

◀Original▶ **A Rapid Preparation of Carrier-Free  
Fluorine-18 for Medical Use**

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**Abstract**

For the rapid production of fluorine-18 for medical use, the up-to-date methods of separation such as the recoil separation, the alumina column chromatography, and the distillation are reviewed. The amount of the residue, the gamma emitting impurity, and the tritium content in the product obtained by each separation method are determined. The product obtained by the nuclear recoil separation or by the alumina column chromatography is inferior to that obtained by the distillation in the purity point of view. Thus, the separation by the distillation is the most effective especially in the case of using a natural lithium carbonate target.

Carrier free fluorine-18 of about 2 mCi can routinely be produced by irradiating 7g of the natural lithium carbonate under the neutron flux of about  $1 \times 10^{13} \text{ n/cm}^2/\text{sec}$  for 3 hrs, and subsequent separation by the distillation. The over-all processing time is 35-40min.

**요 약**

의료용  $^{18}\text{F}$ 을 단시간내에 생산하기 위하여 반조분리(recoil separation), 알루미나 칼럼 크로마토그래피, 증류등 지금까지 알려진 분리방법들을 검토하고 각각의 분리방법으로 얻은 생성물중의 잔사,  $\gamma$  방출불순물, 및  $^3\text{H}$  함량등을 결정하였다. 핵반조분리 생성물이나 알루미나 칼럼크로마토그래피에 의한 분리생성물은 순도면에서 증류 분리 생성물보다 좋지 못하였고 특히 천연탄산리튬을 표적으로 사용하는 경우는 증류법이 가장 효과적임을 알수 있었다.

천연 탄산리튬 7g을 중성자속밀도  $1 \times 10^{13} \text{ n/cm}^2/\text{sec}$ 에서 3시간 중성자 조사하고 증류에 의해  $^{18}\text{F}$ 를 정제함으로써 무담체  $^{18}\text{F}$ 를 대략 2mCi 이상(10mCi 이하)의 규모로 일상생산할 수 있으며 이때 정제에 소요되는 시간은 35~40분이다.

**1. Introduction**

The development of  $^{18}\text{F}$  labelled radiopharmaceuticals has increased the demand of

$^{18}\text{F}$ . Even though a Ci amount of the  $^{18}\text{F}$  can be produced using a suitable accelerator, the laboratories that only access to a small research reactor, cannot make these quantities

and thus cannot fully devote themselves to the development of the  $^{18}\text{F}$  labelled radiopharmaceuticals. Recently, the  $^{18}\text{F}$  in the primary form of  $\text{Na } ^{18}\text{F}$  has also popularly been used for the bone imaging. Considering that the usual dosage of  $^{18}\text{F}$  per patient is the mCi order and that the half life of which is relatively short (110min), the amount of production per batch should at least be more than a few mCi.

For the rapid production and distribution of  $^{18}\text{F}$  of a good quality with the use of an ordinary lithium carbonate and in a relatively short irradiation time in a small reactor, according to the nuclear reactions  $^6\text{Li}(n, ^4\text{He})^3\text{H}$  and  $^{16}\text{O}(^3\text{H}, n)^{18}\text{F}$ , an alumina column chromatography<sup>1, 2)</sup>, a nuclear recoil separation<sup>3)</sup>, and a distillation method<sup>4)</sup> have been reviewed and the adaptabilities of the products obtained therefrom have been assessed. Further, with a modification of the irradiation can and with an improvement of the condensation technique for the distillate, a rapid separation scheme suitable for a routine production of  $^{18}\text{F}$  for the medical use has thus been established.

## 2. Experimental

### (1) Neutron Irradiation

Seven grams of lithium carbonate (CP grade, Wako) was put into the annular space formed in the standard aluminium irradiation

can. The annular space was made to get the better irradiation efficiency in the following methods:

a) To the bottom of the irradiation can an aluminium pipe was attached<sup>5)</sup> so as to fill the target in the annular space(Fig.1.a)

b) A reactor grade graphite rod cut as shown in Fig.1.b. was replaced for the aluminium pipe attachment. The inner wall of the can was also lined with the graphite according to the method applied by Chan et al<sup>4)</sup>.

The samples thus made were irradiated under the neutron flux of about  $1 \times 10^{13}\text{n/cm}^2/\text{sec}$  for 3hrs. Upon completion of the irradiation, they were cooled for 20min prior to be taken out. According to the method

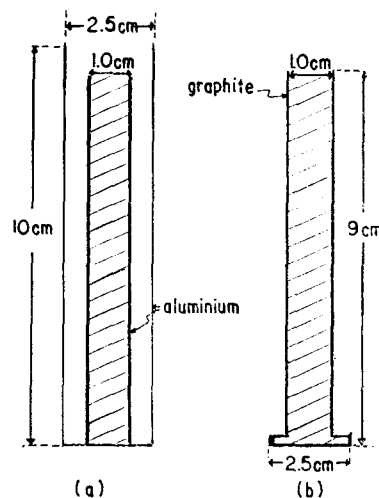


Fig. 1. Irradiation can

Table 1. Irradiation of the Target

Type of the irradiation container	$\text{Li}_2\text{CO}_3$ (g)	Time (min)	Handling characteristics		Approx. mCi* of $^{18}\text{F}$ formed
			Removability of the target from the container	Hazard due to the side reaction	
Ordinary Al can	7	180	not easy	high	>2
Graphite treated Al can	7	180	easy	low	>2

\* The total radioactivity after separation by the distillation. The counting efficiency for the annihilation gamma from  $^{18}\text{F}$  was determined by using a  $^{137}\text{Cs}$  (0.661MeV gamma) standard source (Nuclear Chicago).

**Table 2. The Separation Characteristics and the Assay of the Products**

Method of separation	Recovery (%)	Over-all processing time(min)	Product				
			Residue (g)**	Radionuclide purity(%)***	Radiochemical purity(%)#	Tritium content(uCi)	
						Condensed product##	Treated###
Column chro.	70(2)*	80-90	0.12	99	58	1750	88
Recoil sepa.	80(2)	15-17	0.23	96	—	27200	510
Distillation	67(4)	35-40	0.04	99	97	8500	112

\* Number of the experiments

\*\* Twenty ml of the eluate or the distillate was condensed to dry. For the filtrate, the value obtained from the 1g of the target irradiated for 10 min was converted to the value to be obtained from the 7g of the target irradiated for 3 hrs, for the direct comparison. In the conversion, the irradiation time dependence was roughly corrected by correlating with the values obtained from the non-slurry target.

\*\*\* Determined by the alumina column chromatography, and based on the gamma emitters only. The main impurity has been confirmed to be  $^{24}\text{Na}$  by gamma spectrometry (Fig.5).

# Determined by the radio paper partition chromatography. For the product obtained by the recoil separation, only rough value of 10% was obtained. The exact value for the product could not be determined due to the poor resolution which may be caused by the high salt content(Fig.4).

## For the filtrate (the recoil separation product), the value was obtained by the conversion as described in the footnote\*\*.

### After complete evaporation of water and re-constitution to the original 3ml volume. For the filtrate (the recoil separation product), the value was obtained by the conversion as described in the footnote\*\*.

reported by Parker et al<sup>3)</sup>, the slurry state targets made of 1g of the lithium carbonate and 1ml of water, and 5g of the lithium carbonate and 5ml of water were also irradiated by using the pneumatic system or by putting them in the exposure room of the reactor, respectively.

## (2) Separation

### a) Alumina Column Chromatography

The alumina, acidic for column chromatography (E. Merck), was charged in the 0.8×6cm column. The alumina was pre-treated with concentrated hydrochloric acid, and washed with a plenty of water, and then heated at 400°C for 6 hrs. The irradiated sample was dissolved with concentrated hydrochloric acid and neutralized with a sodium hydroxide solution, and applied on the column. When the whole solution was soaked into the alumina layer it was washed with about 15ml of distilled water, and eluted

with 0.1N sodium hydroxide solution at the rate of 1ml/min. One ml aliquot was taken in each tube and the radioactivity was counted using a scintillation counter (Fig. 2 & Table 2).

### b) Nuclear Recoil Separation

To the irradiated slurry(1g lithium carbonate plus 1ml water, irradiated for 10min) 4ml of cold water was added, stirred, and filtered. The radioactivity recovery was checked(Table 2).

### c) Distillation

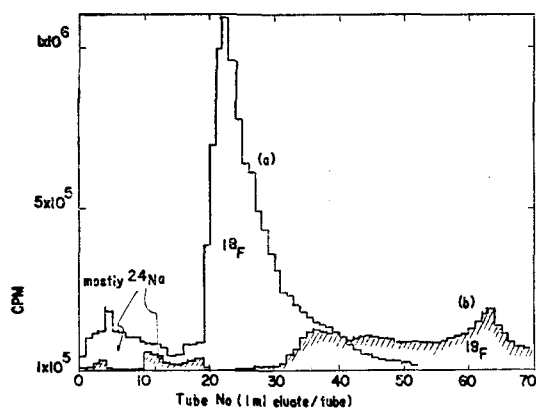
To the distillation receiver, 2-2.5ml of the 0.1N sodium hydroxide solution was added, and the end of the water cooled condenser was dipped into it to bubble out the distillate with the stream of the nitrogen gas, so that the radioactive hydrogen fluoride may effectively be trapped. To a 150ml Claisen flask, the whole content of the irradiated target was placed, and 5ml of distilled water together with 5g of ice pieces was introduced.

**Table 3. Condensation and Reconstitution of the Distillate\***

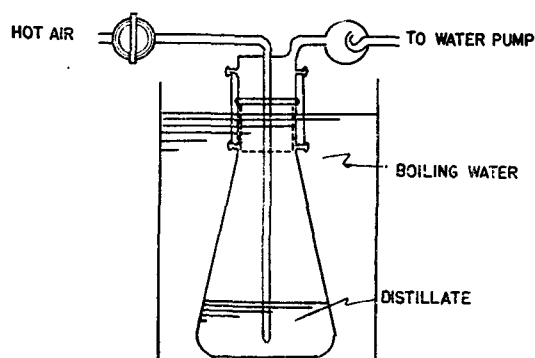
Condensing equipments	Loss of $^{18}\text{F}$ (%)	Decrease of $^3\text{H}$ (%)	Time**(min)
Electric heater(Ni-Cr wire exposed)	17	90	17
Hot plate plus IR lamp	15	86	40
Improved evaporator	12	87	10

\* Twenty ml of the distillate was condensed to 3ml.

\*\* The time required for the complete drying is not much different from these values



**Fig. 2. A Typical Variation of the Separation Pattern in the Alumina Column Chromatography (a) 1 st run (b) 2nd run**



**Fig. 3. A Modified Rapid Evaporator**

A slow stream of the nitrogen gas was passed to aid the distillation. After adding 50 ml of 50% sulfuric acid dropwise to the flask it was heated and about 20ml of the distillate was collected into two separate receiver tubes.

### 3) Condensation and Assay of the Products

After checking the pH of the solution obtained as above with a narrow range pH indicator paper, the eluate, the filtrate, or the distillate was condensed by means of an evaporation to raise the radioactivity concentration. In case of distillation, the condensation of the distillate collected in the first tube was initiated while the second tube was being still in collecting the distillate for the sake of shortening the condensation time. A modified rapid evaporator (Fig 3) was used and the condensation efficiencies were compared with those of a hot plate or an electric heater. When the solutions were condensed to the volume of about 3ml, they were taken out and allowed to be cooled. To confirm the decrease of tritium content in the products, the radioactivities of the tritium and  $^{18}\text{F}$  were measured before and after drying the condensates to a complete dryness (Table 3). The residues in the completely dried condensates were separately measured. The radionuclides were identified by gamma spectrometry, and the radionuclide purities were evaluated by the alumina column chromatography or by the half life measurements. The radiochemical purity of  $^{18}\text{F}^-$  was checked by means of a radio paper partition chromatography using the solvent system of *n*-butanol/methanol/water(1/3/1, v/v).<sup>2)</sup> The tritium content was measured by means of

a liquid scintillation counting with a quench correction. The quench standard set (Nuclear Chicago) and the scintillator solution composed of 1000ml dioxane, 100g naphthalene, 7g P. P. O., and 300mg dimethyl P. O. P. O. P. were used.

### 3. Results and Discussion

#### (1) Neutron Irradiation

The graphite bar attached and graphite lined irradiation can was effective for taking out the irradiated target. In the case of using ordinary irradiation can, the target around the wall side was partly turned to yellow color and not easily be detached. The yellowish cake seemed to be the lithium carbonate partially turned into a glass like material due to the heat developed as a consequence of nuclear reaction in the target. Further advantage is that there was observed no radiation from the graphite of the reactor grade. In the case of an aluminium can of which inner pipe is of a commercial grade (Fig. 1. a.) a quite strong radiation was emitted therefrom due to the activation of impurities (Table 1). In the case of the irradiation of the slurry target, a special facility such as a cryostatic irradiator was needed for the long time irradiation. As it was not available, the slurry target could safely be irradiated for upto 10 min using a pneumatic system. Separately, a larger amount of the slurry made of 5 g of the lithium carbonate and 5ml of water was put in a tightly closed standard plastic irradiation vial and irradiated in the exposure room of the reactor (TRIGA III). Upon 3 hrs' irradiation at the position 1cm appart from the aluminium wall (in which the core is located), the vial was ruptured. A considerable amount of heat was

probably liberated during the course of the irradiation at this position of the reactor.

#### (2) Separation, Condensation, and the Assessment of the Products

It is generally known that the separation pattern as well as the separation efficiency are largely influenced by the slight variation of the pre-conditioning of the alumina in the column chromatography. Fig. 2 shows the typical variation of the separation pattern under an indistinct variation of the pre-conditioning. The time consuming pre-treatment of the alumina and the long elution time are considered as the disadvantageous factors of the column chromatographical separations.<sup>5)</sup> In terms of the quality control of the product obtained by the column chromatography it should be emphasized that there are some chemical impurities in the product; i. e., one day after the purification, the product was turned to turbid (with some floating materials). The residue was observed in the case of the complete evaporation of the eluate, and even when the dried product was re-dissolved with a small quantity of double distilled water. In such a case, a part of the residue was hardly soluble and the most of the radioactivity was observed in the residue. The hardly soluble residue may probably be a Al-F complex as reported by Shikata.<sup>2)</sup> In the paper partition chromatography, as Fig. 4 shows, a solution of the hardly soluble residue displays a higher peak at the origin while the product prior to the complete condensation shows lower. Thus, the peak at the origin may partly be contributed by the insoluble Al-F complex. Further, Stang et al<sup>1)</sup> insisted that the chemical form of the product obtained by an alumina column chromatography is not en-

tirely the simple sodium fluoride but mixed with some insoluble aluminium fluoride complexes, which may be converted to the sodium fluoride by distillation from concentric sulfuric acid, collecting the distillate in a dilute sodium hydroxide solution. In so far as the Al-F complexes are concerned, the insoluble part of the product should be repurified by distillation to get the pure one for a medical application.

Parker et al<sup>3)</sup> reported that the product of recoil separation contained a negligible amount of tritium and it was not contaminated with the lithium carbonate. However, about 27 mCi of tritium and 0.2g of residue (mainly lithium carbonate) were observed in the final product in the present work. The cause of such a deviation may partly be attributable to the direct conversion of the results obtained from the 1g of the target to the value to be obtained from the 7g of the target. However, the time dependent variation in the formation of tritium was roughly corrected by correlating it with the non-slurry targets. It should also be emphasized that the tritium content in the filtrate obtained by the recoil separation was much greater than those in the products obtained by the other separation means for the targets irradiated under the same conditions (1g, 10 min.). In the case of the complete evaporation and the subsequent reconstitution, the tritium content in the product was still greater than those obtained by other separation methods (Table), and the product was inevitably saturated with the lithium carbonate again.

It was impossible to determine the radiochemical purity for the filtrate obtained by the recoil separation due to the poor resolution. The poor resolution may be caused by

the fact that the  $^{18}\text{F}$  is so surrounded by and so adsorbed to the lithium carbonate that it could not be developed by the solvent system used (Fig. 4).

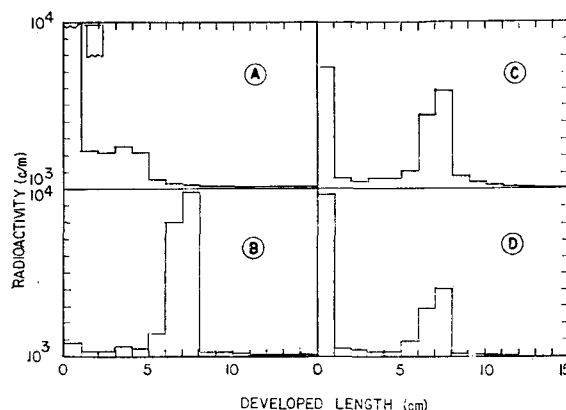


Fig. 4. Determination of the Radiochemical purity by means of a paper chromatography (A; filtrate, B; distillate, C; eluate, D; the hardly soluble fraction in the eluate condensate)

In the distillate obtained from the distillation process, only negligible amount of residues was observed since the trapping solution (4-5ml) of the 0.1N sodium hydroxide placed in the receivers is such an adequate amount to make up a normal saline solution after being neutralized with the slightly acidic distillate, and subsequently with a dilute hydrochloric acid solution.

For labelling use, the salt content can further be minimized by decreasing the volume of the trapping solution to a minimum quantity.

According to the gamma spectrometric data (Fig. 5), the main impurity of the radionuclide is identified to be  $^{24}\text{Na}$  (2754 Kev peak at the channel No. 850) which may be originated from the impure target. This nuclide was remained in the distillation flask in the distillation, in the solution of the irradiated target (Fig. 2) and remained unextracted

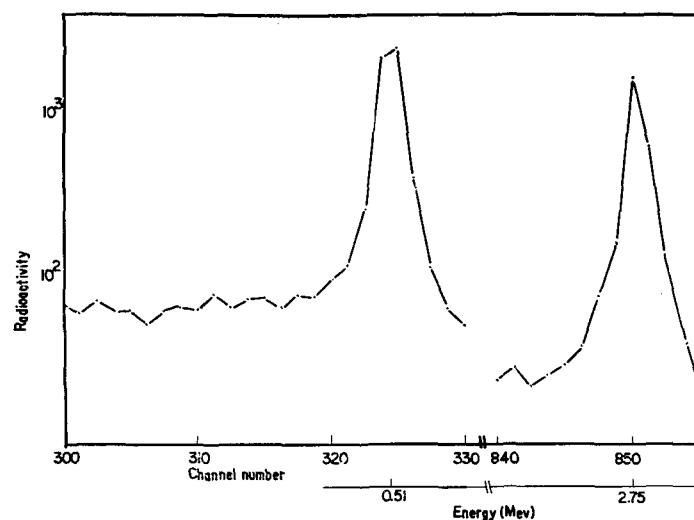


Fig. 5. A Typical Gamma Spectrum for the Distillation Residue

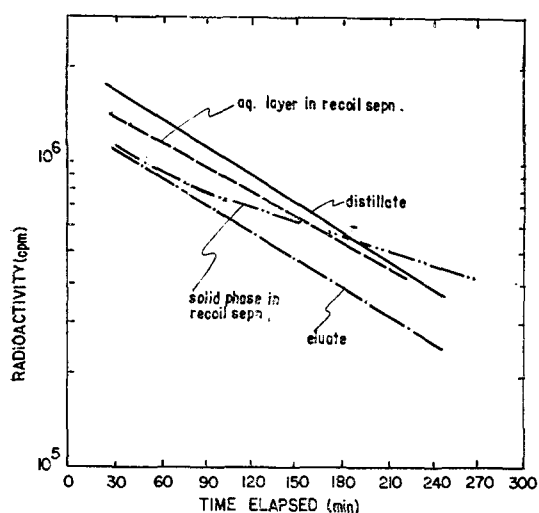


Fig. 6. Measurements of the Half-life

(partially) in the recoil separation process, respectively. In the products separated either by the distillation or by the column chromatography, no gamma emitting impurity could be found while in the filtrate obtained by the recoil separation there was still some impurities confirmed by the half life measurements (Fig. 6) and by an alumina column chromatography (Table 2).

The tritium in the products can effectively

be diminished, in general, by a complete evaporation of water and re-constitution to a desired volume. For the condensation by the evaporation, the modified rapid evaporator is quite effective as the Table 3 shows.

#### 4. Conclusion

The irradiation of the natural lithium carbonate (placed in the annular space made of the graphite bar) under the neutron flux of ca.  $1 \times 10^{13} \text{ n/cm}^2/\text{sec}$  for 3 hrs was effective. For a rapid separation of  $^{18}\text{F}$  of a good quality from the irradiated non-enriched target, a small scale distillation process was the most effective. With the adoption of this established method,  $^{18}\text{F}$  could routinely be produced in a small scale (less than 10mCi). It takes 35-40min. for an entire processing.

#### References

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