2011 International Nuclear Atlantic Conference - INAC 2011
Belo Horizonte,MG, Brazil, October 24-28, 2011
ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR - ABEN
***ISBN:* 978-85-99141-04-5**

Labeling of MDP with ^{188}Re for bone tumour therapy

Angélica B. Barbezan[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
angelbarbezan@uol.com.br
jaosso@ipen.br

ABSTRACT

^{188}Re is one of the most attractive radioisotopes for a variety of therapeutic applications in nuclear medicine, due to its physical decay properties, such as β^-emission of 2.12 MeV, γ emission of 155 keV and half life of 16.9 hours. Biphosphonates are potent inhibitors of osteoclastic bone resorption and are effective in several diseases that cause bone fragility and bone metastases. Because of these characteristics, labeled biphosphonates have been studied for bone pathologies, also acting as palliation of bone pain in case of metastasis.The aim of this study was to optimize the labeling of a phosphonate-MDP (Sodium Methylene Diphosphonate) with ^{188}Re for use in bone pain palliation.^{188}Re was obtained by eluting a ^{188}W-^{188}Re generator from POLATOM. The labeling was perfomed at room temperature using MDP, $SnCl_2$ as reducing agent and ascorbic acid. The variables studied were: Mass of ligant (3, 6 and 10 mg), reducing agent mass (5, 7, 10 and 11 mg), ascorbic acid mass (1, 3, 5 and 6 mg), pH (1 and 2) and time of reaction (15, 60, 120, 360 and 4320 minutes), that also reflected the stability of the radiopharmaceutical. The radiochemical control, that also measures the labeling efficiency was evaluated by paper chromatography using Whatman 3MM paper and the solvents acetone and 0.9%NaCl. The best formulation was the following: Mass of ligand MDP: 10 mg, mass of $SnCl_2$: 5 mg, ascorbic acid mass: 3 mg, time of reaction: 30 minutes, pH: 1. Under optimum conditions, ^{188}Re MDP radiolabeling yield was 98,07% and the radiopharmaceutical was stable up to 72 h.

1. INTRODUCTION

The wide application of radiopharmaceuticals is mainly in nuclear medicine diagnosis, representing around 95% of the procedures in nuclear medicine. In recent years, however, the application of radiopharmaceutical in therapeutical procedures has grown considerably [1]. The physical properties of ^{188}Re are favorable and appropriate, including the fact that it is free of carrier and can be obtained in an economic way as a generator tungstênio-188/rênio-188 (^{188}W/^{188}Re), alumina based, where his father ^{188}W has a long half-life of 69 days, ensuring a daily clinical availability. Thus, the ^{188}Re is obtained as sodium perrhenate (Na [$^{188}ReO_4$]) by eluting the generator with 0.9% saline solution.

^{188}Re emits a γ-ray of 155 keV with an intensity of 15% which can be detected and it is suitable for dosimetric and imaging purposes. It has a physical half-life of 16.9 hours and decays 100% by emission of high energy β^- irradiation (E_β average = 764 keV), so it is considered an attractive candidate for use in therapeutic applications [2].

Radionuclides that emit ionizing particles (particles α, β-and Auger electrons) are indicated for the treatment of tumors [3].

Bisphosphonates (BFs) are synthetic analogs of pyrophosphate, are potent endogenous inhibitors of osteoclastic bone resorption and are effective in treating osteoporosis, Paget's disease, bone metastases (with or without hypercalcemia), multiple myeloma and other diseases that cause bone fragility.

The BFs have been the main agents for bone scanning in nuclear medicine [4].

There are several studies of labeling *BFS* with ^{188}Re for therapy: LIN et al. (1997) presented the biodistribution results of ^{188}Re-HEDP: High selective uptake in the skeleton and bone lesions, low uptake for non-target tissue and rapid clearance [5]. QINGNUAN et al. (2000) used the analogue (1-amino-acid-ethylene-diphosphonic) for the synthesis of ^{188}Re-AEDP free and with the addition of carrier (0.1 mgRe / mL). The ^{188}Re-AEDP was labeled by the direct method, with $SnCl_2$ and the pH adjust between 0.5 to 1.4. The radiolabeling yield was 92% (free of carrier) and 96% (carrier added) [6].

MURPHY et al. (2001a) developed a new *BF*, labeling alendronate (ABP: 4-amino-1-hydroxy-1 ,1-bisphosphonate-butilidene) with $^{188}ReSnF_2$ was used as reducing agent because it has a greater reduction potential. The yield of the direct method of labeling was 95%, and biodistribution of ^{188}Re-ABP revealed a possible new therapeutic agent [7].

PERVEZ et al. (2003) prepared the radiopharmaceutical ^{188}Re-EDTMP based on the complexes formed with ^{153}Sm and ^{166}Ho for the treatment of bone metastases. With the optimization of the conditions of labeling, the yield achieved was approximately 98% [8].

LIEPE et al (2009) studied the autoradiography of ^{188}Re-HEDP in normal skeletal development and bone metastasis osteoblastic in a mouse model of metastatic prostate cancer, in order to quantify the radiation dose absorbed in therapy radionuclides [9]

The objective of this study was to optimize the labeling of sodium methylene diphosphonate (MDP) with ^{188}Re, for use in pain paliation.

2. MATERIALS AND METHODS

2.1. ^{188}Re

The ^{188}Re was obtained through the elution of a ^{188}W-^{188}Re generator from POLATOM.

2.2. Labeling of ^{188}Re MDP

The labeling of MDP with ^{188}Re was performed at room temperature using $SnCl_2$ as reducing agent and ascorbic acid, and the variables studied are described in Table 1:

Table 1 – variables used in the labeling of ^{188}Re-MDP

VARIABLE	
MDP mass	3, 6 and 10 mg
$SnCl_2$ mass	5, 7, 10 and 11 mg
Ascorbic mass	1, 3, 5 and 6 mg
Reaction time	15, 60, 120, and 360 min
pH	1 and 2

The radiochemical quality control, that also measures the labeling yield was evaluated by Paper Chromatography using Whatman 3MM paper and the solvents described in Table 2.

Table 2 – Solvents used in the radiochemical control of ^{188}Re-MDP

Radionuclide Specie	Acetone	0.9%NaCl
	Rf	Rf
^{188}Re - MDP	0	1
$^{188}ReO_4^-$	1	1
$^{188}ReO_2$	0	0

The amount of free ^{188}Re was evaluated using acetone as solvent whereas the colloid form of ^{188}Re using 0.9%NaCl as solvent.
The stability at room of ^{188}Re-MDP was studied up to 72 h aflter the labeling procedure.

3. RESULTS

Figure 1, 2, 3, 4 and 5 show the results of the variation of the mass of MDP, mass of $SnCl_2$, mass of ascorbic acid, reaction time and pH in the labeling yield of ^{188}Re-MDP, respectively.

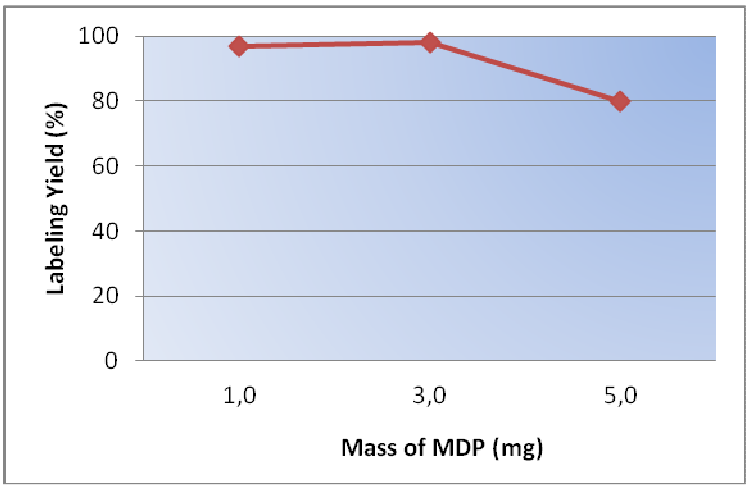

Figure 1 – Variation of the mass of MDP

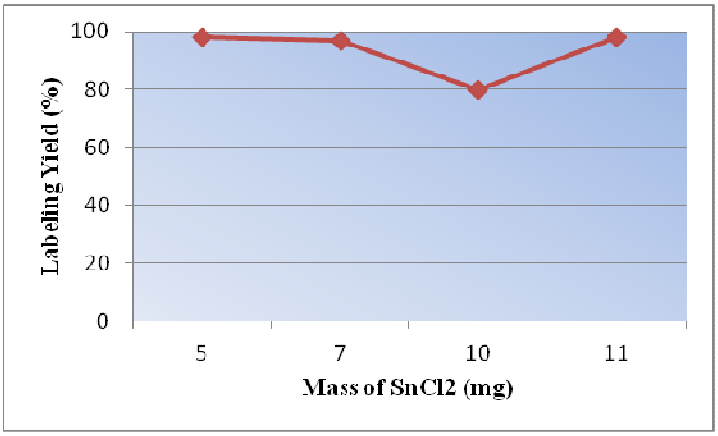

Figure 2 – Variation of the mass of $SnCl_2$

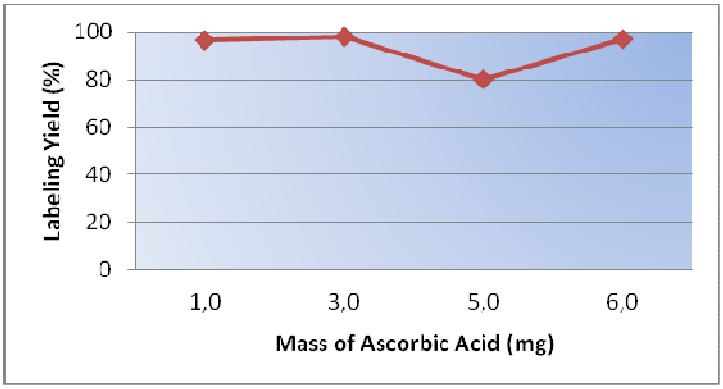

Figure 3 – Variation of the mass of Ascorbic acid

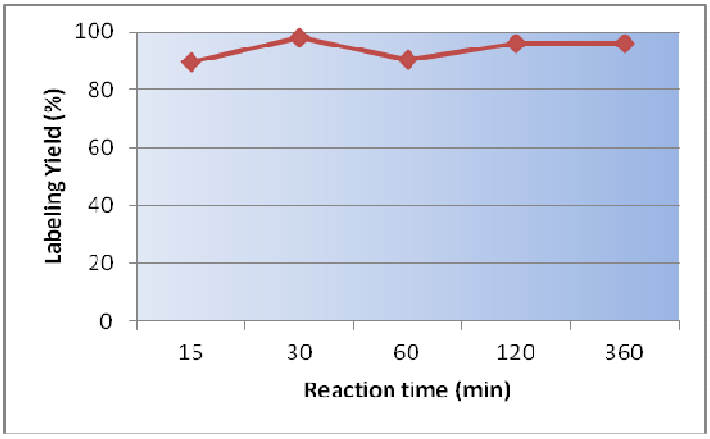

Figure 4 – Variation of reaction time

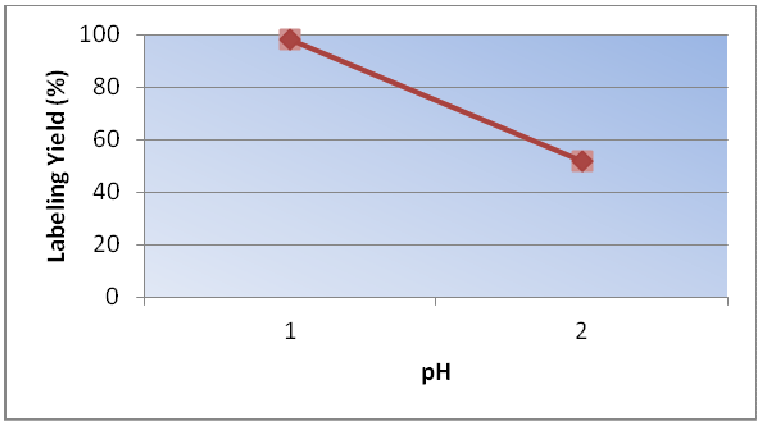

Figure 5 – Variation of pH

According to the results showed in the figures, the best formulation was chosen and can be seen in Table 3

Table 3 – Best formulation for labeling of ^{188}Re MDP

Variable	
MDP mass	10 mg
$SnCl_2$ mass	5 mg
Ascorbic acid mass	3 mg
Reaction time	30 mg
pH	1

With this formulation labeling yields of 98% were achieved. The stability studies were performed with this formulation and the results are show in figure 6

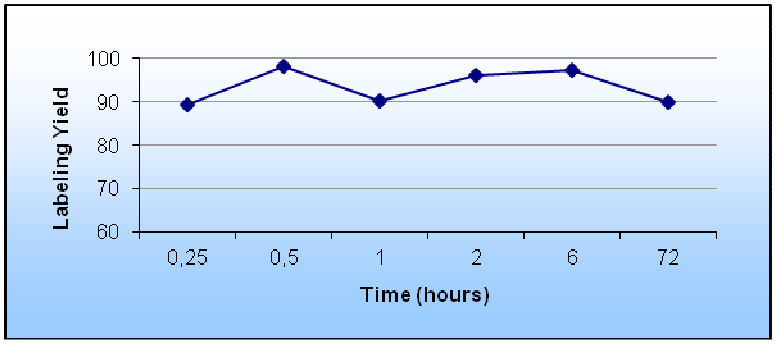

Figure 6 – Stability of ^{188}Re-MDP

The product was stable up to 72 hours after the reaction.

4. CONCLUSIONS

A formulation was achieved that allowed the labeling of MDP with ^{188}Re with a yield of 98%. Next studies will be related to the *in vivo* behavior of this radiopharmaceutical.

ACKNOWLEDGMENTS

The author wish to thank the IAEA for the support and also CAPES for the fellowship for developing this work.

REFERENCES

1 – ARAÚJO, E. *et al.***,** *Garantia da qualidade aplicada à produção de radiofármacos.* Revista Brasileira de Ciências Farmacêuticas vol. 44, n. 1, jan./mar. (2008)

2 – DIAS, C. R. B. R. *Estudo comparativo de diversas rotas de marcação do anticorpo anti-cd20 com 188 Re* (2008) Relatório – Instituto de Pesquisas Energéticas e Nucleares, São Paulo.

3 – OLIVEIRA, R. *et al*., *Preparações radiofarmacêuticas e suas aplicações*. Revista Brasileira de Ciências Farmacêuticas vol. 42, n. 2, abr./jun (2006).

4 – SOUSA, F. R. N. *Osteonecrose associada com o uso dos bifosfonatos*. Pesq Bras Odontoped Clin Integr, João Pessoa – 3 (2008) 375-380.

5 - LIN, W.-Y. *Rhenium-188 hydroxyethylidene diphosphonate: a new generator-produced radiotherapeutic drug of potential value for the treatment of bone metastases*. Eur. J. Nucl. Med., v. 24, n. 6, p. 590-595 (1997)
6 - QINGNUAN, L.; XIAODONG, Z.; RONG, S.; WENXIN, L. *Preparation of ^{188}Re-AEDP and its biodistribution studies.* Appl. Radiat. Isot., v. 53, p. 993-997 (2000).
7 - MURPHY, C. A.; FLORES, G. F.; LÓPEZ, M. P.; ALAFORT, L. M.; CROFT, B. Y.; RAMÍREZ, F.M.; PADILLA, J. *Labelling of Re-ABP with ^{188}Re for bone pain palliation.* Appl. Rad. Isot.**,** v. 54: p. 435-442 (2001)
8 - PERVEZ, S.; MUSHTAQ, A.; ARIF, M.; CHOHAN, H. *^{188}Rhenium-EDTMP: a potential therapeutic bone agent.* **J.** Radioanal. Nucl. Chem., v. 257, n. 2, p. 417-420 (2003)
9 - LIEPE, K. *Autoradiographic studies of rhenium-188-hydroxyethylidine diphosphonate in normal skeleton and osteoblastic bone metastases in a rat model metastatic prostate cancer*. Nuclear Medicine Communications – 30 (2009) 693-699.