A New Generator for Ionic Gallium-68

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To meet the needs created by the rapid development of positron tomographic techniques, a new Ge-68 → Ga-68 generator has been developed. By elution under reduced pressure, this tin dioxide/1 *N* HCl generator provides a sterile solution of Ga-68 in ionic form, ready for use in the preparation of many radiopharmaceuticals. Since the Ga-68 recovery yield is high (75–80%) and the elution time very short (less than 2 min), these products possess maximum activity. Owing to its very slight Ge-68 leakage (<0.0002% per elution), the tin dioxide/HCl generator is long-lasting and, more importantly, the radiotoxicity of the labeled derivatives is kept to a minimum. The ionic Ga-68 obtained in this way has been used to label several radiopharmaceuticals.

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Positron emitters occupy a special place among the radionuclides used in nuclear medicine owing to the emission of two annihilation photons in coincidence, thus providing for good-quality tomographic images.

These radionuclides are in general very short-lived, which gives an advantage dosimetrically but also a major obstacle for clinical use in hospitals not equipped with the considerable means necessary for their production. One exception to this general rule is Ga-68, a 68.3-min positron emitter produced by electron capture from Ge-68 (T = 280 days). If the daughter Ga-68 can be separated rapidly from Ge-68, the result is a self-contained short-lived positron source, durable and ready for use several times a day since the ^{68}Ge-^{68}Ga equilibrium is reached in a few hours. Two such fast separations are available: liquid-liquid extraction, and column chromatography.

Solvent extraction was used for the first Ge-68 → Ga-68 generator (*1*): Ga-68 complexed by acetylacetone in buffered solution is extracted with cyclohexane, Ge-68 remaining in the aqueous phase. More recently a separation based on chloroform extraction of the Ga-68-oxine complex has been proposed (*2*). This type of generator usually gives high extraction yields (>70%) but has disadvantages: chemically the Ga-68 is obtained in complexed form, and technologically the organic-aqueous phase separation is difficult to automate and the risk of irradiation and contamination rises.

Commercial generators* are of the chromatographic type: Ge-68 is fixed on an alumina column and Ga-68 eluted by a 5-m*M* EDTA solution (*3,4*). The Ga-68 yield is satisfactory (70%) but decreases considerably with time. Here again, the Ga-68 is available in a complexed form, which must be destroyed before the nuclide can be incorporated into the required radiopharmaceutical. The main result of this extra stage will be a loss of useful radioactivity.

Replacement of Al_2O_3 by Sb_2O_5, and the EDTA by an oxalate solution, stabilizes the elution yield, but Ga-68 is still obtained in complexed form (*5*). Several systems giving Ga-68 in a directly usable ionic form have been proposed: Al_2O_3 or $Fe(OH)_3$ and dilute HCL (*6*), zirconium or silicon oxides and dilute HNO_3 (*7*), titanium oxide and dilute NaOH (*7*). In all these systems, however, the solubility of the oxide in the eluant is not negligible and this rules out all possibility of clinical use. Recently there has been developed another way to obtain Ga-68 in ionic form using organic adsorbents and dilute HCl or HF (*8*).

After careful examination of the properties of inorganic ion exchangers (*9*), and analysis of first results obtained with tin, zirconium, and titanium oxides (*10*), we decided that an ionic Ga-68 generator could be made with the tin dioxide/HCl couple. As long as its properties are not altered by self-irradiation and solubilization, this system should in fact offer quantitative, permanent Ge-68 fixation and a fast, quantitative, and reproducible elution of ionic Ga-68. Having studied these different criteria, we have achieved the characteristics of a tin dioxide/HCl ionic Ga-68 generator that is easy to use and possesses many advantages over the various systems proposed so far.

MATERIALS AND METHODS

Powdered tin dioxide (SnO_2)† is sifted. The 0.16–0.25-mm fraction is washed with 1 *N* HCl, then placed in a glass column of

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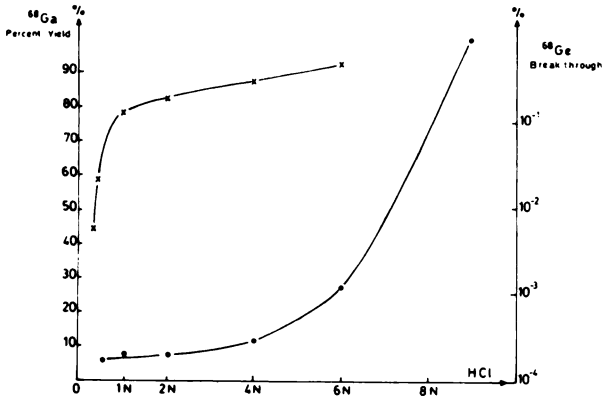

FIG. 1. Percentage Ga-68 eluted (x) and breakthrough of Ge-68 (O), plotted against hydrochloric acid concentration of eluant (3-g SnO_2 generator).

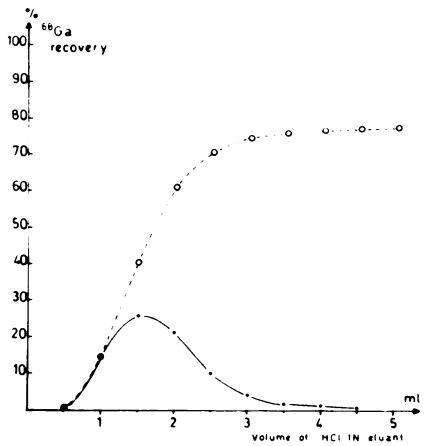

FIG. 2. Elution curve (·), and integrated elution curve (O), of 3-g SnO_2 generator eluted with 1 *N* HCl solution.

internal diameter 10 mm equipped with No. 1 sintered glass at the base, the SnO_2 being held by a glass wool pad fixed with a polyethylene ring. The flow rate is adjusted by a tap at the bottom of the column.

The generator and eluate activities are measured with an ionization chamber. Germanium-68 leakage is determined by an NaI(Tl) scintillator from the Ga-68 present in the eluate 48 hr after the end of elution. The chemical purity is analyzed by neutron activation; an aliquot (100 μl) of the eluate is irradiated for 18 hr in a thermal neutron flux of 3×10^{13} n cm^{-2} s^{-1} (Saclay reactor EL3), and the induced radioactivity is detected with a Ge(Li) diode after a decay time ranging from 1 wk to 1 mo (*11*).

Any self-irradiation problems in the eluate and the SnO_2 are studied by exposing generators charged with tracer doses of Ge-68 to external irradiation. The generators are eluted by 5 ml 1 *N* HCl then placed, with moisture still on the exchanger, at various distances from Co-60 sources so as to obtain the preselected dose rate. At the end of irradiation the generators are eluted again.

RESULTS

Ten-μCi activities of Ge-68 are used to determine the properties of the SnO_2/HCl generator.

Germanium-68 fixation. Fifty milliliters of a 1 *N* HCl solution containing 10 μCi Ge-68 and 100 μg Ge carrier are poured onto 2-, 3-, and 5-g columns of SnO_2. After washing with 50 ml 1 *N* HCl, the Ge-68 fractions recovered in the hydrochloric solutions are 0.3, 0.02, and 0.01%, respectively. The studies thereafter are carried out on 3-g columns of SnO_2, which thus fix the Ge-68 at 99.98%.

Gallium-68 elution. Figure 1 shows how the acidity of the eluant (5 ml) affects the Ga-68 elution and Ge-68 contamination: a stronger acidity improves the Ga-68 elution yield but also causes greater Ge-68 leakage. A normal hydrochloric acid solution — which elutes more than 78% of the Ga-68 formed and less than 0.0002% of the Ge-68 fixed—represents the most suitable compromise.

Figure 2, showing the elution curve of a 3-g SnO_2 column eluted with 1 *N* HCl, indicates that 75% of the generator activity may be obtained in 2.5 ml eluate.

Stability of the generator. To simulate the twice-daily use of a generator for a year, volumes of 1 *N* hydrochloric acid equivalent to 500 elutions of 5 ml were passed over a 3-g SnO_2 column. The eluted activity measurements carried out every ten elutions up to the 100th and every 50 up to the 500th show that at the end of these tests the Ga-68 yield is still higher than 74%. After the 500 elutions the position of Ge-68 on the column has not changed, the maximum activity being on the upper two-thirds of the exchanger as shown by autoradiography of the column.

The generator also retains its properties when dried out or left unused for 1 mo, and the elution yield does not depend on the flow rate of the eluant through the column.

The chemical purity of the eluates is not affected by intensive use of the generator, as shown by the results of analysis carried out on the second and 500th (Table 1). The amount of tin found in 5 ml eluate remains constant (0.5 μg/ml); the other metallic impurities arise mainly from the acid used as eluant. This very slight chemical contamination, which will raise the normal seric tin concentration by less than 2% (*12*), may be considered negligible when we consider for example that to promote radioelement fixation on serum albumin microspheres, about 500 μg of tin are added to the injectable preparation (*13*).

Since self-irradiation of the liquid phase of a generator can lead a drop in the elution yield (*14*), the magnitude of the dose accumulated in a Ge-68 → Ga-68 system was evaluated first.

Using published values (*14-16*), for a 20-mCi generator, we calculate that the dose accumulated by the liquid phase during 5 hr after an elution (yield 75%) is about 50 krad, and during 80 hr about a megarad. In the same way, the dose accumulated by the tin dioxide for the same generator, during 280 days of daily use, is 75 Mrad.

Equivalent external irradiation doses are delivered to three 10-μCi Ge-68 → Ga-68 generators. The various measurements carried out before and after irradiation show no change in the elution yield, Ge-68 leakage, or chemical contamination of the eluate.

Preparation of radiopharmaceuticals. Serum albumin microspheres are labeled with an 80% yield, according to standard techniques (*17,18*), with Ga-68 eluted from the SnO_2/HCl generator by simple neutralization to pH 2 of 2.5 ml eluate.

Similarly the neutralized eluate has been used for the direct preparation of the citrate and pyrophosphate derivatives of Ga-68, identified by paper chromatography (*19*).

DISCUSSION

On the basis of the foregoing results, we have built a 5-mCi Ge-68 → Ga-68 sterile generator, using the well-tried technology of the Tc-99m generators and acid-resistant needles. As predicted, 4 mCi Ga-68 in 5 ml 1 *N* HCl eluate (elution yield around 80%) are available in 1.5 min, the Ge-68 activity of the eluate, 10 nCi,

TABLE 1. MASSES (μg) OF METALLIC CONTAMINANTS MEASURED IN 5 mL 1 *N* HCl ELUATE BY NEUTRON ACTIVATION

	Sn	Ba	Co	Cr	Fe	Hg	Sb	Zn
1 *N* HCl	—	0.04	0.01	0.01	0.9	0.004	—	0.8
2nd eluate	2.5	0.12	0.02	0.02	0.9	0.01	0.004	0.6
500th eluate	2.7	0.03	0.02	0.01	0.8	0.005	—	0.8

remaining below 0.0002% of the activity on the column.

This new SnO_2/HCl generator represents a distinct improvement in the Ga-68 production conditions:

1. The Ga-68 elution yield is high (78-80%)—better than that of the Al_2O_3/EDTA system (70%), and unaffected by self-irradiation phenomena. Ionic Ga-68 is obtained in less than 2 min, whereas at least 30 min are required with systems using solvent extraction or alumina-column chromatography. For a given generator activity, therefore, the SnO_2/HCl couple increases the available activity by 40%.

2. Germanium-68 leakage is small (10^{-4}% per elution) and in any case is one-tenth that recorded with Al_2O_3/EDTA, oxine, or organic adsorbent generators. Extra irradiation of the patient due to the very slight Ge-68 contamination of the eluate may be considered very weak, since the 2 nCi Ge-68 present in 1 mCi Ga-68 eluted from the 5-mCi generator delivers only 1/100th of the absorbed dose (*20*).

3. It is estimated that after a year of intensive use the Ga-68 activity eluted from the SnO_2/HCl generator will still be more than 70% of the available activity because the performance of the generator is dependent neither on the quantity of eluant nor on the dose accumulated by the SnO_2.

FOOTNOTES

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