J. of Nuclear Sci. and Tech.
No. 47, pp. 53-56, 2009

مجله علوم و فنون هسته‌ای
شماره ۴۷، صفحات ۵۶-۵۳، ۱۳۸۸

Production of Strontium-89 Radioisotope by Neutron Activation Method and Preparation of ^{89}Strontium Chloride Radiopharmaceutical

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Abstract: Strontium-89 is one of the most important radioisotopes used in nuclear medicine for therapy of bone pain caused by bone metastases. That is due to the beta radiation with sufficient energy for destroying metastatic sites in bone tissue. The routine application is ensured by introducing $^{89}SrCl_2$ radiopharmaceutical and then injection of a specific dose in human vein, where it leads to reduction of bone pains. In this research, ^{89}Sr was produced in the Tehran Research Reactor (TRR) for both natural Sr (includes ^{84}Sr and ^{88}Sr) and enriched Sr (includes ^{88}Sr of %99 purity) for the comparison and preparation of $^{89}SrCl_2$ radiopharmaceutical. Natural radioactivated Sr which produces gamma radiation was injected in mice and then based on gamma spectroscopy in different tissues, a calculation was made for the dose absorption rate, defined by %ID/g. Also, radioactivated enriched Sr-88 was injected in mice and the %ID/g was calculated due to distribution of the beta radiation in mice tissues. In our biodistribution we observed a rapid blood clearance followed by the high absorption of activity in bone tissues. These data have shown that the prepared compound is a well defined radiopharmaceutical for the bone pain palliation in metastatic lesions.

Keywords: ***Strontium-89, Strontium Chlorides, Neutron Activation Analysis, Therapy of Bone Metastases, Gamma Radiation, Beta Radiation***

1- Introduction

Bone metastases are common cause of morbidity in cancer patients [1]. The pain that occurs in many patients with advanced malignancies is primarily produced by bone metastases. Many malignancies in bone metastases including breast cancer (median survival time is 20 to 30 months), lung cancer (median survival of less than 6 months), and prostate cancer (the second leading cause of cancer deaths in men in the United States) account for more than 80% of bone metastases [2]. Different methods are for relief of bone pain associated with metastatic lesions in the skeleton. For example: Bisphosphonates have been shown to promote healing and lessen pain in patients with osteolytic metastases [3, 4]. Radiation therapy is an effective palliative treatment for incurable cancer. Radiation can be used to palliate pain, bleeding, or obstruction. Pain resulting from bone metastases can be controlled with external localized or wide field radiotherapy [5]. Bone-targeting radiopharmaceuticals, such as the ß-emitters ^{32}P, orthophosphate (NaH_2PO_4) and ^{89}Sr (as strontium chloride, Metastron; Amersham Health) have been used extensively for relief of bone pain associated with metastatic lesions in the skeleton [6, 7]. ^{89}Sr emits pure beta radiation, demonstrates maximum beta energy of 1.46 MeV [8], and penetrates 8mm into susceptible tissue. Because strontium and calcium are both in the family 2 of the periodic table, ^{89}Sr, injected as the chloride, substitutes for calcium in the hydroxyapatite molecule [9]. ^{89}Sr becomes incorporated into the bone metastases by competing with the bound calcium component and damages bone metastasis locations. It is

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Date of Receipt: 1387/3/21 Date of Admission: 1387/10/9

administered in three minutes and remains in the metastatic bone lesions for approximately 100 days. The response time to ^{89}Sr has been reported as early as 3 days, but is most commonly noted in the second or third week after administration. In analyzing data on ^{89}Sr efficacy, one should, therefore, exclude patients who were treated but did not survive for 1 month. The published data on strontium response show a range of 65% to 90%, with complete relief of pain in 5 to 20% of patients injected [10-15]. This product provides a half-life of 50.6 days in bone lesions versus the 14 day half-life in normal bone.

The isotope of ^{89}Sr is obtained by either of the following two methods:

- Thermal neutron bombardment of $^{88}SrCO_3$ (n,γ).
- Separation from the fission products of irradiated ^{235}U (^{235}U(n.f)).

The aim of this work is production of ^{89}Sr, preparation of ^{89}Strontium Chloride radiopharmaceutical and biodistribution studies in mice after injection of this compound.

2- Experimental

1-2 Materials and Instrument

Enriched ^{88}Sr(%99) was purchased from the U.S.A. Trace Company and other chemicals of the analytical grade were obtained from E. Merck and Aldrich.

A liquid scintillation spectrometer of the model of 1220 Quantilus from PerkinElmer was used for beta spectroscopy. The system was particularly useful for samples containing mixed alpha/beta gamma radiation.

Germanium coaxial P type spectrometer of the type: EGPC 80-200-R from Selena was used for gamma spectroscopy. The system consists of a high-purity germanium detector with an efficiency of 80%, relative to a 3*3 NaI (Tl) scintillator.

3- Method

3-1 Irradiation

Radioisotopes with high specific activity and different applications can be produced by the (n, gamma) method. This process entails placing target in a nuclear reactor, where they are bombarded by thermal neutrons. Our work started with (n, gamma) production of $^{88}SrCO_3$ (n,γ) where, we produced ^{89}Sr of both natural Sr (includes ^{84}Sr and ^{88}Sr) and enriched Sr (includes ^{88}Sr of %99) to be used for the comparison. The actived ^{84}Sr becomes ^{85}Sr and is used as a trace element for ^{89}Sr metabolism in dosimetry studies [16, 17].

Both natural and enriched Sr with amounts of about 10mg at one time were enclosed in capsules of quartz. Then, the capsules were transfered into the reactor core of the Tehran Research Reactor. The samples were located in the zone with the flux of 5.0×10^{13} $ncm^{-2}s^{-1}$ for a period of 25 days. After the completion of this step, we transferred the samples to the hot cell and the other processes were applied for forming $^{89}SrCl_2$. These processes are summarized as follows:

3-2 Chemical processing

After opening the quartz capsule, the produced ^{89}Sr was dissolved in 0.24 ml of 1 M of HCl. It was evaporated to dryness and dissolved in water (bulk solution). After controlling the isotonicity of the solution, it was adjusted by addition of NaCl. The solution was filtered by 0.22μm filter and dispensed into glass vials, sealed and autoclaved [18].

3-3 Dispensing, Assay and Quality Control of $^{89}SrCl_2$ Solution

In this process the parameters of the obtained solution are controlled: pH, assay of strontium and sodium chlorides, specific activity, radioactive concentration and radionuclide purity and chemical purity [19].

3-4 Radionuclide Purity

For radionuclide purity we used gamma and beta spectroscopy and also the measurement of the strontium-90 impurity was based on separation of ytrrium-90 (in equilibrium with Sr-90) from the tested sample by solid phase extraction chromatography with stationary phase (Sr-resin) and mobile phase (acid nitric). The pH should be in the range of 4-7. The activity of the strontium-89 in a known volume of the solution was measured by the Liquid Scintillation Method.

3-5 Chemical impurity

Chemical impurities in the ^{89}SrCl2 solution were determined by the inductively coupled plasma optical emission spectrometry (ICP-OES). For applying the technique, the liquid sample was transformed into aerosol in the nebulizer. For the quantitative measurement, calibration of the spectrometer was made using standard solutions of the analytes. According to the European Pharmacopoeia, the limits for chemical impurities in the ^{89}SrCl2 solution have been introduced as follows:

Al < 2 ppm
Fe <5 ppm
Pb < 5 ppm

3-6 Injection Process

In this process 14 different mice in a weight range of 19-25 grams were selected. 0.1cc (0.04 MBq (1.1μCi)) of $SrCl_2$ was prepared by radioactived natural Sr (the reason for the use of natural Sr was mentioned earlier) and the enriched Sr-88. The samples were diluted with 0.1cc water to each mice via tail vein. The animals were slaughter and dissected at various time intervals (4hours and 4, 10, 16, 22, 30 days) after the injection. The absorbed dose was counted in different organs using a gamma counter instrument. Also, the absorbed dose was counted using beta counter instrument, but in 1 and 15 days after the injection and in different organs of the species. The results of the measurement are given in tables 1 and 2 and also in figures 1 and 2.

4-Results

In the process of ^{89}Sr production in the reactor, because of the low thermal neutron flux of 5.0×10^{13} $ncm^{-2}s^{-1}$, the specific activity is about 0.7 MBq per milligram. After the preparation of $^{89}SrCl_2$, it was injected to mice and rat, and after sacrificing and dissecting the animals, the beta and gamma radiation in different tissues were counted. In bone, thyroid and some other tissues as it is indicated in table 1, the %ID/g is almost between 20-30 but, in theses mice, bone has %15 of the body weight and as a result the total %ID is the highest. As shown in table 2, after 24hours, our observations have shown that, the %ID/g in thigh and skull bone have the highest value and in small intestine, large intestine and wishing bone have a low value. After 15 days of injection the %ID/g in thigh and skull bone increased and in the other tissues it decreased. Figures 1 and 2 display diagrams from the gamma and beta spectroscopy in mice corresponding to different organs. Figure 1 and 2 appeared to have significant differences, because after the activation of natural Sr, the Sr-85 that was measured has a low percentage with respect to Sr-89 and thus a low gamma ray was observed. But, in the enriched Sr, Sr-89 that was measured has a high percentage and thus a high beta counting was observed. Figures 4-6 display the beta and gamma spectra of $^{89}SrCl_2$.

5- Conclusion

The specific activity coefficient for human injection should be at least 1.5 MBq (4μCi) per milligram and because of the low neutron flux in TRR; the specific activity is about 0.7 MBq per milligram. But, in this experiment, $SrCl_2$ was prepared with activation of natural and enriched Sr-88. The radioactivated natural Sr has $^{85}SrCl_2$ impurity with the gamma radiation of 0.5 MeV to be used for gamma spectroscopy. In radioactivated enriched Sr-88, the compound has Sr-89 with beta radiation of 1.48 MeV that is suitable for beta spectroscopy. The %ID/g shown in tables 1 and 2 and also in figures 1 and 2 are corresponding to different times and presenting good results as it is compared to other researchers' reports. We found that bone has %15 of the body weight, then a good absorption exists in this tissue. This research is an experimental design of the presentation in biodistribution studies about the introduced compound in mice and then optimizing the production for the human tissue. By using a reactor with neutron flux twice as high as that of the TRR neutron flux, a suitable activity for ^{89}Sr can be obtained to be suitably used in nuclear medicine.

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