Hyperfine Interact (2018) 239:32
https://doi.org/10.1007/s10751-018-1505-3

^{119}Sn Mössbauer study of Sn-containing radiopharmaceutical kits

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Abstract Sn-containing radiopharmaceutical kits, MULTIBONE (composed from stannous chloride dihydrate and EDTMP (ethylene-diamine-tetramethylene phosphonate) and PHYTON (composed from stannous chloride dihydrate and PHYTATE (myo-inositol-hexaphosphate ester) kits, to be used for monitoring in liver tumor therapy, were characterized by ^{119}Sn Mössbauer spectroscopy and XRD measurements. XRD revealed the amorphous nature of the Sn-containing compounds. 80 K ^{119}Sn Mössbauer spectra of both compounds indicated the dominant presence of tin(II) state with characteristic Mössbauer parameters of $\delta = 3.12 \pm 0.01$ mms^{-1} and $\Delta = 1.84 \pm 0.02$ mms^{-1} as well as $\delta = 3.01 \pm 0.01 \pm 0.01$ mms^{-1} and $\Delta = 1.73 \pm 0.02$ mms^{-1} for Sn-PHYTATE and Sn-EDTMP, respectively. The occurrence of tin(IV) in Sn-MULTIBONE was as low as measured in the precursor stannous chloride dihydrate (∼3%).

Keywords ^{119}Sn Mössbauer spectroscopy · Pharmaceutical kits · Sn-Phytate · Sn-Multibone · Occurrence of tin(II) · Stability

1 Introduction

Tin(II) is a crucial ingredient of radiopharmaceutical kits to be labelled with ^{99m}Tc radionuclide 'on the spot' i.e. in the hospital labs just before patient's administration.

This article is part of the Topical Collection on *Proceedings of the 4th Mediterranean Conference on the Applications of the Mössbauer Effect (MECAME 2018), Zadar, Croatia, 27–31 May 2018*
Edited by Mira Ristic and Stjepko Krehula

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Published online: 23 July 2018

MULTIBONE kit, composed from stannous chloride dihydrate and EDTMP (ethylene-diamine-tetramethylene phosphonate), is designed as a "theranostic kit" that can be labelled with ^{99m}Tc and with trivalent beta-emitter radionuclides for imaging and for palliative treatment of painful bone metastases, respectively. PHYTON kit, composed from stannous chloride dihydrate and PHYTATE (myo-inositol-hexaphosphate ester), is for ^{99m}Tc-labelling and used for gamma-camera/SPECT imaging of the liver as well as monitoring of the liver tumour therapy [1–4]. ^{119}Sn Mössbauer study of these two radiopharmaceutical kits were aimed in order to show the chemical microenvironment as well as interactions between the EDTMP or PHYTATE ligands and stannous chloride.

2 Experimental

The samples were prepared from 10 vials of lyophylized radiopharmaceutical kits which are regularly applied for ^{99m}Tc-labelling and used for gamma-camera/SPECT imaging and monitoring at the tumor therapy.

The composition of kits is the following:

Sn-PHYTATE:

150 mg sodium phytate (myo-inositol-hexaphosphate ester), 10 mg tin(II) chloride dihydrate and 100 mg sodium chloride

Sn-EDTMP :

250 mg EDTMP (ethylene-diamine-tetramethylene phosphonate), 10 mg tin(II) chloride dihydrate, 50 mg ascorbic acid and 100 mg glucose.

The Mössbauer samples were prepared and rapidly frozen from the fresh kits in a glove box in Ar gas atmosphere. After the measurements the samples were kept in air atmosphere at 8 °C in a conventional refrigerator.

The ^{119}Sn Mössbauer measurements of radiopharmaceutical samples were carried out with a conventional constant acceleration (WISSEL) Mössbauer spectrometer using integrated multichannel analyzer and scintillation detection in transmission geometry. The samples were measured in a frozen state at 80 K temperature by the means of a JANIS liquid helium cryostat. $Ba^{119m}SnO_3$ source of 40 MBq activity supplied the gamma rays. The isomer shift values are given relatively to $BaSnO_3$ at room temperature. The analysis of the Mössbauer spectra was carried out with the MOSSWINN 4.0 code [5].

Powder X-ray diffractograms of the radiopharmaceutical samples were recorded using a computer controlled powder diffractometer (DRON-2) with $Fe_{K\alpha}$ radiation and β-filter at room temperature.

3 Results and discussion

Figure 1 shows the powder X-ray diffractograms of the Sn-containing radiopharmaceuticals.

The powder XRD pattern of Sn-PHYTATE (Fig. 1) exhibits only a very broad line centered around $2\theta \approx 20$ degrees, typical of amorphous structure. In the diffractogram of Sn-EDTMP a broad line, similar to that of Sn-PHYTATE, also appear, however, narrow reflections indicating crystalline state are also present. The evaluation of this diffractogram resulted that all narrow lines are the fingerprint of NaCl. This can be well understood since sodium chloride is a component of the kit, where NaCl is the only phase being in crystalline

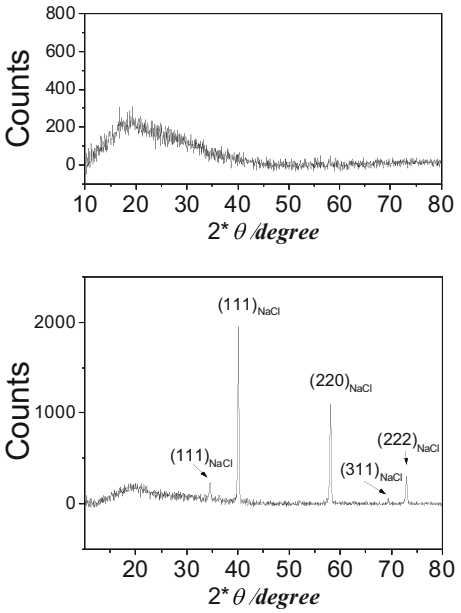

Fig. 1 PXRD patterns of Sn-PHYTATE (top) and Sn-EDTMP (bottom) samples

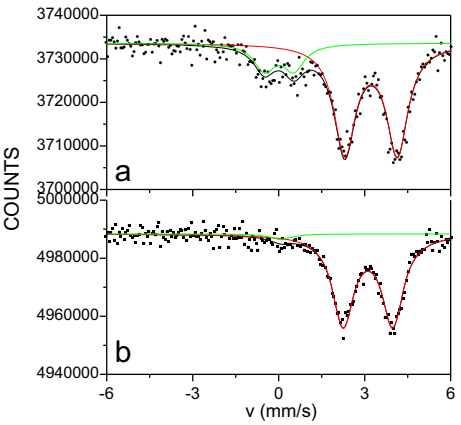

Fig. 2 ^{119}Sn Mössbauer spectra, recorded at 80 K, of liophylized Sn-PHYTATE (**a**) and Sn–MULTIBONE radiopharmaceuticals

form alone. Consequently, the tin-containing compounds in both of Sn-PHYTATE and Sn-EDTMP have amorphous structure. This is consistent with the earlier observation for the related compounds [6–8].

Figure 2 shows the 80 K ^{119}Sn Mössbauer spectra of Sn-PHYTATE and Sn-MULTIBONE kits. Both ^{119}Sn Mössbauer spectra (Fig. 2) were decomposed into two doublets corresponding to tin(II) and tin(IV) components according to their Mössbauer parameters depicted in Table 1. In both compounds tin(II) microenvironments are dominating. The occurrence of tin(IV) in Sn-MULTIBONE was as low as measured in the precursor stannous chloride (3.2%). This means that all tin(II) introduced to the kit from the from stannous chloride dihydrate remained in form of tin(II) in the fresh Sn-MULTIBONE sample. This is a very important knowledge from the point of view of pharmaceutical application,

Table 1 80 K Mössbauer parameters of radiopharmaceuticals

Sample	A/%	δ/mms^{-1}	Δ/mms^{-1}	W/mms^{-1}
Sn-PHYTATE	80.7 ± 1.6	3.12 ± 0.01	1.84 ± 0.02	0.89 ± 0.03
	19.3 ± 2.3	−0.08 ± 0.04	1.02 ± 0.08	0.89 ± 0.03
Sn-MULTIBONE	96.8 ± 2.2	3.01 ± 0.01	1.73 ± 0.02	0.88 ± 0.03
	3.2 ± 1.2	−0.04 ± 0.26	0.48 ± 0.35	0.88 ± 0.03

since only tin(II) can reduce ^{99m}Tc pertechnetate when the kit is successfully labeled with ^{99m}Tc radionuclide in the hospital labs just before patient's administration. Since always Tc(VII) pertechnetate is used for labeling, the reduction of Tc is the necessary precondition of the preparation of acting radiopharmaceuticals, which is not the case with tin(IV). Consequently, the determination of occurrence of tin(II) and tin(IV) in the radiopharmaceutical kits is of fundamental importance. Since ^{119}Sn Mössbauer spectroscopy is among the best methods to determine the relative occurrence of tin(II) and tin(IV) in tin-bearing materials we demonstrate here that its application for radiopharmaceutical kits even in the case of low Sn content is also possible. The ^{119}Sn spectrum (Fig. 2) and the derived Mössbauer parameters (Table 1) reveal that nearly 20% of tin(IV) occurs in the fresh Sn-PHYTATE sample. As the effective applications of this kit in the monitoring indicate 80% tin (II) content may be enough for the resultful ^{99m}Tc labeling.

For tin (II), characteristic Mössbauer parameters of $\delta = 3.12 \pm 0.01$ mms^{-1} and $\Delta = 1.84 \pm 0.02$ mms^{-1} as well as $\delta = 3.01 \pm 0.01 \pm 0.01$ mms^{-1} and $\Delta = 1.73 \pm 0.02$ mms^{-1} were determined for Sn-PHYTATE and Sn-EDTMP, respectively. The obtained isomer shift and quadrupole splitting data of tin(II) components (Table 1) are close to those which were reported for stannous phosphate and related compounds [9, 10], but the parameters are very far from those of the precursor stannous chloride and its hydrate derivatives. This is consistent with the expectation that tin(II) is located in the vicinity of phosphonate/phospate groups in both radiopharmaceuticals [11–13], thus the appropriate compounds were prepared.

There are small but significant differences between both the isomer shifts and quadrupole splitting of radiopharmaceutical kits and Sn-MULTIBONE radiopharmaceuticals. This reveals differences in the Sn microenvironments between the compounds.

The linewidths of all components are narrow enough and indicate that identical tin(II) microenvironments are present in each individual compounds. The exact assignment of these microenvironments requests further studies since no X-ray structure determination is available due to the amorphous character of these compounds as we demonstrated above.

Since the usability time of the kits is a very important parameter for the applications and one can think that tin(II) to tin(IV) oxidation might be in correlation with this, we performed preliminary experiments to get information about this by measuring Sn-MULTIBONE and Sn-PHYTATE samples kept under their conventional conditions (at 10 °C in a refrigerator) in air atmosphere for 70 days after the first measurements of the fresh samples.

80 K ^{119}Sn Mössbauer spectra, of Sn-PHYTATE and Sn–MULTIBONE radiopharmaceuticals after aging at temperature of 8 °C for 70 days can be seen in Fig. 3. The corresponding Mössbauer parameters are shown in Table 2.

As Fig. 3 and Table 2 show, the 80 K Mössbauer spectra of both aged samples and their parameters are very similar to those of fresh samples after keeping them at temperature of 8 °C for 70 days. The isomer shift and quadrupole splitting of tin(II) components are

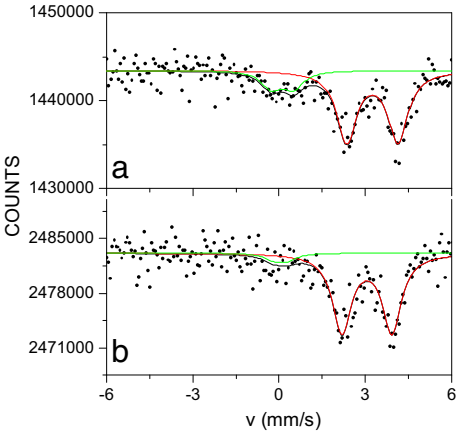

Fig. 3 ^{119}Sn Mössbauer spectra, recorded at 80K, of Sn-PHYTATE (**a**) and Sn–MULTIBONE radiopharmaceuticals after aging at temperature of 8 °C for 70 days

Table 2 80 K Mössbauer parameters of radiopharmaceuticals kept at 8 °C for 70 days

Sample	A/%	δ/mms^{-1}	Δ/mms^{-1}	W/mms^{-1}
Sn-PHYTATE after 70 days	80.4 ± 3.8	3.14 ± 0.02	1.81 ± 0.04	0.85 ± 0.05
	19.6 ± 2.6	−0.06 ± 0.08	0.76 ± 0.16	0.85 ± 0.05
Sn-MULTIBONE after 70 days	93.2 ± 4.7	2.99 ± 0.02	1.72 ± 0.04	0.80 ± 0.06
	7.7 ± 2.8	−0.05 ± 0.17	0.46 ± 0.38	0.80 ± 0.06

identical within the errors. This can reflect that no change occurs in the microenvironments of tin (II) upon the aging. The local parameters of tin (IV) can be determined with a much higher uncertinity than those of tin (II), due to its relatively low occurrence (especially in the case of Sn-MULTIBONE) and low tin content as well as the low source activity. Therefore it is hard to decide whether are or not differences in the tin (IV) microenvironments as an effect of the applied aging, based on the present results. More importantly, no significant changes were observed in the relative occurrence of tin (II) in the samples kept in air at 8 °C for 70 days. The relative occurrence of Sn(II) remained the same within the errors in the Sn-PHYTATE, while it may decrease somewhat in the Sn-MULTIBONE after 70 days in air. These preliminary results related to the limits of usability time of kits indicate, that no significant changes occur in the valence states of tin which may hinder their effective radiopharmaceutical applications after keeping them in air at 8 °C for 70 days.

4 Conclusion

^{119}Sn Mössbauer spectroscopy is a suitable tool for characterization of radiopharmaceutical kits (Sn-PHYTATE and Sn–MULTIBONE). About 97% tin(II) occurs in Sn–MULTIBONE while about 80% tin(II) is in Sn-PHYTATE, which is enough to reduce ^{99m}Tc pertechnetate to the successful ^{99m}Tc labeling of the kits for imaging and monitoring in the liver tumor therapy. XRD revealed the amorphous nature of Sn-containing phases. No significant decrease of tin(II) content occurs in the kits after keeping them in air at 8 °C for

70 days. The characteristic ^{119}Sn Mössbauer parameters determined for Sn-PHYTATE and Sn-MULTIBONE may also serve for the quality control of these pharmaceutical kits.

Acknowledgements The financial supports from the NKFIH-OTKA (No K115913 and K115784) and Hungarian-Croatian S&T (No TÉT_16-1-2016-0002) grants are acknowledged.

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