THE COMPARATIVE SYNTHESIS OF ^{18}F-FLUOROPHENYLALANINES BY ELECTROPHILIC SUBSTITUTION WITH ^{18}F-F_2 AND ^{18}F-AcOF

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SUMMARY

Fluorination with ^{18}F-F_2 and ^{18}F-AcOF were compared for the synthesis of ^{18}F-fluorophenylalanines. L-phenylalanine in CF_3COOH trapped ^{18}F-AcOF more effectively than ^{18}F-F_2. The main product was ortho-^{18}F-fluorophenylalanine when ^{18}F-AcOF was used as a reagent. Lower radiochemical yield of ^{18}F-fluorophenylalanines and significant formation of by-product were observed in the case of ^{18}F-F_2.

Key words: ^{18}F-F_2, ^{18}F-AcOF, ^{18}F-fluorophenylalanines.

INTRODUCTION

Phenylalanine when labelled with a positron emitting nuclide is thought to be a useful tracer in the in-vivo study of amino acid metabolism with positron emission tomography. For this reason, ^{11}C[1], and ^{18}F[2,3] have been introduced to the carboxyl and phenyl group, respectively. The methods of fluorination [2,3] were based on the Shieman reaction that enables position specific fluorination, but required several hours to prepare ^{18}F-fluorophyenylalanine isomers. Recently, ortho-^{18}F-fluorophenylalanine (o-^{18}F-Phe) and para-^{18}F-flurophenylalanine (p-^{18}F-Phe) were synthesized by fluorination with ^{18}F-fluorine (^{18}F-F_2) within 100 min[4,5].

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The fluorination of the phenyl group with ^{18}F-F_2 is an electrophilic substitution reaction. So, it was thought that ^{18}F-acetyl hypofluorite (^{18}F-AcOF) was also available for the synthesis of ^{18}F-fluorophenylalanine isomers. In this paper, we report a comparative study of fluorination, by ^{18}F-F_2 and ^{18}F-AcOF methods to obtain ^{18}F-fluorophenylalanines.

RESULTS AND DISCUSSION

In this study, fluorination by ^{18}F-F_2 and ^{18}F-AcOF were compared with respect to the trapping yield of ^{18}F-radioactivity, the yield of ^{18}F-fluorinated mixture, and the ratio of ^{18}F-fluorophenylalanine isomers.

More than 90 % of ^{18}F-AcOF was trapped in the reaction vessel, but in the case of ^{18}F-F_2 the yield was lower. The yield of ^{18}F-fluorinated mixture based on the trapped ^{18}F-radioactivity was almost the same for the ^{18}F-F_2 and ^{18}F-AcOF methods (Table 1).

Table 1

Yield of ^{18}F-trapping and ^{18}F-fluorination

		F_2		AcOF	
Phenylalanine	(mg)	16.7	16.8	16.6	17.0
Trapping ratio†	(%)	73.4	63.0	91.3	93.5
Fluorinated ratio‡	(%)	54.7	56.0	58.1	64.9

† *The ratio was based on the total radioactivity recovered as ^{18}F-F_2 or ^{18}F-CH_3COOF.*

‡ *The ratio of residual radioactivity after solvent evaporation against the trapped radioactivity is given.*

All data was decay corrected.

The HPLC pattern of ^{18}F-fluorinated compounds obtained by the ^{18}F-F_2 method is shown in Fig. 1. Coenen et al[4,5] did not report m-^{18}F-Phe formation by the ^{18}F-F_2 method. However, we were not able to disprove the existence of m-^{18}F-Phe because the isomers, m-^{18}F-Phe and p-^{18}F-Phe, were not separable in our HPLC and TLC conditions. The peak retention times in HPLC (Rf values in TLC) of o-^{18}F-Phe and m-, p-^{18}F-Phe were 12.0 min (0.48) and 13.5 min (0.56), respectively. The ^{18}F-radioactive compounds all had UV absorbance at 254 nm.

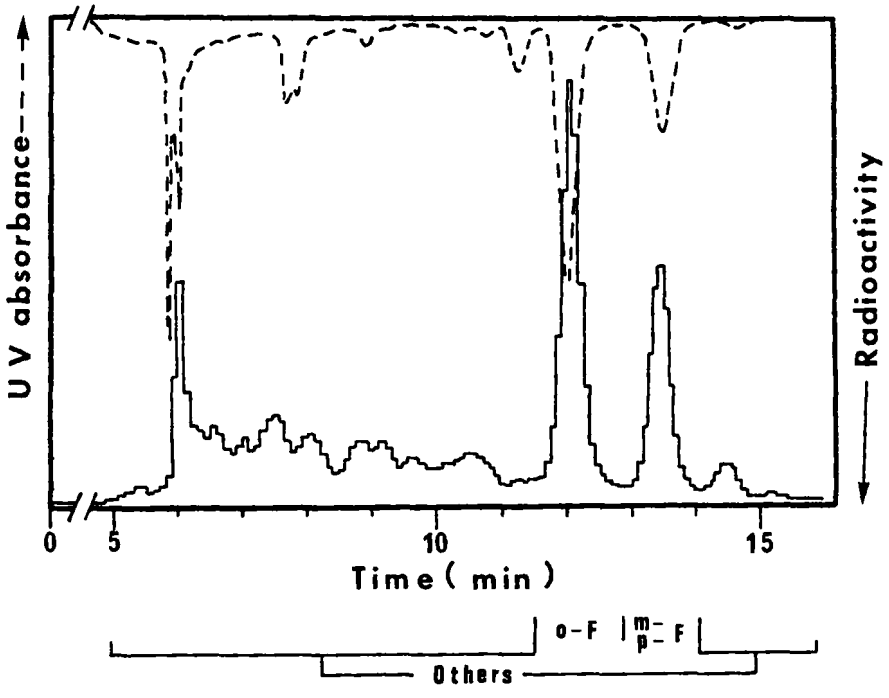

Fig. 1. Elution and fraction pattern of the ^{18}F-fluorinated compounds. HPLC conditions are given in the text.

The yields of ^{18}F-fluorophenylalanines by two synthetic methods are shown in Table 2. In the ^{18}F-AcOF method, the radiochemical yield of ^{18}F-fluorophenylalanines based on ^{18}F-fluorinated mixture was about 70 %, and the main product was o-^{18}F-Phe. When ^{18}F-F_2 was used as the reagent, lower radiochemical yield of ^{18}F-fluorophenylalanines (30 ∿ 40 %), and significant formation of by-products were observed. In this case, the formation ratio of o-^{18}F-Phe against m-, p-^{18}F-Phe was about one to two times greater than that reported by Coenen et al[4]. ^{18}F-fluorophenylalanines were obtained by both methods within 60 min from end of bombardment.

In conclusion, ^{18}F-AcOF is the preferred reagent for the synthesis of o-^{18}F-Phe. However, either reagent is satisfactory for the synthesis of m-or p-^{18}F-Phe.

Table 2

Radiochemical yield of ^{18}F-fluorophenylalanines based on ^{18}F-fluorinated comounds (%)

	F_2		AcOF	
o-^{18}F-Phe	23.6	15.0	59.9	64.0
m-,p^{18}F-Phe	14.8	15.0	7.9	5.3
Others†	47.1	51.3	15.7	16.8
Retained‡	14.5	18.7	16.5	13.9

† *Fractions are shown in Fig. 1.*

‡ *The retained fraction was calculated using the difference between the total eluted radioactivity and that injected onto the HPLC. This fraction was elutable from the column by 18 ∿ 57 ml of CH_3OH.*

All data was decay corrected.

METHODS

^{18}F-F_2 production ^{18}F-F_2 gas was produced by the nuclear reaction ^{20}Ne (d, α)^{18}F. The target gas, neon containing 0.5 % carrier F_2, was loaded into a 141 ml chamber up to 3.0 Kg/cm^2. After bombardment with 6.8 MeV deuterons, the target gas was recovered by 200 ml/min of helium flow.

^{18}F-fluorination In the ^{18}F-F_2 method, ^{18}F-F_2 was bubbled directly into the vessel containing 100 μmole of L-phenylalanine in 10 ml of CF_3COOH for 8 min at 0°C. In the ^{18}F-AcOF method, ^{18}F-F_2 was passed through a column packed with AcOK/AcOH, prepared by the method of Ehrenkaufer et al[6], and was bubbled into the vessel with the same condition described above. The yield of ^{18}F-AcOF from ^{18}F-F_2 was about 40 % in our routine experiments. At the end of bubbling, n-hexane was added and then the mixture was evaporated under vacuum at room temperature. The ^{18}F-radioactive residue was dissolved in 0.8 ∿ 1.0 ml of water.

Purification and identification The ^{18}F-radioactive mixture in H_2O was applied to a reverse phase column (Waters, μBondapak-C18, 7.6 × 300 mm) with 10 % CH_3OH containing 0.1 % AcOH as a mobile phase. The flow rate was 3 ml/min. The ^{18}F-fluorophenylalanines were collected as shown in Fig. 1. Their radiochemical purities were analyzed by HPLC as above, and cellulose TLC (n-butanol 20: AcOH 3: H_2O 5 as a solvent). The identification of the products was carried out by comparing their peak elution times and Rf values with those of commercially available authentic samples.

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