ELECTROCHEMICAL SEPARATION OF 90-YTTRIUM IN THE ELECTROCHEMICAL $^{90}Sr/^{90}Y$ GENERATOR AND ITS USE FOR RADIOLABELLING OF DOTA-CONJUGATED SOMATOSTATIN ANALOG [$DOTA^0$, Tyr^3] OCTREOTATE

by

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Radiopharmaceuticals based on ^{90}Y are widely used in the treatment of malignant deseases. In order to meet the requirements for their future application, a $^{90}Sr/^{90}Y$ generator was developed and ^{90}Y eluted from this locally produced generator was used for the radiolabelling of the DOTA-conjugated somatostatin analog [$DOTA^0$,Tyr^3] octreotate and the preparation of [^{90}Y-$DOTA^0$,Tyr^3] octreotate (^{90}Y-DOTATATE) for peptide receptore radionuclide therapy.
$^{90}Sr/^{90}Y$ generator was based on the electrochemical separation of ^{90}Y from ^{90}Sr in a two-cycle electrolysis procedure. Three electrode cells were used to perform both electrolyses. In both cycles, working electrodes were kept on constant potential. The pH of the solution was adjusted to 2.7 of the value before the electrolyses.
The radionuclidic purity of the ^{90}Y solution was analysed by ITLC and extraction paper chromatography. The labelling of peptide (100 g DOTATATE) with $^{90}YCl_3$ was performed at 95 °C for 30 minutes. Radiochemical purity was determined by HPLC and chromatographic separation, using a solid SepPak C-18 column.
Results obtained confirmed the efficiency of our electrochemical separation technique and quality control methods for ^{90}Y. The achieved efficiency of the $^{90}Sr/^{90}Y$ generator above 96% of the theoretical value represents a good basis for the further development of this generator. The labelling of the DOTATATE with ^{90}Y exhibited a high efficiency, too: there was less than 1% of $^{90}Y^{3+}$ in the ^{90}Y-DOTATATE.

Key words: radionuclide therapy, ^{90}Y, $^{90}Sr/^{90}Y$ generator, radiolabelling, ^{90}Y-DOTATATE

INTRODUCTION

Radionuclide therapy has been known for a long time. The potentials of internal target radiotherapy have also been acknowledged for more than sixty years, but the use of some novel radionuclides and radiopharmaceuticals in the treatment of solid cancer has rapidly increased over the past years.

Radionuclides with short physical half-lives, in the range from a few hours to a few days, could be useful in radionuclide therapy. Recently, Yttrium-90 (^{90}Y) has attracted a lot of attention as a promising therapeutic radioisotope [1]. ^{90}Y has well known favourable features: a half-life (64.1 hour), consistent with the rate of antibody accumulation in tumours and no accompanying gamma ray radiation in its decay. Beta rays have an intermediate energy of 0.9367 MeV(β_{max} = 2.28 MeV) and a stable daughter (^{90}Zr). The major advantage of the use of ^{90}Y in solid tumours is the considerable path length of its β^- particles (r_{95} = 5.9 mm) in tissues.

^{90}Y could be generated by β^- decay of ^{90}Sr ($T_{1/2}$ = = 28.8 years) with which it exists in a secular radioactive equilibrium. A scheme of the breakthrough is presented as

$$^{90}_{38}\mathrm{Sr} \xrightarrow[28.74\ y]{\beta^- (0.54\,\mathrm{MeV})} {}^{90}_{39}\mathrm{Y} \xrightarrow[64.4\ h]{\beta^- (2.28\,\mathrm{MeV})} {}^{90}_{40}\mathrm{Zr(stable)} \quad (1)$$

Because of its long half-life, ^{90}Sr could be used for an indefinite time, but this is also a serious limitation for the development of an adequate $^{90}Sr/^{90}Y$ generator system, as the production of long-lived wastes requires careful handling and storage. This is the problem that the use of such generators poses before nuclear medicine departments. Since ^{90}Sr is a highly toxic radionuclide, it is essential that ^{90}Sr should be handled in a well-established, controlled laboratory, by trained personnel.

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For the separation of ^{90}Y from ^{90}Sr, several separation techniques have been reported, such as: adsorption, solvent extraction, precipitation, electrochemical separation, and ion exchange [2-11]. The separation of ^{90}Y from ^{90}Sr by adsorption chromatography on the column is not convenient because of the degradation of the column matrix. Other techniques, like the separation of carrier-free Y-90 from Sr-90 by cation exchange [12] or ion exchange [13] solvent extraction, chromatographic separation by the Eichrom-treated column [14], the extraction paper chromatography (EPC) technique [15-17] or with liquid membranes [18, 19], could be useful for obtaining ^{90}Y, but they gave more or less specific radioactivity, lower radionuclidic purity, as well as a higher quantity of long-lived wastes.

The electrochemical method was suggested for the separation of pure ^{86}Y from ^{86}Sr and the production of ^{86}Y, an attractive radioisotope for positron emission tomography (PET) [20-23]. Successful electrochemical separations of ^{90}Y from ^{90}Sr were presented by Venkatesh *et al*, as well as by Chukravarty *et al*, [14, 24].

The cost-effective availability of the ^{90}Y from a generator system makes it very attractive. As important is the fact that ^{90}Y can easily bond to many chelate molecules, which is the basis of its use in radionuclide therapy. So, ^{90}Y-labelled compounds, such as peptides, antibodies, microspheres, citrate and phosphates, were developed as a new class of radiotherapeutic agents. Some of these agents were developed at the Vinča Institute [25-29].

The treatment with radiolabelled somatostatin analogues was introduced in the 1990s, as a promising therapy for patients with inoperable or metastatic gastroentero-pancreatric neuroendocrine tumours (GEP-NET) [30]. A majority of GEPNET exhibit abundant levels of the somatostatin receptor which can be visualized in patients by the use of the radiolabelled somatostatin analogue, ^{111}In-diethylenetriamine pentaacetic acid (DTPA)-octreotide [31]. There is a lot of data in literature for the labelled peptide-based radiopharmaceuticals based on various radionuclides: such as, ^{99m}Tc, ^{111}In, for imaging, or ^{90}Y, ^{177}Lu therapy [32-42].

^{90}Y, as a β^--emitting radionuclide with high activities, has proved to be a suitable radioisotope for labelling modified somatostatin analogues, [DOTA^0,Tyr^3] octreotide (^{90}Y-DOTATOC) and [DOTA^0,Tyr^3] octreotate (^{90}Y-DOTATATE). Thus, ^{90}Y-DOTATOC and ^{90}Y-DOTATATE were the next generation of radiolabelled compounds of the peptide receptor radionuclide therapy (PRRT) therapy to be developed [43-45].

Considerable interest concerning the use of therapeutic radiopharmaceuticals exists in Serbia. On the other hand, ^{90}Y is an expensive radioisotope, requiring import on a large scale because of the decay loss, making it inconvenient for everyday medical application in the impoverished healthcare system of Serbia. Therefore, a ^{90}Sr/^{90}Y generator system, based on the electrochemical separation technique and procedures for determining the radiochemical and radionuclide impurity, were developed [46]. Its use in the centralized radiopharmacy at the Vinča Institute was established.

EXPERIMENTAL

Materials

Radioactive sources ^{90}Sr as strontium nitrate, $^{90}Sr(NO_3)$ in equilibrium with ^{90}Y in 1 M HNO_3, with a specific activity of 2.70 GBq/mg Sr, radioactive concentration of 9.240 GBq/cm^3, as well as carrier-free $^{90}YCl_3$ in a 0.05 M HCl solution, radioactive concentration 89.590 GBq/cm^3, were obtained from the Institute of Atomic Energy, Radioisotope Centre, Polatom, Poland.

[DOTA-Tyr3] octreotate (DOTATATE) in lyophilised form was provided from the Institute of Atomic Energy, Radioisotope Centre Polatom, Poland.

[DOTA-Tyr3] octreotate TFA-salt of a purity >95 % was provided by Pi Chem (Graz, Austria). All other reagents and solvents were supplied from commercial sources.

The potentiostat unit, Potentiostat/Galvanostat/ZRA, Series G 750, was composed of licensed software FC 350 (Gamry Instruments Inc., Warminster, Penn., USA).

The equipment for the electrochemical separation was completed with an electrolysis cell made by the Faculty of Technology and Metallurgy, University of Belgrade. A three-electrode system was housed in quartz cells fitted with an acrylic cap. Two electrodes, an anode and a cathode, with a surface of 2 cm^2, were high-purity platinum plats electrodes made by the Institute for Mining and Metallurgy, Bor, Serbia. As a reference electrode, saturated calomel electrode (SCE), (Gamry Instruments, Inc.), in a referent cell, connected by Lugin's capillary with an electrochemical cell, was used. High-purity argon gas was provided from a local supplier.

The radioactivity of ^{90}Sr and ^{90}Y was measured in an ionisation chamber (Capintec CRC-15 Beta Counting Calibrator, Ramsey, N. J., USA) which contains a calibration factor. For calibrating the ^{90}Y dose secondary calibration source of ^{90}Sr, a (radioactive solution ampoule N^o BW/21/10/R_3-0.1, with an activity of 368.3 9.6 kBq/Lg, dated December 15th, 2010), was used. A low level of activity was measured in the NaI(Tl) scintillation counter (Wallace Comp. Gamma Counter, LKB, Finland) by measuring the Bremmstrahlung radiations of ^{90}Sr and ^{90}Y.

The HPLC analysis of the ^{90}Y-DOTATATE was performed using the High Pressure Liquid Chromatograph, Hewlett Packard 1050 S/N (Palo Alto, Cal., USA), with an UV and gamma flow detector (Raytest Austria GmbH, Langenzersdorf, Austria), with a RP C18 column (250 mm 4.6 mm). Chromatographic separation was done by SepPak C-18 column (Waters, Milford, Mass., USA), activated by 95% C_2H_5OH.

Preparation of the ^{90}Sr-^{90}Y generator

^{90}Sr-^{90}Y electrochemical generator was based on the electrolysis of a mixture of ^{90}Sr and ^{90}Y in nitrate form. The electrolysis was performed in a quartz cell with a of volume 100 cm^3 charged with 0.2 ml of ^{90}Sr (NO_3) in 1 M HNO_3 (~1.85 GBq), while the electrolyte of the total volume of 50 ml amounted to 0.003 M HNO_3. The pH value was adjusted prior to the electrolysis with 3% ammonia to 2.7 0.2. Before the electrolysis, argon was bubbled for 15 minutes, passing through a glass tube which was dipped into the electrolysis solution and platinum electrodes were activated in 3 M HNO_3.

The three-electrode system was housed in quartz cells fitted with an acrylic cap. The working and auxiliary electrode, sealed in a glass holder, were fully immersed in the solution, facing each other. They were maintained at a very low distance and the reference electrode (SCE) was kept very close to the cathode, without touching it.

Electrochemical separation of ^{90}Y

The electrolysis was performed in a two-step procedure . During the first electrolysis, ^{90}Y was separated from ^{90}Sr by selective electrodepositing of ^{90}Y on the platinum cathode. This was achieved by applying a fixed potential on the cathode of –2.5 V with respect to SCE. High-purity argon gas was continuously passed through the solution to vent gases like H_2, and the solution continuously mixed by a magnetic stirrer. The first electrolysis lasted 90 minutes. At the end of the selective electrodepositing of ^{90}Y, the electrodes with the acrylic cap were removed from the quartz cell, without switching off the power supply. Then the power supply was switched off, the cathode plate removed from the acrylic cap and washed with 10 ml of acetone. After that, the cathode was transferred to the second quartz cell.

During the second electrolysis, the so cold "purification step", ^{90}Y was removed from the platinum electrode. In this step, the cathode from the first electrolysis containing ^{90}Y was used as an anode, but a new platinum electrode was used as a cathode. The electrods were fully immersed in the solution, in a similar new electrolytic cell filled with fresh 0.0003 M $NaNO_3$ and pH adjusted to 2.7 0.2. This step of the electrolysis took 45 minutes and was performed as a galvanostatic electrolysis, at a fixed potential of –2.5 V on the cathode with respect to SCE. Argon was continuously passed through the solution. In this electrolysis, ^{90}Y was transferred from the first platinum electrode to the fresh platinum electrode (cathode) and then deposited on it. After the electrodepositing of ^{90}Y, the cathode was taken out without switching off the current and washed with 10 ml acetone and then dissolved by dipping it in a small volume of 0.5 M HCl, so as to obtain $^{90}YCl_3$ suitable for labelling.

In the initial experiments, ^{90}Sr in equilibrium with ^{90}Y with relatively low activity (~1.85 GBq) was used.

Quality control of ^{90}Y

The radionuclidic purity of the ^{90}Y solution was analysed by paper and ITLC chromatography. Chromatography paper Whatman N° 1 (18 cm 2 cm) and ITLC SG strips (14 cm 1 cm) of normal saline (0.9% NaCl) were used.

In order to determine the radionuclidic purity of the ^{90}Y solution, the so called "BARC technique" was used [36, 37]. This method is a combination of solvent extraction and paper chromatography (extraction paper chromatography EPC). Whatman N 1 (18 cm 2 cm) paper chromatography strips impregnated with 2-ethyl hexyl, and 2-ethyl hexyl phosphonic acid (KSM-17) at the point of spotting were used. Upon development with normal saline, ^{90}Sr moves to the solvent front, leaving ^{90}Y completely chelated and retained at the point of spotting. The activity at the solvent front was estimated by cutting the chromatograms in 1 cm pieces and by measuring the radioactivity in a NaI(Tl) scintillation counter. Radionuclidic purity was calculated as a percentage of the total spotted activity.

Preparation and quality control of ^{90}Y-DOTATATE

Preparation of DOTATATE and its labelling with ^{90}Y

The solution of the DOTATATE was prepared under aseptic conditions, by dissolving the [DOTA-Tyr3] octreotate in ascorbic acid solution pH = 4.5. 0.5 ml aliquots, dispensed in glass vials and freeze-dried for 24 hours. Thus, samples with 100 g DOTATATE and 50 mg ascorbic acid were obtained as lyophilised powder in a vacuum.

The reconstitution of the freeze-dried DOTATATE was done in the same manner for both the DOTATATE obtained from Polatom, Poland, and the one prepared at the Vinča Institute by adding 0.5 ml aliquots of sterile normal saline into the vials with the DOTATATE and mixing.

The DOTATATE developed at the Vinča Institute was labelled by adding 37 MBq of $^{90}YCl_3$ only

for research purposes. The ^{90}Y-labelling of the peptide was performed at 95 C, for 30 minutes. The heating and shaking was done in a temperature-controlled heating bath. After 30 minutes, the vial was cooled for 1-2 minutes in cold water to room temperature and acetic acid (50 mg/ml, pH 4.5) as a stabilizer added. The final volume was adjusted up to 3 ml.

DOTATATE (Polatom) was labelled with 1.85-5.55 GBq of $^{90}YCl_3$. The content of the vial was quantitatively transferred to a vial with $^{90}YCl_3$. The labelling procedure was the same as for the samples prepared in our Laboratory. These samples of ^{90}Y-DOTATATE (18.5-37.0 MBq/1 g DOTATATE) were prepared for the treatment of patients.

The sterility of the labelled compound was obtained by working under aseptic conditions and with sterilized equipment with additional filtration by 0.22 m filters (Millipore).

Quality control of ^{90}Y-DOTATATE

The radiochemical purity (RCP) of the ^{90}Y-labelled DOTATATE was determined by HPLC and solid phase separation using SepPak C-18 mini columns (cartridges).

HPLC

A sample of the ^{90}Y-DOTATATE was obtained by dissolving ^{90}Y-DOTATATE (5 l) in a mixture of 500 l 0.4 M sodium acetate (pH 4.5) and 1 mg/ml diethylen triamino pentaacetic acid (DTPA). The HPLC analyses of the ^{90}Y-DOTATATE sample was performed by use of two solvents: 0.1% trifluoroacetic acid (TFA) in water (solvent A) and acetonitrile (solvent B), by the gradient elution technique: 0-5 minutes 95% B; 5-10 minutes: from 95%-0% B; 10-15 minutes 0% B; from 15-20 minutes: from 0% to 95% B; 20-25 minutes: 85% B. The flow rate was 0.7 ml/minutes. UV was detected at 254 nm and radioactivity by radiometric detection.

Solid phase SepPak separation

A SepPak C-18 mini column was activated with 5 ml of 95% ethanol (C_2H_5OH) and then washed with 10-15 ml of normal saline (0.9% NaCl). A sample of the ^{90}Y-DOTATATE (10-20 l) dissolved in 500 l of normal saline was loaded onto the column and then washed out with 5 ml of normal saline (fraction A with $^{90}Y^{3+}$). This step was followed by the washing out of the column with 5 ml of 95% C_2H_5OH (fraction B with ^{90}Y-DOTATATE).

RCP was calculated as the percentage of fraction B activity, according to the equation

$$B[\%] \quad \frac{B}{B \quad A} \qquad (2)$$

RESULTS AND DISCUSSION

Electrochemical separation of ^{90}Y and its quality control

$^{90}Sr/^{90}Y$ generator was based on the electrochemical separation of ^{90}Y, according to the method of Chacravatry *et al*. [24]. In this generator, the difference between the electrochemical potentials of Y^{3+} and Sr^{2+} was explored so as to achieve a clean and quick separation of ^{90}Y from the parent radionuclide, ^{90}Sr. The electrolysis was carried out in an electrolysis quartz cell," as apotentiostatical electrolysis with a potential of 2.500 V 0.055 with respect to SCE. During the first electrolysis, the current was increased from 730 mA to 745 mA as the electrolysis neared the end. The electrolytic potential at the platinum cathode was stable during the electrolysis, but could not be maintained at 2.50 V over the duration of the electrolysis. It fell to 2.39 V, still within the allowed limit of <(±0.2)% plus 5 mV, in a constant voltage mode for an used potentiostatic unit. The pH was adjusted at 2.7 0.2.

(a)

(b)

Figure 1. Equipment for electrochemical separation, Laboratory for Radioisotopes, Vinča Institute (a); with electrochemical cell (b)

The second electrolysis was accomplished at a stable potential at the platinum cathode 2.50 V during the electrolysis, at a constant current of 100 mA. The warming of the solution during the electrolysis was remarkable, so that the cooling of the electrolysis cell was necessary. A separation of the H_2 gas was also detected, therefore the stirring during the process seems to be unnecessary. These conditions had to ensure the deposition yield above 90%. There was a need to convert ^{90}Y into a form applicable to medicine therapy.

^{90}Y exists in secular equilibrium with its parent isotope strontium-90 (^{90}Sc) a product of fission reaction. There were many impurities which had to be removed, including pure ^{90}Y. Radioactive ^{90}Sr as $^{90}Sr(NO_3)_2$ in equilibrium with ^{90}Y in 1 M HNO_3, obtained from Polatom, Poland, was of high radionuclidic purity (>99.5%), as well as of high radiochemical purity, so we expected ^{90}Y obtained by the electrochemical separation method from the ^{90}Sr/^{90}Y generator to be of high radiochemical purity.

^{90}Sr breakthrough is a major problem often encountered with the ^{90}Sr/^{90}Y generator. Because ^{90}Sr is a bone seeker, the upper limit of ^{90}Sr in the ^{90}Y solution for human use is 74 kBq (2 mCi) [24]. In order to provide data concerning ^{90}Sr contamination, the development of methods for the determination of chemical and radionuclide impurity was necessary.

The quality of the said separation was investigated by measuring the radioactivity of the ^{90}Y-solution over the course of time, following the half-life of ^{90}Y. The decrease was followed for 31 days *i. e*, a ~11.6 half-life of ^{90}Y. The absence of deviation in the lower part of the curve in fig. 2 confirmed the absence of ^{90}Sr. In the figure presented, the y-axis was given as the logarithm of obtained values.

The radionuclidic purity of the ^{90}Y solution was analysed by paper and ITLC chromatography. Chromatography paper Whatman N 1 (18 cm 2 cm) and ITLC SG strips (14 cm 1 cm) and 0.9% saline solution were used for the analyses. During the chromatography, ^{90}Sr moved with the solvent front, while ^{90}Y stayed at the origin. As the mixture of ^{90}Sr and ^{90}Y was at low activity, at the megabecquerel level, the activity at the solvent front was estimated by use of dose calibrator (Capintec CRC 15R, USA) which contains a calibration factor and then compared with the total spotted activity. In addition, the activity of the solution was tested and measured for a month. Comparative results of the radiochemical purity of ^{90}Y before and after electrolysis, obtained by paper chromatography, were given in fig. 3(a) and fig. 3(b). The solution of strontium and yttrium was in a balance, and its layout shown in fig. 3(a) where two peaks were visible. The absence of a peak at 10 cm representing strontium fig. 3(b) indicates that the separation of yttrium from strontium by electrochemical separation was successful.

In order to determine the radionuclidic purity of the ^{90}Y solution, a combination of solvent extraction and paper chromatography (extraction paper chromatography EPC "BARC technique") was also used in our experiments. This method was suggested as a sensitive and accurate analytical technique for the estimation of the purity of ^{90}Y [13]. The EPC pattern of ^{90}Y obtained upon development with normal saline was

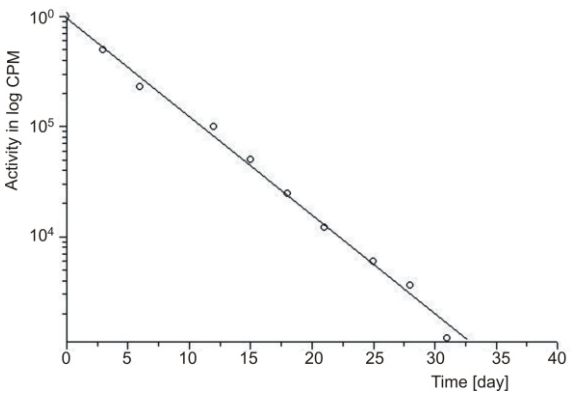

Figure 2. Radioactive decay pattern of ^{90}Y prepared by the electrochemical separation method (>11 half lives)

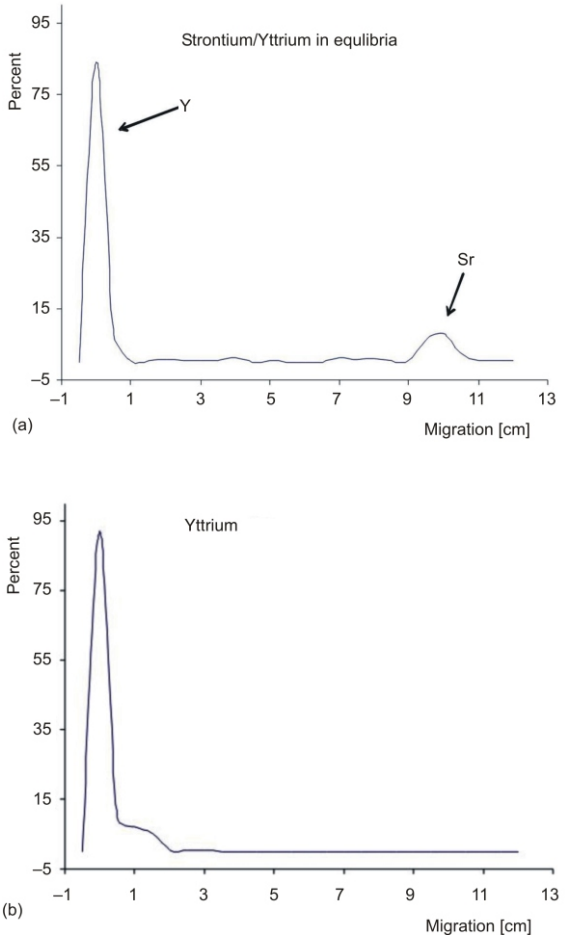

Figure 3. (a) Strontium/Yttrium in equilibrium, and (b) Yttrium after electrolyses

presented in fig. 4. ^{90}Sr moved to the solvent frontleaving ^{90}Y completely chelated and retained at the point of spotting. Radionuclidic purity was calculated as a percentage of the total spotted activity, estimated by measuring radioactivity in a dose calibrator. These results have shown that a very low level of ^{90}Sr, not more than 0.2%, was found for 5 repeated electrolysis procedures.

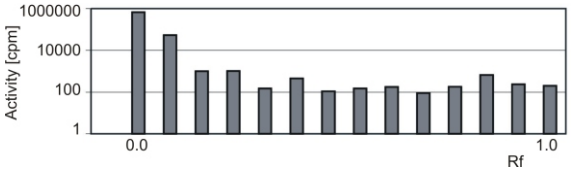

Figure 4. Extraction paper chromatography results (EPC) of ^{90}Y from the ^{90}Sr/^{90}Y electrochemical generator

Preparation and quality control of ^{90}Y-DOTATATE

Fifty-nine labellings of the commercially available DOTATATE with $^{90}YCL_3$ (Polatom, Poland) done over the last five years were observed. Radiochemical purity results of the ^{90}Y-DOTATATE (RCP) obtained by solid phase SepPak separation have shown that in the fifty-three labelled batches prepared and labelled according to procedure, only 49.0% of the batches were on RCP over 99.0%, 73.6% had RCP higher than 98%, 84.9% had RCP higher than 95.0%, while 15.1% of all prepared batches had more than 10% of Y^{3+}.

A part of the RCP results, along with the content of chemical impurities of ^{90}Y in g/ml (Cu, Ni, As, Pb, Fe, Zn), were presented in tab. 1. Because of the insufficient quality control of the results for all of the used batches of ^{90}Y, RCP results for only 33 labelled samples were presented. As can be seen from tab. 1, the content of metals analysed by the ICP OES spectrometry method on the day of their production was within the limits declared by the manufacturer (Cu, Ni, As < g/ml, Pb < 5.0 g/ml, Fe, Zn (<10.0 g/ml). As we have used $^{90}YCl_3$ four days after the date of production and quality control, the content of the element could increase. Quality control results for ^{90}Y-DOTATATE were in accordance with the content of listed metals in yttrium chloride: the higher the content of metals, especially Pb, Fe, and Zn, the higher the percentage of free Y^{3+} in DOTATATE samples labelled with $^{90}YCl_3$. As more than 15% of the prepared batches contained over 10% of Y^{3+}, it was obvious that the influence of the listed metals was high.

For patient application, we have used the batches on RCP over 98%, without any purification. For these samples of the ^{90}Y-DOTATATE, there was (0.79 0.58)% of $^{90}Y^{3+}$in the ^{90}Y-DOTATATE (mean standard deviation SD), determined by solid phase SepPak separation.

In the same way, the quality control of the batches of DOTATATE developed in our Laboratory and labelled with ^{90}Y by the ^{90}Sr/^{90}Y generator (Vinča Institute), was done 15 minutes after the preparation and repeated after 24 hours. The results of the HPLC analyses were presented in fig. 5. Radiochromatograms have shown that the prepared samples of the ^{90}Y-DOTATATE (R_f = 12.532 12.822) were of high radiochemical purity, higher than 99% 15 minutes after preparation and higher than 96%, 24 hours after preparation, again without a stabiliser, confirming the stability of the labelled compound.

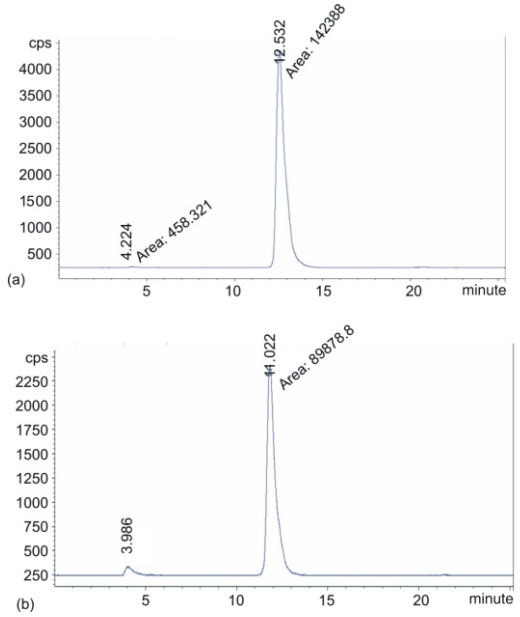

Figure 5. HPLC radiochromatograms for ^{90}Y-DOTATATE (Vinča Institute); (a) 15 minutes and (b) 24 hours after radiolabelling

CONCLUSIONS

First results of the use of the ^{90}Sr/^{90}Y generator have confirmed the feasibility of a practical application of the electrochemical separation procedure. This seems a superior and low-cost technique for a permanent supply of ^{90}Y suitable for therapeutic application.

^{90}Sr in equilibrium with ^{90}Y with a relatively low activity (~1.85 GBq) was used for these experiments. The efficiency of the ^{90}Sr/^{90}Y generator was above 96% of the theoretical value and represents a good basis for further development of the ^{90}Sr/^{90}Y generator. These results were also a confirmation that we have successfully completed the equipment of the ^{90}Sr/^{90}Y electrochemical generator and established a viable electrochemical separation technique.

A procedure for preparing the DOTATATE and its labelling with ^{90}Y was developed, too. The first labelling results of DOTATATE with home-made ^{90}Y have shown high radiochemical purity, possibly confirming the good quality of ^{90}Y obtained from the ^{90}Sr/^{90}Y generator.

Table 1. Influence of chemical impurities on labeling yield of ^{90}Y-DOTATATE

Batch No.	Radioactivity [GBq]	RCP [%]	Cu [<1.0 g/ml]	Ni [<1.0 g/ml]	As [<1.0 g/ml]	Pb [<5.0 g/ml]	Fe [<10.0 g/ml]	Zn [<10.0 g/ml]
1/09	3.70	0.71	<0.3	<0.4	<1.0	<0.7	<0.8	=8.5
2/09	5.55	0.11	<0.6	<0.6	<0.5	<3.9	=1.1	=5.6
4/10	3.70	1.52	<1.0	<0.2	<0.7	<1.3	<2.2	<2.5
5/10	3.70	0.29	<0.2	<0.4	<0.8	<0.9	<0.5	<0.3
6/10	5.55	1.10	<0.1	<0.5	<0.8	<0.6	<0.3	<1.0
9/10	3.70	0.51	<0.1	<0.5	<0.9	0.4	<0.3	<1.8
11/10	4.00	1.07	<0.3	<0.2	<0.9	<1.5	<0.2	<0.3
12/10	5.55	0.24	<0.3	<0.6	<1.0	<0.8	<0.2	<0.2
13/10	5.55	3.50	<0.3	<0.3	<1.0	<0.8	<0.1	<0.3
14/10	5.55	1.96	<0.2	<0.3	<0.9	<1.9	=1.0	=8.3
15/10	3.70	0.08	<0.5	<0.2	<0.8	<1.3	<0.2	<3.6
16/10	5.55	24.16	<0.1	<0.2	<1.0	<2.2	<0.1	<0.7
17/10	5.55	2.40	<0.3	<0.4	<1.0	<0.5	<0.4	<1.3
1/11	3.70	0.84	<0.4	<0.3	<0.4	<2.0	<2.6	<0.2
2/11	5.55	0.44	<0.4	<0.4	<1.0	<0.4	<0.5	<0.1
3/11	5.55	36.30	<1.0	<0.4	<1.0	<2.4	=2.1	=8.6
4/11	2.75	26.75	=0.3	<0.8	<0.8	=4.5	=5.6	=9.4
5/11	5.55	17.4	<0.2	<0.6	<0.9	<2.1	<0.6	<4.8
6/11	5.55	2.02	<0.2	<0.2	<1.0	<0.6	<0.1	<0.1
7/11	1.85	0.12	<0.4	<0.7	<1.0	<1.5	<0.3	<0.1
8/11	5.55	0.22	<0.5	<0.5	<1.0	<2.7	<0.6	<6.7
9/11	3.70	1.6	<0.4	<0.4	<0.8	<1.1	<0.7	<2.6
10/11	5.55	0.11	<0.2	<0.9	<0.5	<0.4	<4.1	<0.2
11/11	5.55	4.58	<0.5	<0.3	<1.0	<1.9	<2.2	<0.1
12/11	5.55	0.81	<0.1	<1.0	<0.8	<0.5	<1.0	<0.4
14/11	5.55	10.47	<0.4	<1.0	<1.0	<3.7	<0.3	<0.4
15/11	2.75	1.25	<0.4	<1.0	<1.0	<3.7	<0.3	<0.4
16/11	5.55	0.12	<0.4	<0.6	<1.0	<1.9	<0.2	<0.4
17/11	3.70	15.47	<0.1	<0.5	<0.4	<0.7	<0.3	<0.3
18/11	2.75	1.1	<0.1	<0.5	<0.4	<0.7	<0.3	<0.3
19/11	5.55	0.98	<0.4	<0.5	<1.0	<2.3	<0.4	<0.1
20/11	5.55	15.74	<0.5	<0.6	<1.0	<1.7	<0.2	<0.1
21/11	2.75	14.02	<0.3	<0.7	<1.0	<4.9	<0.9	<0.8

Our future plans involve the setting up of adequate facilities for handling higher activities and for standardizing procedures for the production and quality control of ^{90}Y. Our next step will be the establishment of protocols for the use of ^{90}Y in the labelling of the DOTATATE and other ligands, as well as the task of providing the nuclear medicine community of Serbia with efficient radiopharmaceuticals for radionuclide therapy in the treatment of cancer diseases.

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ЕЛЕКТРОХЕМИЈСКА СЕПАРАЦИЈА ИТРИЈУМА-90 У ЕЛЕКТРОХЕМИЈСКОМ ^{90}Sr/^{90}Y ГЕНЕРАТОРУ И ЊЕГОВО КОРИШЋЕЊЕ ЗА РАДИООБЕЛЕЖАВАЊЕ ДОТА-КОЊУГОВАНОГ СОМАТОСТАТИНСКОГ АНАЛОГА [DOTA^{0}, Tyr^{3}] OCTREOTATE

Радиофармацеутици базирани на ^{90}Y се све више користе у третману малигних обољења. Да би се изишло у сусрет будућим потребама, развијен је ^{90}Sr/^{90}Y генератор. Добивени ^{90}Y елуат је коришћен за радиообележавање аналога коњугованог DOTA соматостатина [DOTA^{0}, Tyr^{3}] octreotate и припремање [^{90}Y-DOTA^{0}, Tyr^{3}] octreotate (^{90}Y-DOTATATE), пептидним рецепторима у радионуклидној терапији. ^{90}Sr/^{90}Y генератор је базиран на електрохемијском одвајању ^{90}Y од ^{90}Sr у двостепеној електролизи. Систем са три електроде је коришћен за обе електролизе. У свакој електролизи потенцијал радне електроде је одржаван константним, док је pH вредност раствора била подешена на 2,7.

Радионуклидна чистоћа раствора ^{90}Y је анализирана помоћу инстант танкослојне и папирне хроматографије. Пептид (100 g DOTATATE) је обележаван 30 минута на 95 °C. Радиохемијска чистоћа је одређена помоћу HPLC и хроматографским раздвајањем користећи чврсту SepPak C-18 колону.

Добивени резултати потврђују ефикасност како електрохемијског одвајања, тако и методу за контролу квалитета ^{90}Y. Постигнута ефикасност ^{90}Sr/^{90}Y генератора од 96% теоријске вредности је добра основа за будући развој овог генератора. Обележавање DOTATATE са ^{90}Y је такође било високо ефикасно јер је било мање од 1% слободног Y^{3+} у раствору након обележавања ^{90}Y-DOTATATE.

Кључне речи: радионуклидна терапија, ^{90}Y, ^{90}Sr/^{90}Y генератор, радиообележавање, ^{90}Y-DOTATATE