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STUDIES ON THE PREPARATION OF ^{68}Ge-^{68}Ga GENERATOR WITH INORGANIC MATERIALS

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ABSTRACT

^{68}Ga as a positron emitter is of great interest because of some important advantages. It has a physical half-life of 67.71 min, which is compatible with the pharmacokinetics of many radiopharmaceuticals of low molecular weight. Other important characteristic is its cyclotron-independent availability via the ^{68}Ge-^{68}Ga radionuclide generator system. In Brazil only one positron emitter radionuclide is produced, ^{18}F, and the medical class has a great interest in using ^{68}Ga labeled molecules, in particular peptides such as DOTA-octriotide. A project for developing a home made ^{68}Ge-^{68}Ga is under way at IPEN-CNEN/SP. The aim of this work is to develop an efficient and simplified generator system of ^{68}Ge-^{68}Ga that offers $^{68}Ga^{3+}$ adequate for clinical use. Initial results will be reported concerning the behavior of Ge and Ga in adsorbers such as calcinated acid and basic Al_2O_3, HZO (hydrous zirconium oxide), TiO_2, microspheres of Zr (Zr mic) and microspheres of Al (Al mic). Adsorption studies were carried out using γ-emitting tracers, ^{67}Ga and ^{68}Ga and chemical tracer, GeO_2. The samples containing $^{67/68}$Ga were analysed using a dose calibrator CRC-15R from Capintec and the samples containing Ge were evaluated by the Optical Emission Spectrometry using Inductively Coupled Plasma (ICP-OES). The ICP-OES equipment used was a Varian Vista-MPX from Varian and calibration curves for Ge were constructed in the range of 0.2 to 1.0 μg.mL^{-1}. The use of basic Al_2O_3, TiO_2, HZO and Zr mic showed the more promising results.

1. INTRODUCTION

Positron emission tomography (PET) is a powerful diagnostic imaging technique, and has become the dominant imaging method in the field of nuclear medicine. Because of this fact new radionuclides are required for these applications, and their development has attracted considerable interest. ^{68}Ga as a positron emitter is of great interest because of some important advantages. It has a physical half-life of 67.71 min, which is compatible with the pharmacokinetics of many radiopharmaceuticals of low molecular weight. Other important characteristic is its cyclotron-independent availability via the ^{68}Ge-^{68}Ga radionuclide generator system. Currently, the most prominent radiopharmaceuticals prepared with ^{68}Ga are ^{68}Ga-DOTATOC e ^{68}Ga-DOTANOC indicated for localization of neuroendocrine tumors. The compounds labeled with ^{68}Ga have a great potential for applications in PET, especially in the diagnosis of tumors and planning for radiotherapy dosimetry. The ^{68}Ga has also been used as a tracer for studying infectious diseases [1].

Since the design of the first $^{68}Ge/^{68}Ga$ generator in the 60's, continuous efforts are being made to study the system production and optimization. The most used separation method for ^{68}Ge and ^{68}Ga is the ion exchange chromatography system due to its convenience of operation, but generators systems with separation method by solvent extraction and evaporation have also been proposed [2-4]. The first chromatographic generator of $^{68}Ge/^{68}Ga$ was proposed in 1961 by Green et al [5]. In this system the ^{68}Ge was adsorbed on an alumina column and ^{68}Ga was eluted with 0.005 mol L^{-1} ethylenediaminetetraacetic acid (EDTA). The ^{68}Ga-EDTA solution was used directly to attempt to tumors image. The major limitation of this generator system is that the preparation of others complexes labeled with ^{68}Ga require the dissociation of ^{68}Ga-EDTA, which has high stability, requiring several steps to occur the dissociation, so it is not feasible due to the short physical half life of ^{68}Ga. For this reason it was necessary to develop $^{68}Ge/^{68}Ga$ generators to provide ^{68}Ga as a free ionic species, $^{68}Ga_3^+$. The ^{68}Ge adsorption was evaluated in a variety of inorganic materials such as Al_2O_3, SnO_2, ZrO_2, TiO_2, Fe_2O_3 and SiO_2. Organic resins were also studied: 1,2,3-trihidroxibenzeno (pyrogallol)-formaldehyde (100-200 mesh), AG1-X8 (200-400 mesh) and R-Mglu resin (Diaion CRB-02) [6-13].

In Brazil only one positron emitter radionuclide is produced, ^{18}F, and the medical class has a great interest in using ^{68}Ga labeled molecules, in particular peptides such as octriotide. A project for developing a home made ^{68}Ge-^{68}Ga is under way at IPEN-CNEN/SP. The aim of this work is to develop an efficient and simplified generator system of ^{68}Ge-^{68}Ga that offers $^{68}Ga^{3+}$ adequate for clinical use. Initial results will be reported concerning the behavior of Ge and Ga in adsorbers such as calcinated acid and basic Al_2O_3, HZO (hydrous zirconium oxide), TiO_2, microspheres of Zr (Zr mic) and microspheres of Al (Al mic).

2. MATERIALS AND METHODS

2.1. Adsorber Materials

- Calcinated acid Al_2O_3 was prepared at IPEN-CNEN/SP, and routinely used in home made ^{99}Mo-^{99m}Tc Generators.
- Basic Al_2O_3 – activated, Brockmann I (100-200 mesh).
- HZO is from BIO-RAD: HZO-1 Ion Exchange Crystals (50-100 mesh).
- TiO_2 was homemade (100-200 mesh).
- Microspheres of Zr and Al were prepared at IPEN-CNEN/SP (Centro de Células a Combustível e Hidrogênio - CCCH).

2.2. Experimental procedures

2.2.1. Calcinated acid and basic Al_2O_3, HZO and TiO_2

Glass columns with a diameter of 12 mm were used for the experiments with Al_2O_3, HZO and TiO_2 containing 1.0-2.0 g of the adsorbers and the solutions were percolated using vacuum. The columns were previously conditionated with 0.1 mol L^{-1} HCl. Then they were loaded with $^{67/68}GaCl_3$ solution (7.4 to 55.5 MBq/ mL) or with a Ge solution (100 µg Ge/mL)

in a proper pH. The columns were further eluted with 10 mL of 0.1 mol L^{-1} HCl. The variables studied were the pH of the conditioning, loading and eluting solutions (1.5 and 4.0).

2.2.2. Microspheres of Zr and Al

Glass columns with a diameter of 6 mm were used for the experiments with ZrMS. containing 0.5-1.0 g of the microspheres. The microspheres were heated in 1 mL of Ge solution (100 µg Ge/mL) (pH=14) and transferred to the glass column, then the loading solution was colleted. The column was further eluted with 6 mL of 0.1 mol L^{-1} HCl. The experiment with ^{68}Ga was performed with the same glass column, that was conditionated with 0.1 mol L^{-1} HCl and loaded with $^{68}GaCl_3$ solution (~20MBq/mL). The solutions were percolated using a constant flow (1.4 mL/min.)

2.2.3. Determination of $^{67/68}$Ga and Ge

The samples containing $^{67/68}$Ga were analysed using a dose calibrator CRC-15R from Capintec and the samples containing Ge were evaluated by the Optical Emission Spectrometry using Inductively Coupled Plasma (ICP-OES). The ICP-OES equipament used was a Varian Vista-MPX from Varian and calibration curves for Ge were constructed in the range of 0.2 to 1.0 µg mL^{-1}.

3. RESULTS AND DISCUSSION

3.1. Adsorber: Al_2O_3

3.1.1. Calcinated acid Al_2O_3

Figures 1, 2 and 3 show the elution profile of Ge and Ga in acid and calcinated Al_2O_3 chromatographic column. When pH 1.5 was used for the conditioning, loading and eluting, the elution of Ga reached 90%, but only 30% of Ge was adsorbed in the column (fig.1). When pH was increased to 4 for the conditioning, loading and eluting, high adsorption (~100%) of Ge and Ga was achieved (fig.2). On the other hand, if only the pH of the loading solution was changed to 4, the adsorption of Ge reached 80% and the elution of Ga was more than 90% (fig.3).

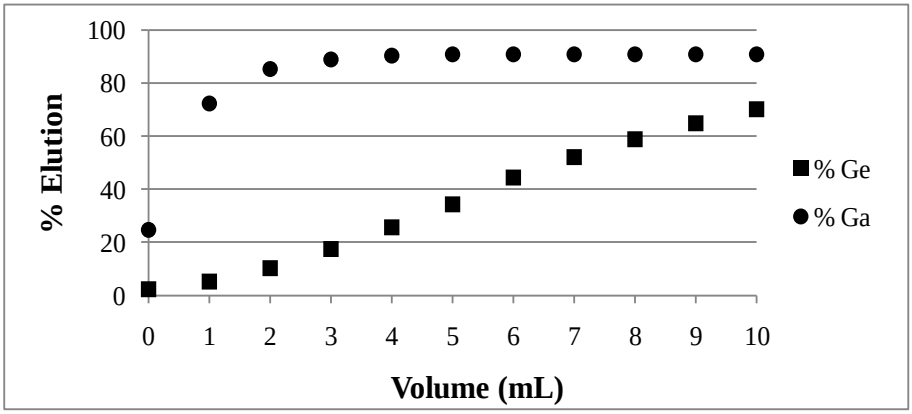

Figure 1. Elution profile of Ge and Ga in acid and calcinated Al_2O_3 chromatographic column with pH 1.5 for conditioning, loading and eluting.

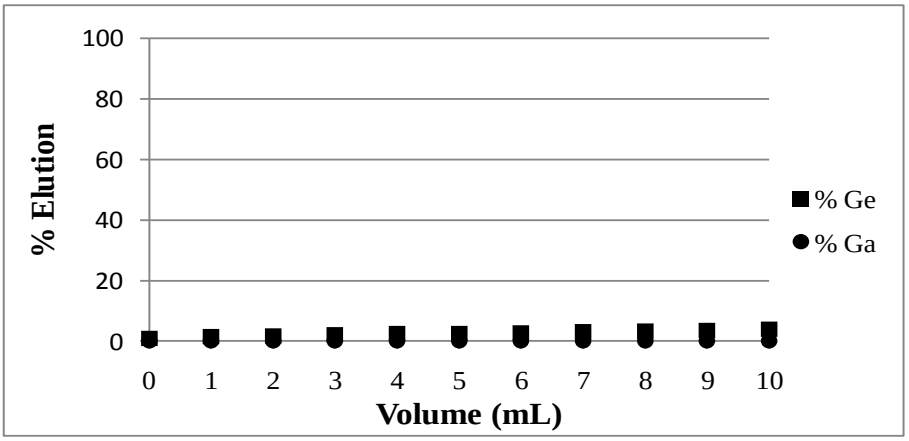

Figure 2. Elution profile of Ge and Ga in acid and calcinated Al_2O_3 chromatographic column with pH 4 for conditioning, loading and eluting

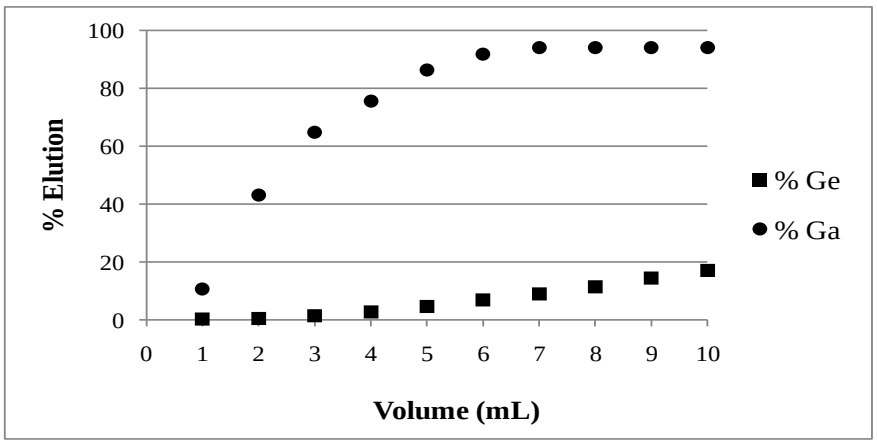

Figure 3. Elution profile of Ge and Ga in acid and calcinated Al_2O_3 chromatographic column with pH 1.5 for conditioning and eluting and pH 4 for loading.

3.1.2. Basic Al_2O_3

The elution profile of Ge and Ga in basic Al_2O_3 chromatographic column was studied using pH 1.5 for the conditioning and eluting and pH 4 for the loading solution. The adsorption of Ge reached almost 100% and the elution of Ga was more than 97% (fig.4). This result was much better than the one with calcinated acid Al_2O_3 column in the same conditions.

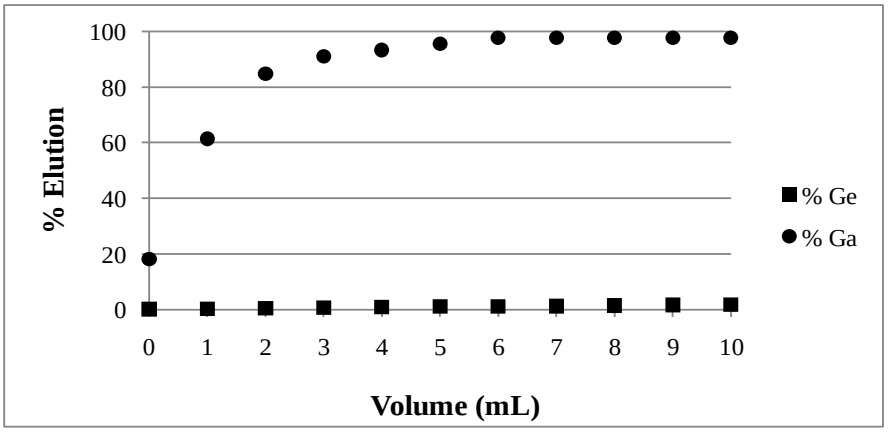

Figure 4. Elution profile of Ge and Ga in basic Al_2O_3 chromatographic column with pH 1.5 for conditioning and eluting and pH 4 for loading.

3.2. Adsorber: HZO

Figures 5, 6, 7 and 8 show the elution profile of Ge and Ga in HZO chromatographic column. When pH 1.5 was used for the conditioning, loading and eluting, the elution of Ga reached 80% and 80% of Ge was adsorbed in the column (fig.5). The result was better than the one with calcinated acid Al_2O_3 chromatographic column in the same conditions, althought the percentage of Ge eluted is still high.

When pH was increased to 4 for the conditioning, loading and eluting, high adsorption of Ge and Ga was achieved (fig.6), the same behaviour observed with calcinated acid Al_2O_3.

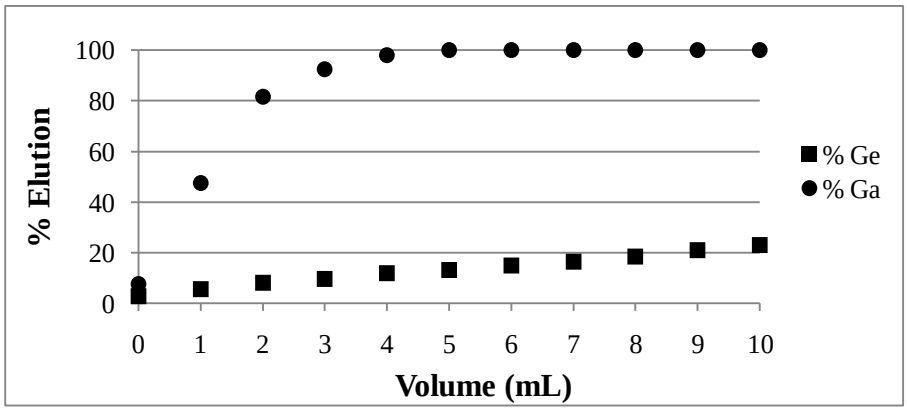

Figure 5. Elution profile of Ge and Ga in HZO chromatographic column with pH 1.5 for conditioning, loading and eluting.

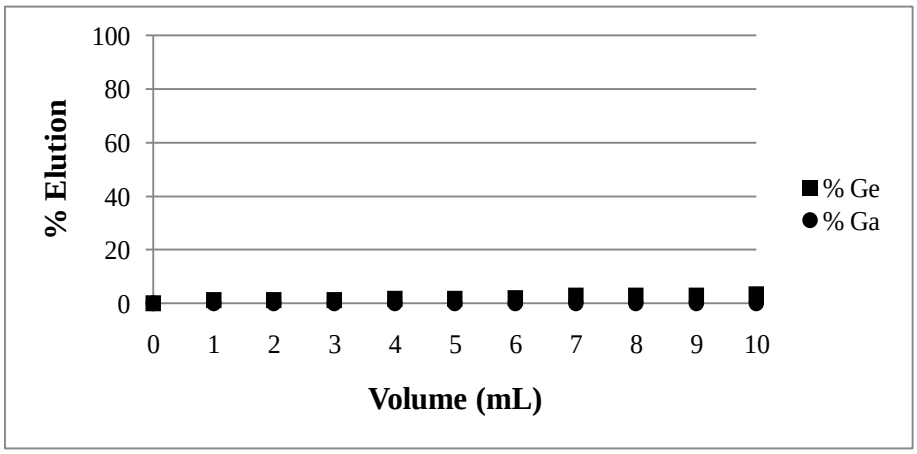

Figure 6. Elution profile of Ge and Ga in HZO chromatographic column with pH 4 for conditioning, loading and eluting.

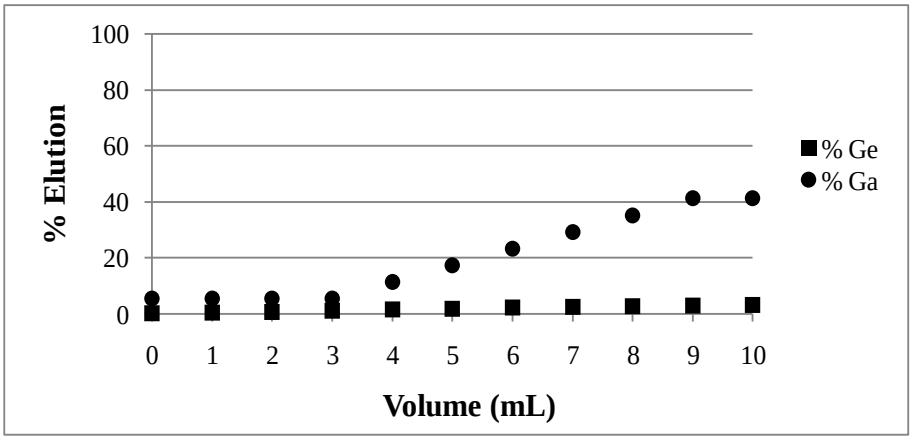

Figure 7. Elution profile of Ge and Ga in HZO chromatographic column with pH 4 for conditioning and loading and and pH 1.5 for eluting.

It can be seen in figure 7 that when pH was increased to 4 only for conditioning and loading, the adsorption of Ge in column remain high and the elution of Ga increased to 40%.

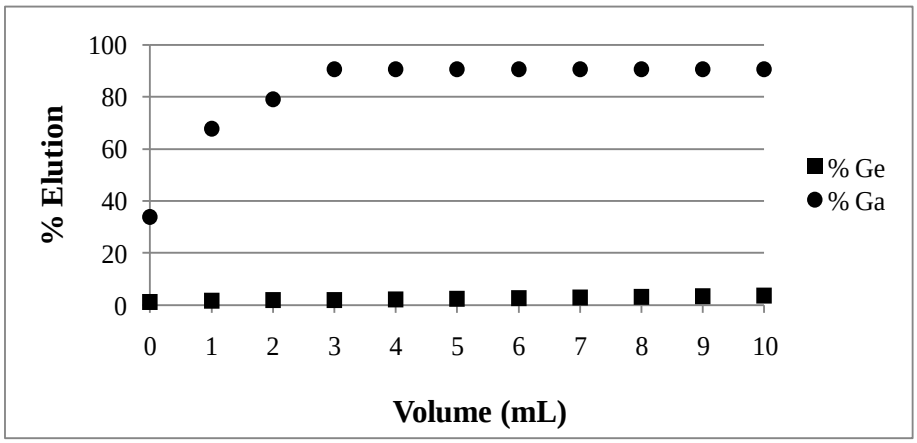

Figure 8. Elution profile of Ge and Ga in HZO chromatographic column with pH 1.5 for conditioning and eluting and pH 4 for loading.

When pH was increased to 4 only for the loading solution, the adsorption of Ge was more then 97% and elution of Ga achieved 90% (fig.8).

3.3. Adsorber: TiO_2

The behavior of Ge and Ga in TiO_2 chromatographic column was studied using pH 1.5 for the conditioning and eluting and pH 4 for the loading solution. The Ge adsorption and Ga elution were almost 100% (fig.9). This result was similar the one achieved with basic Al_2O_3 and HZO column in the same conditions.

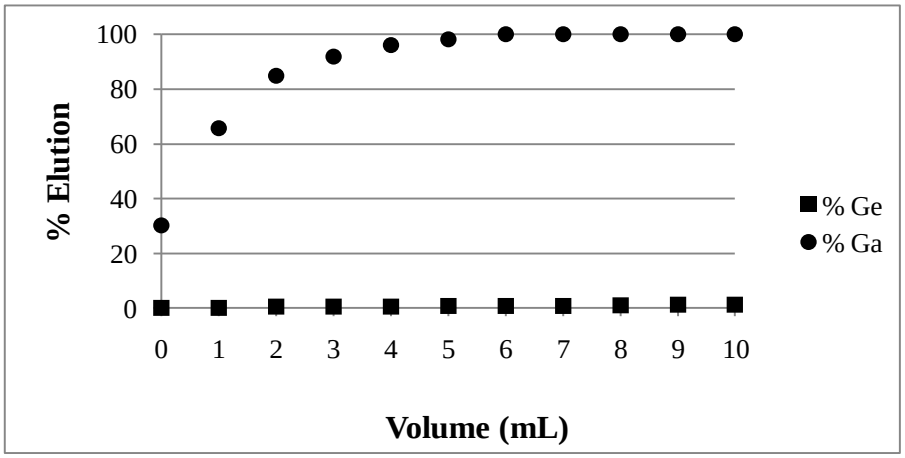

Figure 9. Elution profile of Ge and Ga in TiO_2 chromatographic column with pH 1.5 for conditioning and eluting and pH 4 for loading.

3.4. Adsorber: Microspheres of Zr and Al

3.4.1. Microspheres of Zr

Figure 10 shows the chemical behavior of Ge and Ga in Zr mic chromatographic column. A high percentage (~100%) of Ge was adsorbed in microspheres and 100 % of Ga was eluted.

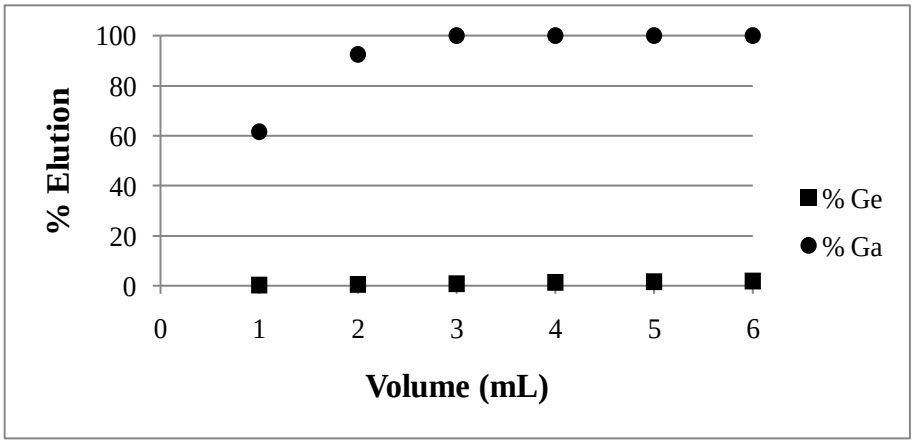

Figure 10. Elution profile of Ge and Ga in Zr mic chromatographic column.

3.4.1. Microspheres of Al

Figure 11 shows the chemical behavior of Ge and Ga in Al mic chromatographic column. A high percentage (~100%) of Ge was adsorbed in microspheres and ~70 % of Ga was eluted.

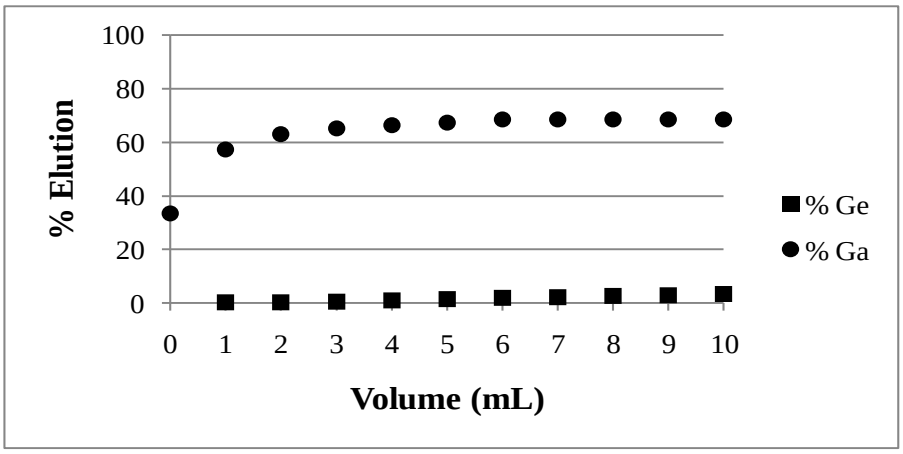

Figure 11. Elution profile of Ge and Ga in Al mic chromatographic column.

4. CONCLUSIONS

The adsorbents materials that achieved the best results were: basic Al_2O_3, HZO and TiO_2. The use of microspheres was also very promising, since they presented a high retention of the Ge (> 96%) and very good elution of Ga (~ 99%) in low volumes (<5 mL), with smaller masses of sorbent material when compared to the other materials.

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REFERENCES

1. KHAN, M.U.; KHAN, S.; EL-REFAIE, S.; WIN, Z.; RUBELLO, D., AL-NAHHAS, A. "Clinical indications for Gallium-68 positron emission tomography imaging". *Eur J Surg Oncol*, (2009). Article in press.
2. GLEASON G.I. "A Positron Cow". *Int. J. Appl. Radiat. Isot.* **Vol. 8**, pp. 90-94 (1960).
3. EHRHARDT, G.J.; WELCH, M. J. "A New Germanium-68/Gallium-68 Generator". *J. Nucl. Med.* **Vol. 19**, pp. 925-929 (1978).
4. MIRZADEH, S. "Evaporation-Based Ge/Ga(68) Separation. U.S. Patent No. 4.268.730", fevereiro (1981).
5. GREENE, M. W.; TUCKER, W. D. "An Improved Gallium-68 Cow". *Int. J. Appl. Radiat. Isot.* **Vol. 12**, pp. 62-63, Issues 1-2 (1961).
6. YANO, Y.; ANGER, H.O. "A Gallium^{68} Positron Cow for Medical Use". *J. Nucl. Med.* **Vol. 5**, pp. 485-488 (1964).
7. KOPECKÝ, P.; MUDROVÁ, B.; SVOBODA, K. "The Study of conditions for the Preparation and Utilization of ^{68}Ge-^{68}Ga Generator". *Int. J. Appl. Radiat. Isot.* **Vol. 24**, pp. 73-80 (1973).
8. KOPECKÝ, P.; MUDROVÁ, B. "^{68}Ge-^{68}Ga Generator for the Production of ^{68}Ga in an Ionic Form". *Int. J. Appl. Radiat. Isot.* Vol. 25, pp. 263-268 (1974).
9. MALYSHEV, K.V.; SMIRNOV, V.V. "A Generator of Gallium-68 Based on Zirconium Hydroxide". *Translated from Radiokhimiya*, **Vol. 17**, nº 1, pp. 137-140 (1975).
10. ARINO, H.; SKRABA,W. J.; KRAMER, H.H. "A New ^{68}Ge/^{68}Ga Radioisotope Generator System". *Int. J. Appl. Radiat. Isot.* **Vol. 29**, pp.117-120 (1978).
11. NEIRINCKX, R.D.; DAVIS, M.A. "Potential Column Chromatography Generators for Ionic Ga-68. I. Inorganic Substrates". *J. Nucl. Med.* **Vol. 20**, pp. 1075-1079 (1979).
12. LOC´ H, C., MAZIERE, B., COMAR, D. "A new generator for ionic gallium-68". *J. Nucl. Med.* **Vol. 21**, pp. 171-173 (1980).
13. NEIRINCKX, R.D.; DAVIS, M.A. "Potential Column Chromatography for Ionic Ga-68. II: Organic Ion Exchangesrs". *J. Nucl. Med.* **Vol. 21**, pp. 81-83 (1980).