2009 International Nuclear Atlantic Conference - INAC 2009
Rio de Janeiro,RJ, Brazil, September27 to October 2, 2009
ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR - ABEN
ISBN: **978-85-99141-03-8**

LABELING PROCEDURES FOR THE PREPARATION OF ^{188}Re-DMSA(V)

Tânia P. Brambilla[1], João A. Osso Jr.[1]

[1] Instituto de Pesquisas Energéticas e Nucleares (IPEN / CNEN - SP)
Av. Professor Lineu Prestes 2242
05508-000 São Paulo, SP
taniabrambilla@yahoo.com.br
jaosso@ipen.br

ABSTRACT

^{188}Re has received a lot of attention in the past decade, due to its favorable nuclear characteristics [$t_{1/2}$ 16.9 h, $E_{\beta\ max}$ 2.12 MeV and E_γ 155 keV (15%) suitable for imaging], including the fact that it is carrier-free and can be obtained cost-effectively through the generator ^{188}W-^{188}Re. Besides the therapeutic usefulness of ^{188}Re, the emission of the 155 keV gamma photon is an added advantage since the biodistribution of ^{188}Re-labeled agents can be evaluated *in vivo* with a gamma camera. Biodistribution studies of ^{188}Re-DMSA(V) have shown that its general pharmacokinetic properties are similar to that of ^{99m}Tc-DMSA(V), so this agent could be used for targeted radiotherapy of the same tumors, i.e., medullary thyroid carcinoma, bone metastases, soft tissue, head and neck tumors. The aim of this work is to evaluate two labeling procedures for the preparation of ^{188}Re-DMSA(V). ^{188}Re-DMSA(V) was prepared by two methods. The first method was prepared using a commercial kit of DMSA(III) for labeling with ^{99m}Tc, at high temperature (100^{o}C). The second method was prepared in a vial containing 2.5 mg of DMSA, 1.00 mg of $SnCl_2.2H_2O$ and 30 mg of sodium oxalate, in a total volume of 1.1 mL. The pH was adjusted to 5 with 37% HCl. After labeling the solution was stirred and incubated for 15 min at room temperature. The radiochemical purity was determined using TLC-SG developed with two different solvent systems. Preliminary results for both methods of labeling ^{188}Re-DMSA(V) showed that the labeling yield was >90%.

1. INTRODUCTION

Radionuclide therapy (RNT) is emerging as an important tool of nuclear medicine. Apart from the well established ^{131}I, several other promising radionuclides have been identified, among them ^{188}Re, ^{90}Y and ^{177}Lu are considered to be the most promising radionuclides for *in vivo* therapy [1]. ^{188}Re has received a lot of attention in the past decade, due to its favourable nuclear characteristics: $t_{1/2}$ 16.9 h, $E_{\beta\ max}$ 2.12 MeV and E_γ 155 keV (15%) suitable for imaging, including the fact that it is carrier-free and can be obtained cost-effectively through the generator ^{188}W-^{188}Re. Besides the therapeutic usefulness of ^{188}Re, the emission of the 155 keV gamma photon is an added advantage since the biodistribution of ^{188}Re-labeled agents can be evaluated *in vivo* with a gamma camera. Biodistribution studies of ^{188}Re-DMSA(V) have shown that its general pharmacokinetic properties are similar to that of ^{99m}Tc-DMSA(V), so this agent could be used for targeted radiotherapy of the same tumors, i.e., medullary thyroid carcinoma, bone metastases, soft tissue, head and neck tumors [2,3]. In therapy of medullary thyroid carcinoma, the ^{188}Re-DMSA(V) would be an excellent alternative, once this specific type of tumor doesn't uptake ^{131}I [4].

Technetium and rhenium belong to group 7 of the periodic table of elements, so it's expected that they exhibit similar chemical properties, but their reduction potential are different. That's because technetium belongs to the second transition series, whereas rhenium occupies the bottom position in the group as a third series transition metal. Thus, the reduction potential of pertechnetate turns out to be greater than that of perrhenate. Because of this fact, the preparation conditions of these two radiopharmaceuticals are also different. ^{99m}Tc-DMSA(V) is prepared in alkaline solution, whereas ^{188}Re-DMSA(V) has to be prepared in acidic solution. The commercial kit of DMSA (III) for labeling with ^{99m}Tc, used for kidney scintigraphy, is done in acidic solution, thus it can be used to prepare the ^{188}Re-DMSA (V) [5]. Different formulations are also found in literature [2,3,6].

The aim of this work is to evaluate two labeling procedures for the preparation of ^{188}Re-DMSA(V) by two different methods.

2. MATERIALS AND METHODS

2.1. Preparation of ^{188}Re-DMSA(V)

2.1.1. Method I

Initially ^{188}Re-DMSA(V) was prepared using a commercial kit of DMSA (III) for labeling with ^{99m}Tc (IPEN-CNEN/SP). The kit contained 1.0 mg de DMSA, 0.44 mg de $SnCl_2.2H_2O$, 0.70 mg of ascorbic acid and 50 mg de inositol. The labeling was done with 1 mL of $^{188}ReO_4^-$ (~185MBq) and the reaction time was 30 minutes at high temperature (100 ^oC). The variables studied were: reaction temperature (100 °C and room temperature), reaction time (20 and 30 minutes) and volume of $^{188}ReO_4^-$ (1.0 and 2.0 mL).

2.1.2. Method II

The second method was prepared in a vial containing 2.5 mg of DMSA (dimercaptosuccinic acid), 1.00 mg of $SnCl_2.2H_2O$ and 30mg of sodium oxalate, in a total volume of approximately 1 mL. The pH was adjusted to about 5 with 37% HCl. The labeling was done with 1 mL of $^{188}ReO_4^-$ (~185MBq) and the reaction time was 15 minutes at room temperature. The variables studied were: reducing agent mass (0.2; 0.6; 1.0; 1.5 e 2.0 mg) and mass of DMSA (1.25; 2.5 e 5.0 mg).

2.1.3. Radiochemical quality control

The radiochemical purity was evaluated by thin layer chromatography on silica gel (TLC-SG) to determine the labeling efficiency and impurity formation. TLC-SG strips (1.5 x 12

cm) were developed in two different solvent systems. Acetone was used in order to separate ReO_4^- (R_f 1) from ^{188}Re-DMSA(V) and ReO_2 (R_f 0) and 5% glycine was used in order to separate ReO_2 (R_f 0) from ^{99m}Tc-DMSA(V) and ReO_4^- (R_f 1).

The distribution of radioactivity on the TLC-SG strips was determined using a calibrated Germanium hyperpure detector model GX1518 (HPGe) coupled to a multichannel analyzer system (Canberra Inc., USA).

3. RESULTS AND DISCUSSION

3.1. Preparation of ^{188}Re-DMSA(V)

3.1.1. Method I

Figures 1, 2 and 3 show the results of the effect of the variation of reaction temperature and time and volume on the labeling efficiency of ^{188}Re-DMSA (V) prepared with a commercial kit of ^{99m}Tc-DMSA (III). The best results of labeling yield (> 98%) were achieved when it was used 30 minutes of reaction time with heating at 100 °C and 1 mL of $^{188}ReO_4^-$.

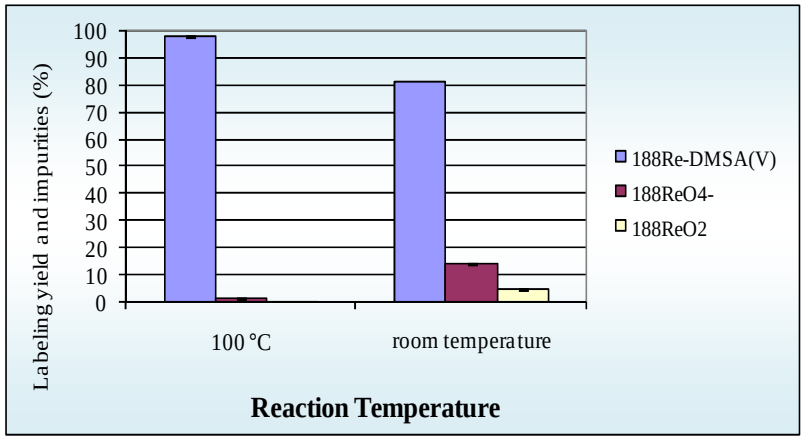

Figure 1. Labeling yield with the variation of reaction temperature.

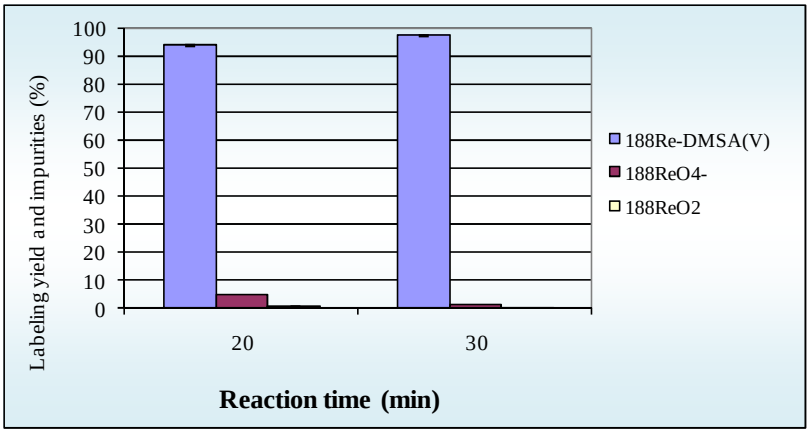

Figure 2. Labeling yield with the variation of reaction time.

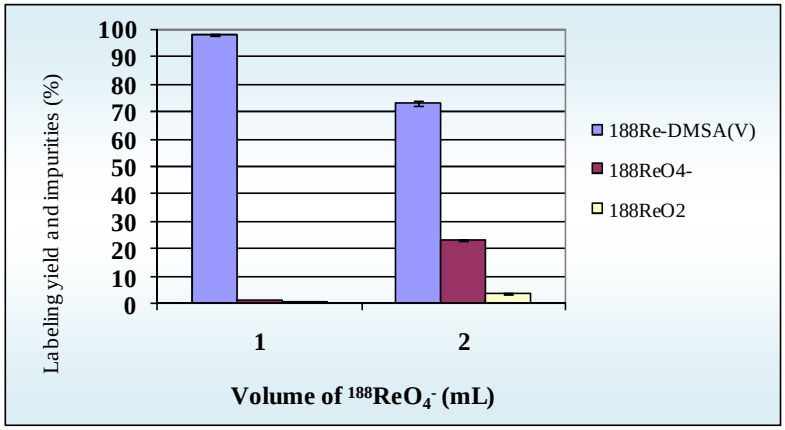

Figure 3. Labeling yield with the variation of volume of $^{188}ReO_4^-$.

3.1.2. Method II

Figures 4 and 5 show the results of the effect of the variation of the reducing agent and DMSA masses, respectively on the labeling efficiency of ^{188}Re-DMSA (V) prepared with method II. The best labeling yield was achieved using 1.0 mg of $SnCl_2.2H_2O$ and 2.5 mg of DMSA but other parameters have to be studied for the optimization of the radiolabeling.

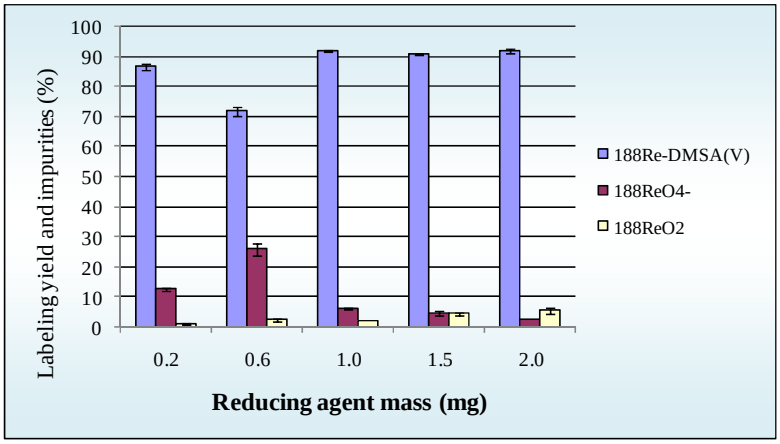

Figure 4. Labeling yield with the variation of reducing agent mass.

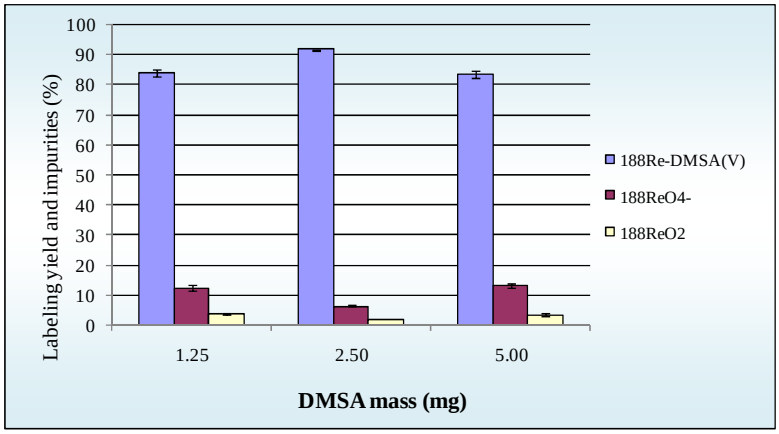

Figure 5. Labeling yield with the variation of DMSA mass.

The advantage of this method is that it does not require high temperatures to achieve good labeling yields due to the use of oxalate. This compound complexes with Re in a more appropriate geometry and kinetics promoting a more efficient reduction of $^{188}ReO_4^-$ when compared with the method I [6].

4. CONCLUSIONS

Preliminary results for both methods of labeling ^{188}Re-DMSA(V) showed that the labeling yield was >90% but method II requires milder conditions. Further experiments are also necessary to optimize the labeling methodology of ^{188}Re-DMSA(V).

ACKNOWLEDGMENTS

This study was supported by CNEN in the program of scholarships for post graduation. Gratefulness to the IPEN-CNEN/SP for participation in 2009 International Nuclear Atlantic Conference - INAC 2009.

REFERENCES

1. SARKAR, S.K.; VENKATESH, M.; RAMAMOORTHY, N.; *Evaluation of two methods for concentrating perrhenate (^{188}Re) eluates obtained from ^{188}W-^{188}Re gerador*. Applied Radiation and Isotopes. Vol. 67, p. 234-239, 2009.
2. SALINAS, L. G.; FLORES, G. F.; MURPHY, C. A.; LÓPEZ, M. P.; GUTIÉRREZ, S. H.; NIETO, J. A. *Uptake of the 188Re(V)-DMSA complex by cervical carcinoma cells in nude mice: pharmacokinetics and dosimetry.* Applied Radiation and Isotopes, nº 54, pp. 413-418, 2001.
3. PIRMETTIS, I.; LIMOURIS, G.S.; BOUZIOTIS, P. ; PAPADOPOULOS, M. ; KNAPP JR., F.F.; CHIOTELLIS, E.; *Pentavalent rhenium-188 dimercaptosuccinic acid: a new kit formulation and its inicial evaluation in mice*. Radiochim. Acta 89, 115-118, 2001.
4. SAHA, G. B. *Fundamentals of Nuclear Pharmacy*. 4ed. Springer Verlag, 1998.
5. SINGH, J.; REGHEBI, K.; LAZARUS, C.R.; CLARKE, S.E.M.; CALLAHAN, A.P.; KNAPP JR, F.F.; BLOWER, P.J. *Studies on the preparation an isomeric composition of ^{186}Re and ^{188}Re- pentavalent rhenium dimercaptosuccinic acid complex.* Nuclear Medicine Communications, 14, 197-203, 1993.
6. BOLZATI, C.; BOSCHI, A.; UCCELLI, L.; DUATTI, A.; FRANCESCHINI, R.; PIFFANELLI, A. *An Alternative Approach to the Preparation of ^{188}Re Radiopharmaceuticals from Generator-Proced [^{188}ReO$_4$]$^-$: Efficient Synthesis of ^{188}Re(V)-meso-2,3-Dimercaptosuccinic Acid*. Nuclear Medicine and Biology, vol. 27, pp. 309-314, 2000.