Routine Production of PET Radiopharmaceuticals at CYRIC in 1992

III. 1. Routine Production of PET Radiopharmaceuticals at CYRIC in 1992

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Throughout 1992 seven PET radiopharmaceuticals have been prepared regularly for PET studies at CYRIC. They are 2-deoxy-2-[^{18}F]fluoro-*D*-glucose (FDG), *L*-6-[^{18}F]fluoro-DOPA (FDOPA), 2-deoxy-2-[^{18}F]Fluoro-*D*-galactose (FDGal), *L*-[^{11}C]methionine (MET), [^{11}C]doxepin (DOX), [^{11}C]YM09151-2 (YM) and [^{11}C]benztropine (BZT). Table 1 lists their average yields shipped for clinical PET studies with the total run number in parentheses. No PET study was carried out for 2'-deoxy-5-[^{18}F]fluorouridine in the year. The decrease in the run number of the [^{11}C]MET production was provoked mainly by fatal trouble with the old automated [^{11}C]methyl iodide system which had long been exclusively used for the production of [^{11}C]MET. An automated [^{11}C]methyl iodide system[1] (NKK Corp.) was installed and connected with a new [^{11}C]MET system adopting on-line [^{11}C]methylation. This decrease was therefore compensated for by a slight increase in the production run number of [^{15}O]gas. As a result nearly half of the cyclotron machine time available for routine PET radiopharmaceutical production was allotted for the ^{15}O production in the year as shown in Fig. 1. One new PET radiopharmaceutical, [^{11}C]BZT, was introduced for mapping muscarinic cholinergic receptors by PET in the year. It was explanted from Brookhaven National Laboratory in 1991[2-3], and after several pre clinical runs the first clinical PET study was successfully done late in 1992. A new automated for the production of [^{18}F]FDG from no-carrier-added (nca) [^{18}F]fluoride (NKK Corp.) was also installed and evaluated for its clinical use.

Development and installation of a new automated system for the [^{11}C]MET

In 1983 the clinical PET study with [^{11}C]MET began at CYRIC. Since then 220 runs of the routine production of [^{11}C]MET have been totally made for these 10 years. In the meantime, the synthetic procedure was sometimes modified for improving the procedure from manual operation to semi-automated operation although the basic synthetic method[4] was unchanged as follows: [^{11}C]methyl iodide, produced using the automated system, was trapped in acetone cooled at -78°C followed by the addition of homosyteine thiolactone

hydrochloric acid and sodium hydroxide solutions. The mixture was then stirred at 60°C for 5 to 10 min.

In 1991 we developed the efficient, rapid on-line method for *N*-[^{11}C]methylation suitable for automation, especially for *N*-[^{11}C]methylation requiring HPLC purification after the reaction[5], and we have recently succeeded in applying this solid supported [^{11}C]methylation to the preparation of [^{11}C]MET[6]. A new automated system shown in Fig.2 was designed based on this method and tested for routine production of [^{11}C]MET. In the original method NaOH, which is necessary for converting the substrate into sulfide ion by breaking the thiolactone ring after neutralization of the HCl included by the substrate, was introduced into the reaction column from outside together with the mixed solvent of ethanol and water (70/30). However, the radiochemical purity of [^{11}C]MET produced with the system was found to be not reproducibly high enough as can been seen in Table 2. A high concentration of the substrate, one of the advantageous features of the on-line [^{11}C]methylation which can be easily obtained by coating it on solid support, was assumed to cause insufficiency of the base in some local areas in the reaction column probably because of ununiformity of the packed support, resulting in the [^{11}C]methyl iodide with a free base form of the substrate to yield a by-product. A slight change in the concentration or amount of NaOH had nevertheless no effect on improvement in the radiochemical purity. This problem was therefore overcome by altering the method of adding NaOH as follows: NaOH and the substrate were coated on separate support, respectively and then the coated supports and adsorber (Porapak Q) were mixed with each other. After [^{11}C]methyl iodide was trapped by the column, the mixture of ethanol and water (70/30) was introduced into the column and then heated for 3 min at 60°C. Table 2 clearly shows that this modification can provide reproducible high radiochemical purities of [^{11}C]MET. Installation of a new automated system for [^{18}F]FDG from nca [^{18}F]fluoride

It is commonly accepted that nca [^{18}F]FDG has many advantages over conventional [^{18}F]FDG prepared from carrier-added [^{18}F]acetyl hypofluorite. Some of them are 1) high specific activity, 2) high radiochemical purity and 3) high radiochemical yield. However, its synthetic procedure[7] is more complicated and seems rather inconvenient.

We have been collaborating with NKK corp. to develop an automated system for the preparation of nca [^{18}F]FDG[8-9]. The prototype system as shown in Fig. 3 was installed at CYRIC and its performance was evaluated for its routine use. It employs the method for the recovery of nca [^{18}F]fluoride from expensive [^{18}O]water with anion exchange membrane[10]. A one-pot synthesis is enabled by adopting a specially designed small rotary evaporator where the [^{18}F]fluoride recovered is collected, the substitution reaction takes place and the hydrolysis is carried out.

The requirement for the quantification of Kryptofix 2.2.2, important phase transfer catalyst for the substitution of [^{18}F]fluoride, contained in a final solution is also an inevitable

disadvantage. It was analyzed by TLC according to the recommendation of the literature[11-12]. As listed in Table 3, the automated system showed a very satisfactory result. Now it is expected that nca [^{18}F]FDG will soon begin to take a place of carrier-added [^{18}F]FDG for routine clinical PET studies at CYRIC after the approval is obtained from the university committee.

References

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Table. 1. PET Radiopharmaceuticals Supplied for Clinical Use at CYRIC in the Last 3 Years.

Year	[^{18}F]FDG	[^{18}F]FDOPA	[^{18}F]FdUrd	[^{18}F]FDGal	[^{11}C]MET	[^{11}C]PYR	[^{11}C]DOX	[^{11}C]YM	[^{11}C]BZT	[^{15}O]Gas
1990	29.7±7.4 (36)	8.0±3.4 (12)	24.5±11.5 (8)	- (0)	36.1±12.7 (26)	31.0±8.8 (7)	- (0)	15.5±13.0 (7)	- (0)	(75)
1991	28.1±6.9 (37)	10.9±3.5 (12)	21.3±9.4 (3)	23.8±13.7 (4)	32.1±13.3 (25)	- (0)	23.6±9.1 (8)	18.7±5.5 (11)	- (0)	(77)
1992	25.0±6.9 (36)	9.3±2.6 (11)	- (0)	19.1±9.2 (4)	58.0±21.9 (10)	- (0)	20.1±9.1 (11)	16.8±9.5 (9)	40.0 (1)	(82)

Average yield shipped for PET use, mCi
(total run number)

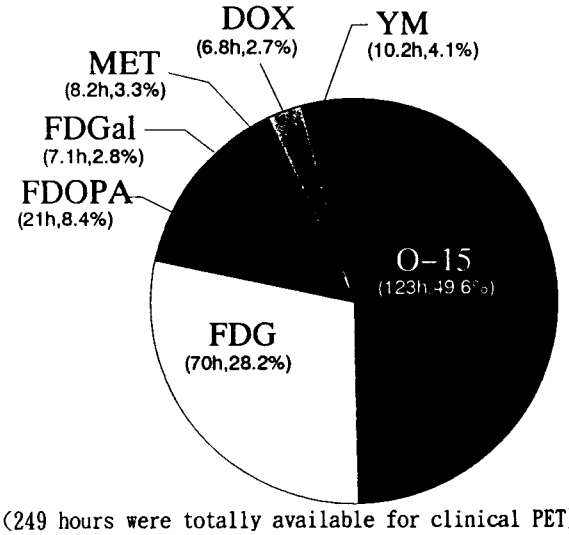
FDG:2-Deoxy-2-fluoro-D-glucose, **FDOPA**:6-Fluoro-L-DOPA, **FdUrd**:5-Fluoro-2'-deoxyuridine,
FDGal:2-Deoxy-2-fluoro-D-galactose, **MET**:L-Methionine, **YM**:YM-09151-2, **PYR**:Pyrilamine, **DOX**:Doxepin, **BZT**:Benztropine

Table. 2. Preparation of [^{11}C]methionine by on-line [^{11}C]methylation.

Run No.	Reaction solvent			Radiochemical purity	[^{11}C]MET yield(EOB)
	NaOH conc.	EtOH content	Volume		
1	0.6 M	70 %	0.2 ml	>99 %	200 mCi
2	0.6 M	70 %	0.2 ml	?	307 mCi
3	0.6 M	70 %	0.2 ml	95.2 %	257 mCi
4	0.6 M	70 %	0.2 ml	97.1 %	303 mCi
5	0.6 M	70 %	0.2 ml	97.0 %	273 mCi
6	0.6 M	70 %	0.3 ml	98.8 %	228 mCi
7	0.2 M	70 %	0.3 ml	58.0 %	105 mCi
8	0.6 M	70 %	0.3 ml	>99 %	192 mCi
9	0.6 M	70 %	0.3 ml	82.8 %	243 mCi
10	0.6 M	70 %	0.3 ml	96.0 %	256 mCi
11	0.8 M	60 %	0.3 ml	90.0 %	259 mCi
12	0.6 M	70 %	0.4 ml	78.7 %	206 mCi
13	1.5 M	70 %	0.3 ml	>99 %	203 mCi
14	Coated	70 %	0.3 ml	>99 %	204 mCi
15	Coated	70 %	0.3 ml	96.6 %	283 mCi
16	Coated	70 %	0.3 ml	>99 %	215 mCi
17	Coated	70 %	0.3 ml	>99 %	212 mCi

Table. 3. Production of no-carrier-added [^{18}F]FDG using the automated system.

Run No.	Starting [^{18}F]F$^-$	[^{18}F]FDG yield		Radiochemical purity	Kryptofix 222 found	Pyrogenicity	Sterility
		EOS yield	(%)				
1	50 mCi	12.9 mCi	(39.4)	99.1 %	<380 μg	Negative	Negative
2	100 mCi	9.9 mCi	(14.9)	97.8 %	<380 μg	Negative	Negative
3	63 mCi	17.1 mCi	(49.7)	97.7 %	<380 μg	Negative	Negative
4	209 mCi	14.2 mCi	(12.0)	95.4 %	<380 μg	Negative	Negative
5	311 mCi	74.3 mCi	(45.5)	95.7 %	<380 μg	Negative	Negative
6	157 mCi	33.0 mCi	(31.7)	95.3 %	<380 μg	Negative	Negative
7	178 mCi	55.2 mCi	(44.3)	97.9 %	<380 μg	Negative	Negative



(249 hours were totally available for clinical PET)

Fig. 1. Cyclotron machine time occupation for PET radiopharmaceutical preparation at CYRIC in 1992.

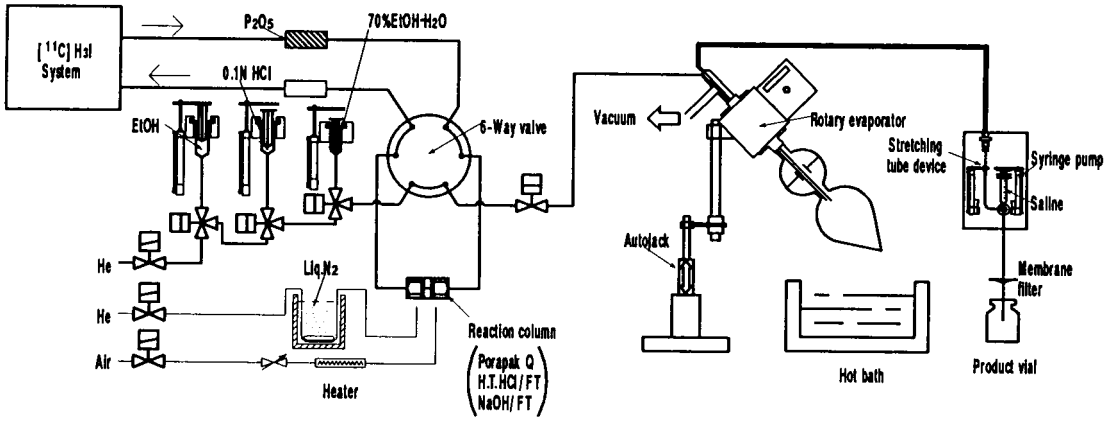


Fig. 2. A flow chart of the automated system for the [^{11}C]methionine using the on-line [^{11}C]mehylation.

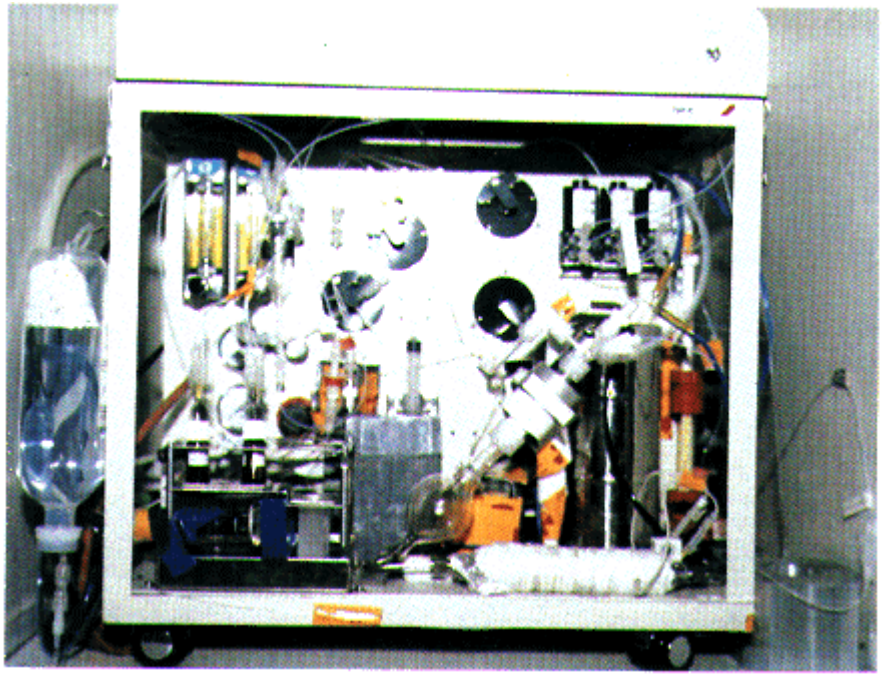


Fig. 3. A photohraphic view of the automated system for the no-carrier-added [^{18}F]FDG.