Technical Note

The Use of Computed Radiography for the Determination of the Impurities in $^{68}$Ga-EDTA by Paper Chromatography

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1. Introduction

An ionic generator has been developed for preparation of gallium-68-labeled radiopharmaceuticals. This generator can be easily applied to the preparation of $^{68}$Ga-EDTA but some trials are necessary to determine the proper doses of EDTA.

The half life of $^{68}$Ga is about 68 min and in our experiments, as it was necessary to check the purity of many samples at one time, we employed simplified mini paper chromatography in combination with autoradiography using a computed radiography system.

2. Materials and Methods

2.1 $^{68}$Ga solution

The ionic $^{68}$Ga generator was obtained from New England Nuclear Co., Boston MA, USA. The $^{68}$Ge was fixed by tin (IV) dioxide (SnO$_2$) in a glass column. Elution tests using this generator showed that about 185 MBq (5 mCi) of $^{68}$Ga could be eluted by 10 ml of 1 N HCl one half life time of $^{68}$Ge after the preparation of the generator. Therefore, the experiments in this study were carried out after this period. Over 95% of the elutable $^{68}$Ga was obtained in the first 5 ml of the eluate, and the maximum concentration was about 24 MBq/0.1 ml (0.65 mCi/0.1 ml). A 511 keV energy peak was detected in the eluate using a Ge(Li) semiconductor detector.

2.2 Preparation of $^{68}$Ga-EDTA

Analytical reagent grade chemicals were used. An aqueous solution of EDTA-2Na (10 mg/1 ml) was made and then diluted decimally by water to obtain solutions of several varying concentrations. Each EDTA solutions (0.1 ml) was added to 0.1 ml of the $^{68}$Ga eluate and then the mixtures were neutralized with 1 N NaOH.

2.3 Paper chromatography

Three solvents already tested in the quality control of $^{68}$Ga radiopharmaceuticals were used to estimate the purity of the preparations. The composition of the solvents were as follows; Solvent A (700 ml water, 200 ml ethanol and 0.35 ml conc. ammonia), Solvent B (275 ml isopropanol, 125 ml water and 15 g trichloroacetic acid) and Solvent C (400 ml water, 200 ml ethanol and 100 ml pyridine).
Whatman No. 1 chromatographic paper was used for the paper chromatography. As quick results were desired the paper was cut into small pieces (mini paper chromatography, 1 × 10 cm) with an effective developing length of 5.5 cm. Ascending paper chromatography was performed in a small 10 ml plastic tube with 1.5 ml of solvent in the bottom after spotting a sample at the origin. After the run, the paper was dried and wrapped with thin polyethylene film or treated with a fixing spray after developing and drying to avoid contamination before contact exposures.

2.4 Computed radiography system

We used imaging plates (standard type) normally used for a computed radiography system (Fuji computed radiography system, Fuji Medical System Co. Ltd., Tokyo, Japan) using a scanning laser-stimulating luminescence technique instead of conventional X-ray film. The size of the imaging plate was 20.3 × 25.4 cm (8 × 10 in) making it possible to measure 50 specimens. Imaging plates of different sizes are also applicable (35.6 × 43.2 cm for 149 specimens, 35.6 × 35.6 cm for 120 specimens, 27.9 × 35.6 cm for 91 specimens and 25.4 × 30.5 cm for 75 specimens).

After the treatment to avoid contamination as mentioned above the radioactive specimens were contacted on the imaging plate for an appropriate time (10 – 30 min). The exposed imaging plates were processed by the system, and the digitalized exposure data was printed out on the recording films and stored on magnetic tapes.

2.5 Image data processing system

The digital data on the magnetic tapes was transferred by another computer system and the image data was processed in several ways, mainly with a SIMIS-III system (Sopha Medical, Paris, France) and an Eclipse 32 bit computer (Nippon Data General Co. Ltd., Tokyo, Japan) used in a positron computed tomography system (Simadzu Co. Ltd., Kyoto, Japan).

3. Results

Several autoradiographic images using the computed radiography system were obtained, and these images and the digitalized data were more than sufficient for the simplified analysis. A five min exposure was enough to check the purity of the ⁶⁷Ga-EDTA. However, the quality of the image was improved with longer exposures. Autoradiograms of developed papers obtained with this system are shown in Fig. 1. The results shown in this figure were obtained using the three solvent systems (A, B, C) and three different EDTA doses.

The density histograms (Fig. 2) were obtained directly from the image data shown in Fig. 1. These curves were generated by the data processing system. The peaks are somewhat dull due to the scatterings seen in Fig. 1. It was revealed that EDTA at the dose of 100 μg per 1 ml gave essentially one peak, while other EDTA doses (10 μg, 1 μg) produced extra peaks. The results were also confirmed by the images.

The mean $R_t$ values determined for ⁶⁷Ga-EDTA were 0.98, 0.45 and 0.95 for solvent A, B and C. The content of ⁶⁷Ga-EDTA was more than 99% when 1 ml of the eluate was incubated with more than 100 μg of EDTA (data not shown). Therefore, an EDTA dose of at least 1 mg for each 1 ml of eluates will be sufficient for the preparation of ⁶⁷Ga-EDTA.
4. Discussion

There are 2 types of ⁶⁸Ga generators commercially available. Gallium-68-ethylenediaminetetraacetic acid (⁶⁸Ga-EDTA) is easily obtained from the EDTA extraction type generator, but the ⁶⁸Ga obtained is in a tight complex form with EDTA. An ionic generator is more appropriate for the preparation of ⁶⁸Ga-labeled radiopharmaceuticals.

Paper chromatography technique is a simple but relatively inaccurate technique when used as a purity check. However, it is convenient to determine the global distribution of the tracer. Our present experiments indicate that the use of paper chromatography in combination with a computed radiography system gives satisfactory results to check the purity of ⁶⁸Ga-EDTA. As a solvent system which gives complete separation of impurities from ⁶⁸Ga-EDTA has not yet been established, it is safer to use a system with a combination of solvents.

The $R_f$ values of ⁶⁸Ga-EDTA previously reported using the same solvent systems used in this study were 0.95, 0.60 and 0.95 for Solvents A, B and C. The $R_f$ values obtained in our study were not exactly the same as the published data but similar results were obtained. We think that the differences were probably due to the differences in paper size.

The impurities in the insufficient EDTA dose in ⁶⁸Ga-EDTA labeling (Figs. 1 and 2) were thought to be gallate ion and gallium-hydroxide but further identification was not carried out.

The exposure times for the imaging plates were only 10–15 min in this study and all the procedures were carried out within 3–5 h after the elution of ⁶⁸Ga from the generator.
As the radioactivity applied to the paper was at most 37 kBq (1 μCi) and the exposure time could be reduced even more judging from the quality of the images shown in Fig. 1, it can be said that the present system is much more radiosensitive than the usual autoradiography system using X-ray films.

Another advantage is that the results of paper chromatographic procedure can be obtained at one time, which is convenient for the comparison of many specimens in any one situation. The imaging plate can be recurrently used after erasing the exposure data on the plate and stable results are expectable.

Moreover, the results are directly transferable to digital data and no more additional procedures which affect the original data, such as density measurements, are required, thus promoting the credibility of the study. Image processing is easier if the data is already transferred in digital form and it is very easy to do direct calculations of the image data. This is an important point concerning the superiority of this technique to the traditional film technique.

5. Conclusion

We tested a combination of paper chromatography with computed radiography system. Measurements of many specimens were possible at one time and digitalized imaging data were obtained. This combination technique is thought to be simple and practical for checking the purity of 68Ga-EDTA. One mg of EDTA is sufficient for 1 ml of eluate from the ionic 68Ga generator.

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