LABELING OF MONOAMINE-MONOAMIDE DITHIOLS (MAMA) LIGAND WITH GENERATOR-PRODUCED ¹⁸⁸Re USING CITRIC ACID AS A TRANSFER LIGAND

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The radioisotopes of rhenium (¹⁸⁶Re and ¹⁸⁸Re) are attractive radionuclides for radiotherapy because of their energetic beta particles and gamma rays suitable for imaging. Oxorhenium(V) and oxotechnetium(V) complexes with quadridentate ligands such as N₃S and N₂S₂ ligands are often used as radiopharmaceuticals. Mercaptoacetyltriglycine, MAG₃ (N₃S ligand, Fig. 1), labeled with ¹⁸⁶Re was prepared in a high yield (91 - 93%) by stannous ion reduction in the presence of citric acid as a transfer ligand [1]. Monoamine-monoamide dithiols (MAMA) ligands are also useful in preparing radiopharmaceuticals, typically form of $M(V)O(N_2S_2)$ complexes [2]. In this study, the labeling of MAMA ligand with no-carrieradded ¹⁸⁸Re from a ¹⁸⁸W/¹⁸⁸Re generator was investigated in detail. Stannous chloride was used as a reducing agent for the reduction of rhenium and citric acid was used as a transfer ligand.

The ¹⁸⁸W/¹⁸⁸Re generator was prepared by the alumina column system with ¹⁸⁸WO₃ produced by the irradiation in JAERI JMTR (a thermal neutron flux of 2.7×10^{14} n cm⁻² s⁻¹) for 26-52 days. Rhenium-188 solution ($2 \times 10^5 - 3 \times 10^6$ Bq ml⁻¹) was obtained from the generator in a 0.9% NaCl solution and was used for labeling purposes without further purification.

Triphenylmethyl-MAMA (Tr-MAMA), as shown in Fig. 1, was prepared by reaction of S-(triphenylmethyl)-2aminoethanethiol with bromoacetyl bromide. Triphenylmethyl group of Tr-MAMA was deprotected by treatment with trifluoroacetic acid (TFA) and triethylsilane just before radiolabeling. After the removal of the solution by a flow of N₂ gas, HCl, NaOH and/or sodium acetate solution for adjustment, a stannous chloride pН solution in 0.1 M citrate-buffer (pH=5), and a ¹⁸⁸Re solution from the generator



Fig. 1. Chemical structures of MAG₃ and Tr-MAMA.

were added to the MAMA ligand. The reaction mixture was vigorously stirred and allowed to react in boiling water for 1 h. The solution was filtered through a 0.22 µm filter before HPLC analysis. Radiochemical yield of ¹⁸⁸Re-MAMA was determined by reversed phase HPLC (Hypersil C18 BDS-5, 4.6 mmØ×150 mm) using a gradient system comprising 0.1% TFA in H₂O (solvent A) and 0.1% TFA in acetonitrile (solvent B). The flow rate was 1.0 ml/min and the gradient was defined by the following points (min-%B): 0-5, 30-100. Typical chromatograms are shown in Fig. 2. Retention times of ¹⁸⁸ReO₄, ¹⁸⁸Re-citrate and ¹⁸⁸Re-MAMA are 2.4 min, 2.4 min and 10.2 min, respectively.



Fig. 2. Chromatograms of carrier-added ¹⁸⁸Re-MAMA synthesized at different pH.

The dependence of the labeling yield upon the reaction conditions such as pH, the concentration of the reducing agent and the addition of a carrier was examined. The influence of the labeling yield on pH is shown in Fig. 3. The maximum labeling yields of both carrier-added and no-carrier-added ¹⁸⁸Re-MAMA were obtained in the acidic pH region less than pH 3 and the labeling yields decreased sharply above pH 3. Under the optimum conditions, the

labeling yield of ¹⁸⁸Re-MAMA was more than 98% using no-carrier-added ¹⁸⁸Re as well as carrier-added ¹⁸⁸Re (20 ig Re/ml).

To evaluate the stability of ¹⁸⁸Re-MAMA, the pH of ¹⁸⁸Re-MAMA solution obtained under the optimum conditions was changed by adding HCl, NaOH and/or sodium acetate solution. The radiochemical yield of ¹⁸⁸Re-MAMA was determined by HPLC at appropriate time intervals. The result of the stability of carrier-added ¹⁸⁸Re-MAMA is shown in Fig. 4. Radiochemical vield of carrier-added ¹⁸⁸Re-MAMA after pH change decreased with increasing of pH and the elapse of time when the pH was over 8. However,



Fig. 3. Influence of pH on the labeling yield of ¹⁸⁸Re-MAMA.

the radiochemical yield of carrier-added ¹⁸⁸Re-MAMA was over 97% in the pH 6 to 7 region even after 70 hours. The same results were obtained for no-carrier-added ¹⁸⁸Re-MAMA.



Fig. 4. Stability of carrier-added ¹⁸⁸Re-MAMA in different pH solutions.

References

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