Development of an ethanol-based post-processing for generator-produced ^{68}Ga for medical applications

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Post-processing using a cation-exchanger in hydrochloric acid/acetone media represents an efficient strategy for concentration and purification of generator-derived ^{68}Ga eluates [1,2]. It assures the removal of ^{68}Ge, and provides high labeling yields of injectable ^{68}Ga-labeled radiopharmaceuticals for routine medical applications.

The aim of this work is to replace acetone by ethanol to combine the very efficient strategy for concentration and purification based on cation-exchangers with the superior properties of ethanol.

We developed a processing of generator-produced ^{68}Ga eluates including the labeling of DOTA-octreotide derivatives. A ^{68}Ge/^{68}Ga Obninsk generator was used with a ^{68}Ga yield of 100 MBq and 85 kBq breakthrough of ^{68}Ge. Pre-concentration and purification of the initial generator eluate were performed using a cation exchange resin, Biorad (AG 50W-X8, -400 mesh; AG 50W-X4) or Phenomenex (SCX), along the lines of the solutions N1 and N2 known from hydrochloric acid/acetone systems, but this time using hydrochloric acid/ethanol mixtures. Distribution of ^{68}Ga and metallic impurities like ^{68}Ge(IV), Fe(III) and Ti(IV) on the cation-exchange column was investigated. The purified fraction was used for labeling of nanomolar amounts of octreotide derivatives in pure aqueous solution and in different buffer systems.

We successfully developed a post-processing on cation-exchange resin hydrochloric acid/ethanol along the lines of the state-of-the-art post-processing based on hydrochloric acid/acetone media. Using this post-processing system with AG 50W-X8 up to 95% ^{68}Ga activity was obtained in a 1 mL fraction of 90% ethanol/0.9N HCl within 4 min. With AG 50W-X4 up to 90% ^{68}Ga activity was obtained in 1 mL fraction of the same eluate composition. ^{68}Ge(IV) passes both columns in the original 0.1N HCl solution. Remaining traces were further reduced by washing with 80% ethanol/0.15N HCl solution. In relation to the initial eluate, the final ^{68}Ga fraction contains less than 0.01% of ^{68}Ge. Also impurities with Fe(III), Zn(II) and Ti(IV) could be reduced by the use of the optimized solutions. With Strata-XC tubes (Phenomenex) as cation-exchange resin only 40%-50% of ^{68}Ga activity was obtained under optimized conditions. Due to the fact that the major part of activity remains on the column further investigations of the impurity distributions were not performed.

Due to the fact that the hydrochloric acid/ethanol systems have a lower pH than its acetone equivalent, buffer solutions are utilized for labeling octreotide derivatives. In pure aqueous solutions the labeling yields were very low (<15%). The amount of HCl contained in the final labeling solution (1 mL 90 % ethanol/0.9 N HCl

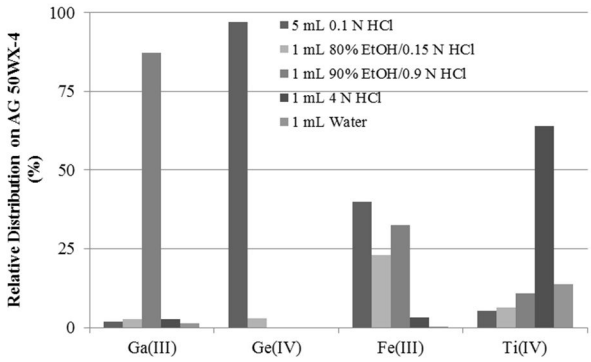

Figure 1: Relative Distribution of Ga(III) and metal impurities on AG 50W-X4

the final labeling solution (1 mL 90% ethanol/0.9N HCl ≡ $9*10^{-4}$ mol H^+) provided an overall pH of 1.68 ± 0.02 without added buffer. At 95 °C and under these acidic labeling conditions, radiolabeling yield was less than 15%. Adjusting pH to 2.30 ± 0.02 with the help of phosphate saline buffer resulted in radiolabeling yields higher than 95%. Purification of the ^{68}Ga-labeled peptide from unreacted ^{68}Ga species was obtained by reversed-phase chromatography (Phenomenex Strata-X tubes, 30 mg) providing quantitative retention of the peptide on reverse phase. After washing with water, more than 90% of the ^{68}Ga-labeled peptide was recovered in 0.4 mL pure ethanol.

Appropriate processing of generator-produced ^{68}Ga on the basis of cation-exchange chromatography is effective in hydrochloric acid/ethanol media. It successfully removes the breakthrough of ^{68}Ge and allows the concentration of ^{68}Ga generator eluate with yields as good as with established post-processing methods. The whole process guarantees safe preparation of injectable ^{68}Ga-DOTATOC (or other ^{68}Ga-labeled radiopharmaceuticals) for routine applications and can be successfully used in clinical environment. However, application of several generators in a cascade scheme can be used with this ethanol-based post-processing.

References

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[2] Zhernosekov, K.P. *et al., J. Nucl. Med.* **2007**, *48,* 1741.