina column, another ^{t}C18 Sep Pak cartridge (previously activated as described above) and a 0.22 µm Millipore filter. The resulting solution was recovered into a sterile multi-dose vial. The residual [^{18}F]FDG was eluted from the cartridges with additional sterile water (5 ml). After this purification step, [^{18}F]FDG in about 16 ml is provided reliably with yields ranging from $61 \pm 4\%$ EOS ($n > 100$). The total time for the preparation is 22 min. The radiopharmaceutical is a colourless, sterile, bacteriostatic-free, isotonic solution with a pH of 5.5 ± 0.5.

The radiochemical purity of the final FDG solution checked by thin layer chromatography (TLC) and by high performance liquid chromatography (HPLC) was above 98%. The chemical purity was examined by HPLC (see below). Pyrogen test was carried out with a Limulus Amebocyte Lysate kit. First FDG syntheses were manually evaluated with low dose (<2 mCi) and after few assays implemented on our robotic system (> 10 mCi).

Hydrolysis optimization

For the optimization of the hydrolysis of the protective groups of the 2-[^{18}F]fluoro-1,3,4,6-tetra-*O*-acetyl-D-glucose ([^{18}F]TAG), all the cartridges selected were wetted with the same volume of sodium hydroxide and the yield of the hydrolysis step evaluated at different times (1.5, 2, 5 and 15 min) with various concentrations of sodium hydroxide (0.3; 1.0; 1.5 and 2*N*). The support was then eluted with water and neutralized with a 2.0 M hydrochloric acid solution (900 µl). The resulting [^{18}F]FDG

acidic solution was then immediately analysed by TLC and HPLC. Although lower volume of sodium hydroxide solution was required to wet the support, only reproducible results were obtained in the remote control system with 800 µl of sodium hydroxide solution.

Analytical methods

HPLC analyses of [^{18}F]FDG solutions were performed according to the European Pharmacopoeia requirements. A Dionex CarboPacPA10 column (4 × 250 mm) with a CarboPac Pac guard column (3 × 25 mm) was eluted in the isocratic mode using 55 mM NaOH maintained under inert atmosphere (He). TLC was performed using precoated silica gel TLC plates (0.25 mm) from Macherey-Nagel. The chromatographic development was carried out with acetonitrile/water (90/10). The distribution of the radioactivity was recorded with an Automatic TLC-linear Analyser from Berthold (Rf: [^{18}F]fluoride = 0, [^{18}F]FDG = 0.55; [^{18}F]TAG = 0.86).

Results and Discussion

The synthesis of [^{18}F]FDG presented here consists in a modification of the procedure previously described by Hamacher *et al.*[12] However, instead of an aqueous acid hydrolysis, a basic hydrolysis on a solid support was considered. Indeed, in comparison with the acid catalysed hydrolysis, the alkaline approach, previously reported in liquid phase by Füchtner *et al.*[3] presents several advantages. This more easy procedure which allows a much faster removal of the acetyl protection groups while avoiding the generation of 2-chloro-2-deoxy-D-glucose simplifies the production of the radiopharmaceuticals considerably. However, this fast aqueous alkaline hydrolysis of 1,3,4,6-tetraacetyl-2-fluoro-deoxyglucose (5 min) can only be achieved without significant epimerization (max 0.5%) to the corresponding mannose derivative with 0.33M sodium hydroxide at temperatures below 40°C;[3,5] higher concentration and temperature will lead to defluorination of the acetylated [^{18}F]FDG and epimerization of [^{18}F]FDG to [^{18}F]FDM.

A part of this work consisted of improving the alkaline hydrolysis by performing the basic hydrolysis on a solid phase extraction (SPE) column on which the labelled precursor has been previously trapped

and purified. Reaction parameters such as the type of solid support, the base strength, the reaction time which may influence yield were then primarily evaluated. In the second part, the absence of [^{18}F]FDM in the final sample was validated by different analytical methods.

Labelling and hydrolysis on SPE

In the first step, labelling was performed by the classical approach using 1,3,4,6-*tetra*-*O*-acetyl-2-trifluoromethane-sulphonyl-β-D-manno-pyranose as precursor, and the aminopolyether potassium complex ([K/2.2.2]$^{+}$ ^{18}F^{-}) as phase-transfer catalyst. The yield of [^{18}F]TAG was about 80–90%, provided 30 mg of freshly prepared precursor solution was used. After labelling, the acetonitrile was diluted with water, transferred into a syringe and passed through a solid phase extraction (SPE) cartridge. Several kinds of solid phase extraction supports from Waters and 3 M were evaluated in terms of efficiency and ability for trapping [^{18}F]TAG (Table 1).

Table 1. Percentage of [^{18}F]TAG trapped on various solid support cartridges (values reported are mean $\pm$ SD and $n = 3$)

Sorbents	Diameter and cartridge volume	Sorbent mass	%
Empore extraction disk cartridge with microbond elut-C18	7 mm/3 ml	13 mg	72 $\pm$ 3
Empore extraction disk cartridge with microbond elut-C8	7 mm/3 ml	13 mg	73 $\pm$ 3
Empore extraction disk cartridge with microbond elut-C2	7 mm/3 ml	13 mg	0
Empore extraction disk cartridge with microbond elut-PS/SDB	7 mm/3 ml	13 mg	70 $\pm$ 4
Sep-pak cartridges vac ^{t}C18	1 ml	50 mg	79 $\pm$ 2.5
Sep-pak cartridges vac ^{t}C18	3 ml	200 mg	98 $\pm$ 1.5
Sep-pak plus cartridges C18		360 mg	97 $\pm$ 2
Sep-pak plus cartridges ^{t}C18		400 mg	99 $\pm$ 1
Sep-pak cartridges plus environmental C18		840 mg	99.8 $\pm$ 0.2
Waters oasis HLB extraction cartridges	3 ml	60 mg	83 $\pm$ 3
Waters oasis HLB extraction cartridges	6 ml	200 mg	99 $\pm$ 1
Waters oasis HLB extraction cartridges	6 ml	500 mg	99.8 $\pm$ 0.2

Since [^{18}F]TAG can be considered as a lipophilic compound, only sample extraction products with low polarity were investigated. As seen from Table 1, [^{18}F]TAG trapping efficiency increased with the sorbent mass encapsulated in the cartridges. The [^{18}F]TAG was practically quantitatively trapped on all the cartridges containing more than 200 mg of sorbent (> 96%). With less sorbent mass, lower [^{18}F]TAG trapping occurred (70%) but no significant differences were observed between C2, C8, C18 and Oasis HLB supports.

^{t}C18 cartridge has similar application to C18. It is also an endcapped bonded phase with strong hydrophobicity, but the trifunctional bonding chemistry gives it an increased hydrolytic stability over C18. This support is the recommended sorbent for application involving long sample contact times with a sample with pH > 7. Oasis HLB cartridge is also a reverse phase polymeric sorbent on which strong bases with pH greater than 13 may be used without significant degradation of the support (technical information from Waters). Experiments on this support were performed with cartridges loaded with 60, 200 and 500 mg of sorbent. In this case, only cartridges with more than 200 mg of sorbent were adapted for our application as more than 99% of [^{18}F]TAG was trapped on the cartridge. In the light of all these results, the ^{t}C18 support with 400 mg and the Oasis one with 200 mg of sorbent were selected for studying the alkaline hydrolysis step.

The hydrolysis of the protective groups of [^{18}F]TAG was evaluated at different times with various concentrations of sodium hydroxide (0.3; 1.0; 1.5 and 2N) (Figure 1).

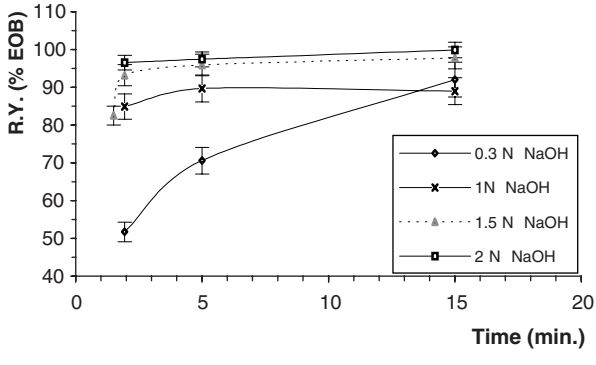

Figure 1. Hydrolysis yields of [^{18}F]TAG versus time on a ^{t}C18 cartridge (values reported are mean ± SD (n = 5))

From the results summarized in Figure 1, it appears that basic hydrolysis is feasible on a ^{t}C18 solid support at room temperature and that the time required to reach the maximum yield depends mainly on the concentration of sodium hydroxide. With increasing hydroxide concentration, the rate of [^{18}F]TAG hydrolysis increases. The maximum yield of [^{18}F]FDG was obtained with 2N NaOH around 2 min. Under these conditions, more than 99% of the [^{18}F]TAG was converted into [^{18}F]FDG. However, with the same time and the same volume of 0.3N NaOH, the hydrolysis yield in [^{18}F]FDG decreases to 50%. Comparatively, for the same sodium hydroxide concentration, in homogenous solution, Füchtner *et al.*[3] reported about 100% yield for the hydrolysis after 1 min. At higher hydroxide concentrations (1.0 N) these authors observed a higher by-product level concentration and a lower [^{18}F]FDG yield (50%). However, in our case, at this relatively high hydroxide concentration (2N) little radio degradation was observed on the SPE.

Oasis coating (200 mg) was also investigated. Although this product can theoretically present major advantages, it did not suit our application as in the conditions described above (NaOH 2N, 2 min), only 57% of the [^{18}F]TAG was hydrolysed. No further optimizations were conducted with this support.

From this study, it appears that [^{18}F]TAG trapped on a ^{t}C18 Sep Pak column is easily hydrolysed at room temperature in the presence of a small volume of 2N NaOH solution (800 µl). The reaction is fast and does not require heating. After 2 min the basic solution is eluted from the support with water and acidified with aqueous hydrochloric acid. The resulting mildly acidic [^{18}F]FDG solution can then be easily adjusted for isotonicity and pH by addition of calculated amounts of water and citrate buffer. As a result, the neutralization of [^{18}F]FDG on an ion retardation resin is avoided.

At this stage, the radiochemical purity of the [^{18}F]FDG solution was already above 95%. Nevertheless, radiochemical and chemical purities were increased by passing this resulting solution (pH $\pm$ 5.5) through another ^{t}C18 cartridge. Traces of [^{18}F]fluoride were removed on a neutral alumina oxide Sep Pak. Sterilization of the radiopharmaceutical solution was achieved by filtration on a 0.22 µm membrane. Using this modified method, the radiochemical yield of [^{18}F]FDG averaged between 61 $\pm$ 4% (EOS, $n > 100$) in an overall synthesis time of about 22 min. The final product (about 16 ml), collected in a closed vial, is colourless and presents high radiochemical (> 98%) and chemical purities as demonstrated below.

Analytical results

In order to validate this new radiochemical [^{18}F]FDG, various radiochemical and chemical analyses were conducted in accordance with the Pharmacopoeia requirements.[13]

Radiochemical purity

HPLC and TLC assays. TLC analysis shows that more than 98% of the radioactivity was present as [^{18}F]FDG and less than 1% of the activity stayed at the starting point.

The cold and radioactive references of FDG and FDM being available, the isomeric purity of the [^{18}F]FDG prepared by basic hydrolysis on a solid support, was estimated on a Dionex CarboPac PA10 analytical column with radiochemical and pulse-amperometric detections (PAD). Among different solvent concentrations, best separation of [^{18}F]FDG from [^{18}F]FDM was obtained with 55 mM NaOH. In these conditions [^{18}F]FDM and [^{18}F]FDG compounds were characterized by the retention times illustrated in Figure 2 (Chromatograms A and C).

Analytical HPLC of an [^{18}F]FDG sample synthesized on a solid support by alkaline hydrolysis (2 min) shows a single radioactive peak which has the same retention time as a reference sample of commercially available [^{19}F]FDG. Moreover no radioactive and electrochemical peaks were detected for FDM (Chromatogram C and D, Figure 2).

The same results were also observed for hydrolysis time of 10 mins. Owing to the fact that electrochemical and radiochemical detection methods associated with high performance liquid chromatography are very sensitive techniques for detecting and quantifying organic sugars, it can be concluded that in our conditions, no epimerization occurs during sodium hydroxide hydrolysis on the solid support. Results of a more systematic study (base concentration, reaction time, temperature, etc), confirming this fact has been published elsewhere.[14]

With the same chromatographic system, the [^{18}F]TAG which can be easily recovered from the tC18 cartridge with acetonitrile, also affords only a single radioactive peak which has the same retention time as a radioactive peak of [^{18}F]FDG. This result indicates that during the Dionex analysis, the tetraacetyl groups of the [^{18}F]TAG compound are cleaved making the method inappropriate both for radiochemical purity and radiochemical yield evaluations. However, in these conditions (55 mM NaOH, 20 min) as well as in more basic conditions (220 mM

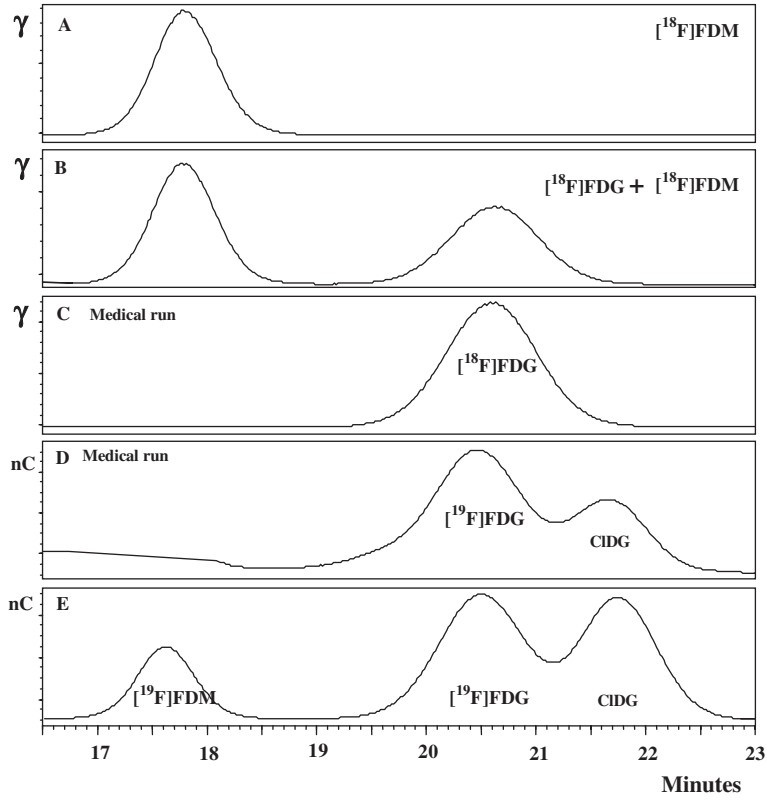

Figure 2. HPLC analyses were realized on a Dionex Carbopac PA10 column (1 ml/min; NaOH 55 mM: (A) radiochemical profile of an [^{18}F]FDM solution*; (B) radiochemical profile of a mixture of [^{18}F]FDM and [^{18}F]FDG (53/47)*; (C) radiochemical profile of an [^{18}F]FDG solution (medical run)*; (D) typical electrochemical profile of an [^{18}F]FDG solution (medical run), FDG and ClDG were detected at 4 and 5 μg/ml, respectively. No FDM was detected; (E) electrochemical detection of a mixture of "authentic" [^{19}F]FDM, [^{19}F]FDM and ClDG (12.5 μg of each/ml)**. *γ = gamma radioactive response (cpm), **[Parameters used for the PAD: $E_1 = 0.05$ V ($t_1 = 400$ ms); $E_2 = 0.75$ V ($t_2 = 200$ ms); $E_3 = -0.15$ V ($t_3 = 400$ ms), (nC = nanoCoulomb)**

NaOH, 30 min) no [^{18}F]FDM formation was observed on the analytical column.

Chemical purity

The chemical purity was also investigated on the same Carbopac analytical column by PAD. In the conditions described above, the main by-product of the reaction detected at 7.5 min was glucose (< 3.2 mg/

batch). As previously observed with radiochemical detection, the reaction on solid support leads to undetectable amounts of [^{19}F]FDM even after 10 min of hydrolysis (Figure 2).

As previously published, ClDG is known as another possible chemical contaminant of the nca [^{18}F]FDG preparation.[15] This by-product can either be formed during the labelling step, or during the hydrolysis of the starting mannose triflate with hydrochloric acid. The alkaline hydrolysis presented in this paper excludes the ClDG formation during this step and consequently the nucleophilic substitution of the mannose triflate by chloride ions remains the main source for ClDG.

Potential sources of chloride include target water, kryptofix, potassium carbonate, vessels and chloride contaminations from recovery resins (QMA). This column purchased in the chloride form was found to be the main source of contamination. In all cases, careful preparation of this ion exchange resin with carbonate reagent and water containing low chloride ions minimized the ClDG formation. Typically, low values of ClDG (64 ± 9 μg/batch) were detected in the final solution of [^{18}F]FDG. The ClDG contamination was always far below the Pharmacopoeia limit of $0.5\,\text{mg}/V$, where V is the maximum volume injected per patient.[13] A typical chromatogram separation of FDG (12.5 μg/ml) from ClDG (12.5 μg/ml) is illustrated in Figure 2 (Chromatogram E). From electrochemical data (Chromatogram D, Figure 2), it appears that low amounts of these two compounds are present in the final sample. In the example shown, amounts of 7 and 3.5 μg/ml of FDG and ClDG were detected, respectively.

Kryptofix 222, the kryptand used during the labelling step, was eliminated during the loading and washing of the ^{t}C18 column. The concentration of Kryptofix 222 in the final solution was determined with the colour spot test developed by Mock *et al.*[16] (sensitivity 2 μg/ml). This methodology was previously validated by LC-MS/MS (unpublished results). Although, no special method has been used so far to eliminate this chemical impurity from the final product,[17–20] the Pharmacopoeia limit of $2.2\,\text{mg}/V$ was never reached, the usual values being lower than 320 μg/batch.

Residual solvents (CH_3CN, ethanol) were removed during the various purifications on the Sep Pak cartridges. The determination of these organic solvents was realized according to the previously published method.[21] Only traces of CH_3CN (<0.015 mg/ml) lower than the Pharmacopoeia limits were found in the final product. The other main

quality control issues (pH, isotonicity) were also in accordance with the requirements of the Pharmacopoeia publication.[13]

Specific activity

In the analysis conditions used, although FDG and FDM peaks were baseline resolved, a slight overlapping of the FDG and ClDG peaks was always observed, leading to more difficult quantification of these two products (Figure 2). However, in routine runs, the cumulative amount of FDG (2–7 μg/ml) and ClDG for the total batch of 16 ml was always lower than the maximum amount allowed by the Pharmacopoeia for FDG and even ClDG.[13] Based upon our experiments, the specific activity of [^{18}F]FDG was estimated to average between 1 and 20 Ci/μmol (EOS).

Conclusion

For different reasons, the preparation of [^{18}]FDG by alkaline hydrolysis on a solid support at room temperature with a small volume of 2N NaOH presents several advantages over the classical acid and basic hydrolysis procedures.

In this approach, the same solid support is used to remove the solvent used for the [^{18}F]fluorination (i.e. acetonitrile), the unreacted [^{18}F]fluoride and to perform the alkaline hydrolysis. As a result, before the hydrolysis step, no additional heating is required to remove organic solvents. Moreover, this fast hydrolysis (2 min) proceeds with high yield ($>98\%$) and reproducibility at room temperature without [^{18}F]FDM formation. The other side-products, like ClDG, are only present in trace amounts in the final product. The very near-to-neutral [^{18}F]FDG solution recovered after elution of the ^{t}C18 cartridge with water allows the use of a buffer solution rather than a cation exchange resin to afford the final isotonic solution. The overall synthesis time is minimized (about 20 min) and the radiochemical yield is high ($70 \pm 6\%$ EOB). The hardware is greatly simplified and the procedure, easy to automate, allows the single use sterile kit approach to become cost effective.[22]

Acknowledgements

The authors are grateful to the ''Fonds National de la Recherche Scientifique'' (Grant 1.5.08699) for financial support. C. Brihaye and A. Plenevaux are research associates of FNRS Belgium.

References

1. Hamacher K. *Carbohydr Res* 1984; **128**: 291–296.
2. Mulholland GK. *Nucl Med Biol* 1995; **22**: 19–23.
3. Füchtner F, Steinbach J, Mäding P, Johannsen B. *Appl Rad Isot* 1996; **47**: 61–66.
4. Varelis P, Barnes RK. *Appl Radiat Isot* 1996; **47**: 731–733.
5. Meyers G-J, Matzke KH, Mamacher K, Füchtner F, Steinbach J, Notohamiprodjo G, Zijlstra S. *Appl Radiat Isot* 1999; **51**: 37–41.
6. Lemaire C, Damhaut P, Plenevaux A, Comar D. *J Nucl Med* 1994; **35**: 1996–2002.
7. Pavliak V, Kovac P. *Carbohydr Res* 1991; **210**: 333–337.
8. Haradahira T, Maeda M, Omae H, Yano Y, Kojima M. *Chem Pharm Bull* 1984; **32**: 4758–4766.
9. Luxen A, Satyamurthy N, Bida GT, Barrio JR. *Appl Radiat Isot* 1986; **37**: 409.
10. Brihaye C, Lemaire C, Damhaut P, Plenevaux A, Comar D. *J Label Compd Radiopharm* 1994; **35**: 160–162.
11. Mosdzianowski C, Lemaire C, Lauricella B, Aerts J, Morelle J-L, Gobert F, Herman M, Luxen A. *J Label Compd Radiopharm* 1999; **42**: S515–S516.
12. Hamacher K, Coenen HH, Stöcklin G. *J Nucl Med* 1986; **27**: 235–238.
13. Pharmacopoeia E. Fludeoxyglucose (^{18}F) injection. *European Pharmacopoeia (4th edition)*, 2002: 1325.
14. Mosdzianowski C, Lemaire C, Simoens F, Aerts J, Morelle J-L, Luxen A. *Appl Radiat Isot*, in press.
15. Alexoff DL, Casati R, Fowler JS, Wolf AP, Shea C, Schlyer DJ, Shiue C-Y. *Appl Radiat Isot* 1992; **43**: 1313–1322.
16. Mock BH, Winkle W, Vavrek MT. *Nucl Med Biol* 1997; **24**: 193–195.
17. Hamacker K, Blessing G, Nebeling B. *Appl Radiat Isot* 1990; **41**: 49–55.
18. Alexoff DL, Fowler JS, Gatley S. J *Appl Radiat Isot* 1991; **42**: 1189–1193.
19. Chaly T, Dahl JR. *Nucl Med Biol* 1989; **16**: 385–387.
20. Moerlein SM, Brodack JW, Siegel B, Welch M. J *Appl Radiat Isot* 1989; **40**: 741.
21. Lemaire C, Plenevaux A, Aerts J, Del Fiore G, Brihaye C, Le Bars D, Comar D, Luxen A. *J Label Compd Radiopharm* 1999; **42**: 63–75.
22. Damhaut P, Monclus M, Van Namen J, Mulleneers E, Morelle J-L, Lemaire C, Luxen A, Lauricella B. Method for synthesizing labelled compounds: US Patent 6.172.207, 2001.

