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Synthesis and Stability Studies of ^{225}Actinium Tin Colloid Radiopharmaceutical

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Abstract

Synthesis of novel ^{225}Ac-Sn particles was described for the first time. Detailed experimental and stability studies were successfully exhibited. Treatment of excess amount of $SnCl_2$ with 0.2 mCi ^{225}Ac furnished highly stable ^{225}Ac tin colloid with 90% of radiochemical yield (RCY) at optimized reaction condition. R-TLC analyses indicated 95% of radiochemical purity (RCP). Stability studies showed that colloidal structure also retained free daughter radionuclides formed by the ^{225}Ac decay chain. ^{225}Ac tin colloids could be ideal nanocarriers for localized cell killing due to high linear energy transfer and prevention of free radioisotope daughters.

Keywords

^{225}Actinium Tin Colloid, Radiosynovectomy, Stability, Targeted Alpha-Particle Therapy

1. Introduction

Radiosynovectomy (RSV) is a kind of local radiotherapy for joint synovitis and synovial processes [1] [2] [3]. Considerable attention has been afforded to RSV application due to the cost effective, lack of surgial risk, low radiation dose, 70% - 80% of response rate and local treatment option without side effects [4] [5]. The main concept of RSV is that colloidal particles supported radionuclides easily undergo in the inflamed synovial membrane by intra-articular process. Recently beta particle emitters such as ^{90}Y [6], ^{188}Re [7] and ^{169}Er [8] have been frequently utilized for the treatment of different types of arthritis approved by European authorities [9]. The administration of those radiactive colloids depends on the size of the joints and amount of inflamation. For example, ^{90}Y colloid is mainly administered to larger size joint such as knee with approximately 5 - 6 mCi, whereas ^{186}Re colloid is suitable for hip, shoulder, elbow, wrist, ankle and

subtalar joints with 1 - 5 mCi and ^{169}Er colloid is injected for small joints of fingers and toes with small amount of activity (0.3 - 1.0 mCi). ^{177}Lu tin colloid has also attracted interest for use in RSV due to the ideal decay characteristics and palliative treatment ($T1/2 = 6.73$ days, $E\beta_{max} = 497$ keV; $E\gamma = 113, 208$ keV) [10].

Targeted alpha-particle therapy (TAT) is of great importance for cancer treatment [11] [12] [13] [14]. Alpha particles are more effective than beta particles for elimination of solid tumors due to the sufficient shorter range, greater linear energy transfer and higher cytotoxicity. Those potentials provided more advantageous about destroying of tumor cells with specific target with minimum toxicity. 15 Numerous alpha emitter radionuclides such as ^{223}Ra [16] [17], ^{211}At [18], ^{212}Pb [19], ^{213}Bi [20] and ^{225}Ac [21] have been administered to patients for various cancer treatments with desirable positive response. Nowadays, ^{225}Ac radionuclide has become more popular among them for alpha radiotherapy which emits four alpha particles with sufficient energies (from 5.8 to 8.4 MeV) with a long-lived high life of 9.9 days (**Figure 1**) [22] [23]. Even ^{225}Ac based radiopharmaceuticals have been frequently employed *in* various *vitro* and *vivo* studies, its chemistry about RSV has not been worked yet.

In this study, detailed chemistry studies of ^{225}Ac tin colloid have been discussed for the first time. Radiochemical yield and labeling efficiency were also examined. The vitro stability of ^{225}Ac-Sn particles has been monitored in synovial fluid up to 5 days after preparation.

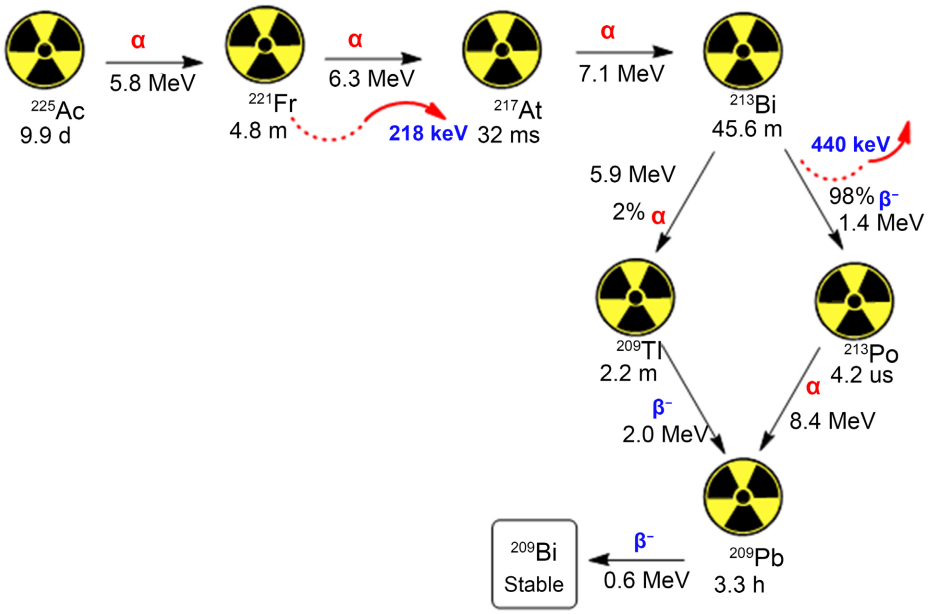


Figure 1. Decay chain scheme of ^{225}Ac.

2. Materials and Methods

2.1. Materials

^{225}Ac (0.2 mCi) was obtained from Polatom, tin(II) chloride dihydrate (purity 98%) and *L*-ascorbic acid (purity 99.7%) were purchased from Sigma-Aldrich.

di-Sodium hydrogen phosphate dihydrate (purity 99.5%) and sodium dihydrogen phosphate dihydrate (purity 99.0%) were supplied from Isolab for preparation of 0.5 M sodium phosphate buffer (PBS) solution. Synovial fluid was obtained from Semical Biosurgery. Other chemicals and materials were obtained from Merck and Waters.

2.2. Synthesis of ^{225}Ac-Tin Colloid

50.0 mg of $SnCl_2$ and 10.0 mg of *L*-ascorbic acid were dissolved in 1.0 ml of 0.1 M HCI(aq) solution respectively. These solutions were transferred to reaction vial and 200 μCi of ^{225}Ac was added to this solution. The reaction was continued at 98˚C for 100 minutes and reaction vial was removed from the heater and allowed to be cooled for 20 minutes. Then, colloidal structure was successfully obtained by adding 2 mL of PBS solution (pH: 7.8) followed by centrifugation at 3500 rpm for 10 minutes for the precipitation of particles. The supernatant was carefully decanted and residue was washed by ultrapure water with three times. Finally, the colloids were diluted with 1.0 ml of saline for both quality control and stability studies (Table 1).

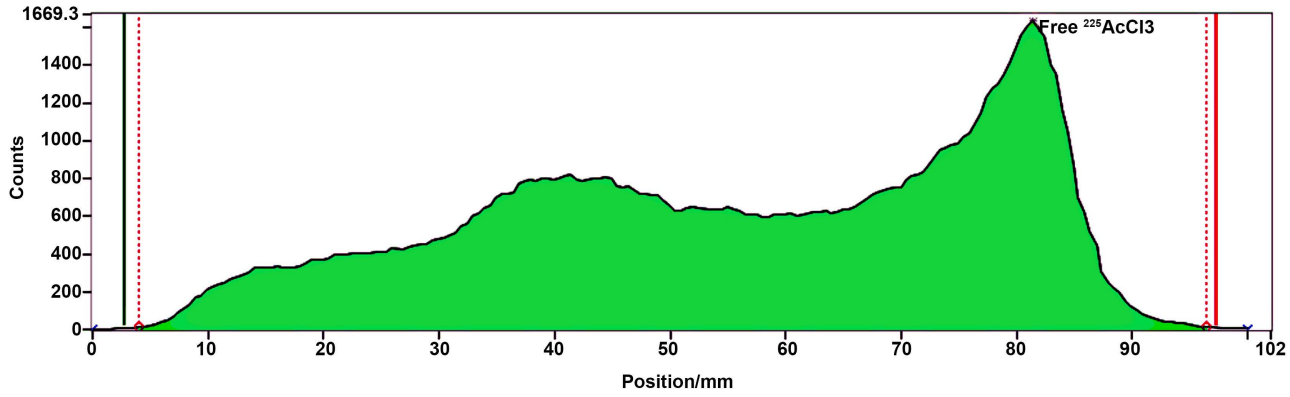
Table 1. Amount of activity studies on ^{225}Ac-tin colloid.

Entry	$SnCl_2$ (mg)	Ascorbic Acid (mg)	Activity of free ^{225}Ac (μCi) (before reaction)	Activity of ^{225}Ac tin Colloid (μCi)	Activity of supernatant (free ^{225}Ac, μCi)	Radiochemical Yield (RCY) (%)
1	5	2	200	97	85	49
2	10	4	200	116	71	58
3	30	6	200	175	22	87.5
4	**50**	**10**	**200**	**180**	**17**	**90**

2.3. Characterization Methods

TLC analyses were performed by Whatman 3 mm, ITLC-SG Agilent TLC plates and Eckert & Ziegler TLC Scan device. The amount of radioactivity of residue and supernatant were measured using a dose calibrator, Capintec Inc., New Jersey, USA.

2.3.1. Quality Control of ^{225}Ac Tin Colloid (Figure 2)



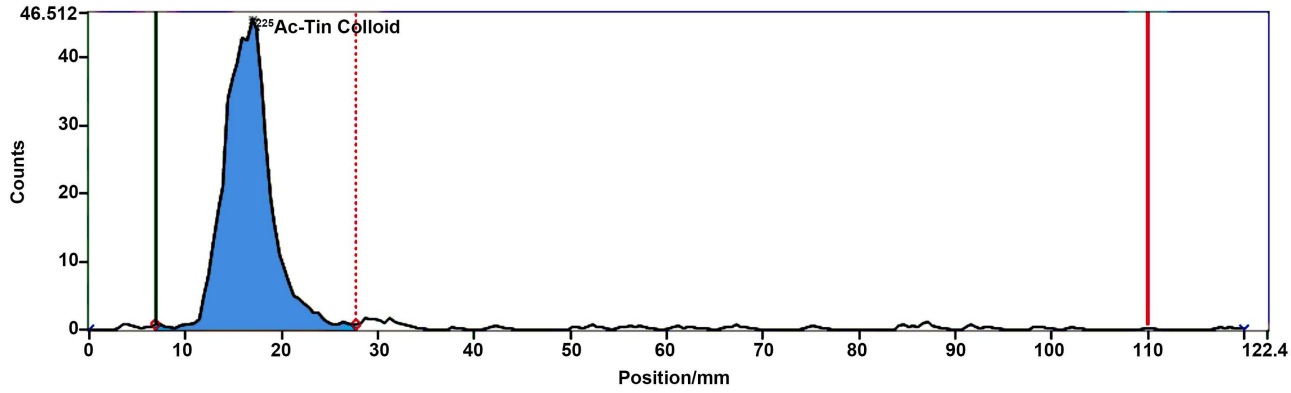


Figure 2. Radio-TLC chromatograms of (a) Free ^{225}Ac (b) ^{225}Ac tin colloid, TLC plate: Whatman 3 mm, mobile phase: 0.9% isotonic saline.

2.3.2. Stability Experiments of ^{225}Ac Tin Colloid

^{225}Ac tin colloid was dissolved in the mixture of 1 ml of synovial fluid and 1 ml of PBS and it was incubated at 37˚C at 5 days (Table 2).

Table 2. Stability studies on ^{225}Ac tin colloid (Entry 4, Table 1) (T_0 = end of the synthesis).

Time	Total Activity (μCi)	Activity of ^{225}Ac tin Colloid (μCi)	Activity of supernatant (free ^{225}Ac, μCi)
T_0	200	180	17
1 d	162	154	8
2 d	146	136	10
5 d	114	105	8

3. Results and Discussion

Recently, nanoparticle supported radionuclides have attracted interest as promising alternatives due to the increasing the therapeutic efficacy and reducing undesired side effects with strong multivalent interactions [24] [25] [26]. More recently, Cędrowska *et al.* [27] has described a highly stable functionalized TiO_2-decorated ^{225}Ac nanoparticles for TAT application. Woodward *et al.* [28] and Kruijff *et al.* [29] also emphasized that nanoparticles could retain free daughter radionuclides emerged during the ^{225}Ac decay chain in addition to the more efficiency for radiotherapy. McLaughlin *et al.* [30] showed that multilayered nanoparticles (NPs) $\{La_{0.5}Gd_{0.5}\}PO_4$@$GdPO_4$@Au supported ^{225}Ac provided to retain 99% of the ^{225}Ac within three weeks. In the light of those previously published articles, we have focused on the chemistry of ^{225}Ac-Sn particles with experimental studies.

Optimization of reaction medium and stability studies are of critical cases for exact synthesis of ^{225}Ac tin colloid. In our experimental studies, temperature was kept constant since the reaction of ^{225}Actinium with various precursors was well performed between 90˚C - 100˚C [15] [21] [31]. Recently, Arora *et al.* [32] has successfully demonstrated that optimum labeling efficiency of ^{177}Lu tin colloid

was obtained within 120 - 150 minutes. Therefore, the reaction of ^{225}Ac tin colloid was carried out in two hours without any different reaction time formulations. The effect of the amount of $SnCl_2$ and ascorbic acid are important for optimization protocol. 0.2 mCi $^{225}AcCl_3$ was treated with different amount of tin(II) chloride. Table 1 indicated that amount of thin(II) chloride dramatically affected RCY of ^{225}Ac tin colloid. 0.2 mCi ^{225}Actinium and 50.0 mg of thin(II) chloride afforded high RCY of colloidal structure (Entry 4, Table 1). We assume that 0.18 mCi could be quite high amount of activity for the possible applications of further preclinical/clinical trials. However, we wanted to work with high amount activity to check the stability and product yield. Table 2 also summarized the stability studies of ^{225}Ac tin colloid. Colloid structure was dissolved in synovial fluid and PBS mixture and was exposed to incubation process at 37˚C within 5 days. In the light of the experiments, it was observed that there was no significant loss of activity after five days. Even ^{225}Actinium has more daughter radionuclides 13 as illustrated in Figure 1, stability experiments exhibited that there was no significant deviation from colloidal structure.

4. Conclusion

Synthesis procedure, stability studies of ^{225}Ac tin colloid have been well described for the first time. The colloidal structure was obtained with high RCY with more than 95% RCP. Stability studies at 37˚C in synovial fluid were also discussed in details to demonstrate the formation of highly stable ^{225}Ac tin colloids without any free daughter radionuclides. These promising results could lead to the preclinical/clinical trials in the future for RSV applications and four alpha particles formed by each of ^{225}Ac decay, could lead to very effective towards treatment of arthritis.

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Conflicts of Interest

The authors declare no conflicts of interest

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