Physical and chemical processes on the $^{212}$Pb radionuclide production for nuclear medicine

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Abstract. An automated $^{212}$Pb radionuclide generator with $^{228}$Th as a parent isotope has been designed. The generator operation principle is based on transport by an airflow of gaseous $^{220}$Rn radionuclide emanating from DOWEX ion exchange resin containing $^{228}$Th into a helix-shaped collector vessel where post-decay $^{212}$Pb is collected and deposited on the collector walls. After a 72-hour operation cycle of the generator, sampling of $^{212}$Pb in the form of solution in 0.1M HCl is executed with approximately 30% yield of $^{212}$Pb. The generator is remotely controlled by a PC-based automatic system. The generator is reloaded once in a few years. The generator is intended for medicobiological and radiochemical investigations in the field of developing antineoplastic drugs of targeted delivery.

1. Introduction

The development of Kohler and Milstein, the future Nobel laureates (1984), of methods for creating monoclonal antibodies opened a new era in biology and medicine [1]. A promising method for diagnosis and treatment of cancer began to be developed on its basis – immunotherapy (or targeted delivery). Artificially created antibodies for certain markers of cancer cells have a specific ability of directed delivery to malignant cells the attached drugs. Such drugs, or therapeutic agents, can be realized by radionuclides, which radiation during its decay can lead to the cell death. In addition to the radioimmunotherapy, it is possible to develop radiopharmaceuticals based on synthetic peptides, such as, for example, octreotide and its modifications [2,3].

Radionuclide therapy with $\alpha$-particle emitters is a promising tool in cancer therapy with $^{211}$At, $^{212}$Bi, $^{213}$Bi and $^{212}$Pb ($in\ vivo$ generator of $^{213}$Bi) as the most promising radionuclides [4]. $\alpha$-particles are highly cytotoxic, namely, it has been shown in vitro that a single $\alpha$-particle traversal of a cell nucleus has a 20–40% probability of killing the cell [5-7].

$^{212}$Pb is of particular concern, since it is a $\beta$-emitter, but its daughter radionuclides $^{212}$Bi and $^{212}$Po undergo $\alpha$-decay, whereby $^{212}$Pb is to be considered as an $in\ vivo$ $\alpha$-particle generator [8]. $^{212}$Pb is a member of decay chain of the parent $^{228}$Th and can be produced by generators.

$^{233}$U is produced by the neutron irradiation of $^{232}$Th, but its production invariably produces small amounts of $^{232}$U as an impurity, because of parasitic (n,2n) reactions on $^{233}$U itself, or on protactinium-
233, or on $^{232}$Th. The amount of $^{232}$U in the accumulated $^{233}$U increases with increasing neutron flux density and time of thorium irradiation and depends on the neutron spectrum in the reactor. After recirculation of the irradiated mixed oxide fuel (Th, U)O$_2$, the amount of $^{232}$U in $^{233}$U can reach 0.08-0.1%. Further, the $\alpha$-decay of $^{233}$U occurs with a probability of almost 100% with $^{228}$Th formation. $^{228}$Th decay chain is presented on figure 1 (scheme from [9]), one of its daughter nuclide is $^{212}$Pb.

For efficient therapeutic use of $^{212}$Pb/$^{212}$Bi 10 GBq should be readily available at the treatment site [10]. The current generator principle for producing $^{212}$Pb/$^{212}$Bi involves elution of a $^{224}$Ra-loaded cation-exchanger column with HCl or HI [11]. If the $^{224}$Ra–based generator could accommodate radioactivity levels of 10–20 GBq, generator replacement would be needed every 3–6 d. Such frequent generator replacement would be expensive and inconvenient, due to the high-energy $\gamma$-rays emitted from the decay of $^{208}$Tl. If the longer-lived $^{228}$Th was used as the primary source instead of $^{224}$Ra, replacements would only be necessary every 2–4 yr. Thus, a significant reduction in production and transportation costs, and reduction in the radiation dose to the workers involved, could be achieved.

Previous efforts to construct $^{228}$Th-based generators have failed to achieve therapeutic levels of radioactivity due to radiolytic damage of the parent nuclide materials [12,13]. Elimination of this obstacle was described in paper [10], where destructive radiolytic effect was reduced due to procuring low radioactivity-to-mass ratio by special source compartment construction. Namely, dry air was passed through a number of thin source frames with $[^{228}\text{Th}][\text{Ba(C}_{18}\text{H}_{5}\text{O}_{2})]$, carrying emanated $^{220}$Rn out into a radon collector, where radon gas was rapidly extracted into the organic solvent at temperatures below -71°C and solidified. At the end of a collection period, the required decay product $^{212}$Pb could be recovered.

Other scheme for producing $^{212}$Pb and $^{212}$Bi [14] was proposed. The technology is based on two generators operating in tandem: $^{228}$Th/$^{212}$Pb and $^{212}$Pb/$^{212}$Bi. The first one is based on separation from an initial solution containing thorium isotopes the gaseous $^{220}$Rn. After conditioning, the $^{212}$Pb solution from the $^{228}$Th/$^{212}$Pb generator was used to charge a column, which functioned as a $^{212}$Pb/$^{212}$Bi generator, with a cation exchanger.
In this paper a novel $^{228}$Th-based generator for the $^{212}$Pb production for nuclear medicine investigations is proposed. It is based on the principle of collecting $^{212}$Pb, daughter nuclide of $^{220}$Rn emanating from $^{228}$Th-containing ion-exchange resin.

2. Materials and methods

2.1. Production of ion exchange resin with $^{228}$Th
The starting material in the generator was powdered $^{228}$Th-containing ion-exchange resin. The resin was produced by adding DOWEX ion-exchange resin to the solution containing a mixture of $^{228}$Th, $^{229}$Th, $^{232}$Th radionuclides and their daughter products. The isotope composition of such solution extracted from $^{233}$U of long-term holding (about 50 years) was as follows: $^{229}$Th – 6.81%; $^{230}$Th $\cong$ 0.08%; $^{228}$Th – traces; $^{232}$Th – 93.11%. 

20 ml of the solution of the mixture of $^{228}$Th, $^{229}$Th radionuclides and their daughter products in 8M HNO$_3$ were mixed with 5-6 ml of DOWEX-1 anion-exchange resin making use of the thorium ability to bind tightly with the functional group of the anion-exchange resin. After 1-hour holding, practically all thorium is sorbed on the resin. Then the solution was decanted, and wet resin was dried up.

According to the values of the constants of formation of thorium anion nitrate complexes [15] in the environment of 8M HNO$_3$, all thorium is in the form of anion complexes Th(NO$_3$)$_5$$^-$ (2%), Th(NO$_3$)$_6^{2-}$ (98%) which replace chloride-ion (nitrate-ion) on the DOWEX-1 resin. When dried, thorium anion nitrate complexes, similarly to chloride ions, remain bound with ammonium groups on the resin which permits subsequent use of this dry resin as a "radon generator".

This $^{228}$Th-containing resin was produced some time ago, so specific activity namely at the time of the generator testing (July of 2017) was approximately 1.2 MBq/g. The works were conducted with the total activity values of about 7 MBq (i.e. 5 g of resin).

2.2. Generator principle of operation
The layout diagram of the $^{212}$Pb generator based on the distinction feature of the $^{228}$Th decay chain consists of two interconnected module loops (see figure 2), namely:

- an "air loop" consisting of a $^{220}$Rn source (thorium reactor – TR), an air pump – MP1 and a $^{212}$Pb collector vessel – HC;
- a "fluid loop" containing vessels for $^{212}$Pb rinsing and after-rinse collection of the solution, a fluid pump – MP2 and the collector.

Such modular layout makes it possible to use different TRs and collectors independently of one another. Ion-exchange resin with the $^{228}$Th isotope was located in a special vessel referred to as a thorium reactor (figure 3). A membrane pump continuously pumped air through the system during the accumulation cycle. The air passed through the reactor and carried away gaseous $^{220}$Rn emanating from $^{226}$Ra into the helix-shaped collector vessel. The $^{220}$Rn decay results in the formation of $^{212}$Pb which deposited on the collector surface and when accumulation ceased it was flushed with 0.1M solution of hydrochloric acid. Owing to such separation of the solid phase with the parent nuclide and the gaseous phase with $^{220}$Rn, a probability of long-lived parent isotopes getting into the final preparation is eliminated, thereby ensuring high radionuclide purity of the preparation and permitting to avoid operations of its purification. Elimination of long-lived parent radionuclides was confirmed by $\gamma$-spectrometric measurements.
To ensure effective deposition of lead on the collector walls, firstly, a saturated steam condition was maintained in the system by providing the system with an air humidifier (AH) containing 0.1M solution of hydrochloric acid, and secondly, a condition of essential excess of the collector volume over parasitic volumes (those of the thorium reactor and communications) was satisfied.

All the elements of the installation were connected among themselves with silicone tubes and all the connections were made with leak-tight joints.

2.3. Thorium reactor

The thorium reactor (see figure 3, all sizes are given in mm) was formed by welding metal elements to form a cylinder-shaped container, with two openings for air inlet and outlet. All elements, except a rubber sealing disc, were made of circonium because of its high chemical resistance.

On the one hollow cylinder (1) face an opening was made, the other side cut off; inside this structure a glassful (3) was placed for immersion in it \(^{228}\text{Th}\)-containing ion-exchange resin. Further, from the side of the cut face, the construction was covered with a cover (2); the tightness was ensured by sealing with radiation-resistant rubber (6). In order to prevent the entrainment of solids from the reactor, Petryanov filters (7) were placed at the inlet and outlet, which were attached to the sides of the glass with special support disks (4).

Figure 2. Process flowsheet of the generator. TR — thorium reactor, MP1-MP2 — membrane pumps, HC — helical collector, AH — air humidifier, DG — differential pressure gauge, F1-F2 — gas filters, V1-V2 — solenoid valves, P1-P2 — vessels for chemical agents.
2.4. $^{212}$Pb collector vessel

A helix-shaped collector vessel is intended for collecting the $^{212}$Pb target radionuclide. It is made as a coiled thin fluorinated ethylene propylene (FEP) tube, wrapping around a hollow metal drum. The tube is 30 m long with the inner diameter of 2 mm, providing the 94 ml total volume of the collector. Radionuclide $^{212}$Pb formed on a decay of $^{220}$Rn passing through the collector with an air flow is deposited on its walls. FEP has been chosen because of its convenient chemical and physical properties, mainly, high chemical resistance and low wettability. The latter circumstance has favored washing-down of the deposited $^{212}$Pb.

In the 0.1M HCl medium, according to constants [16], Pb$^{2+}$ is present in the solution as PbCl$^+$ (60%), Pb$^{2+}$ (20%) and PbCl$_2$ (20%), which ensures its rinsing from the collector walls. In view of a high value of the solubility product of PbCl$_2$, the formation of insoluble compound in the presence of 0.1M Cl$^-$ may take place only with the Pb$^{2+}$ content (Pb$^{2+}$)$>1\cdot10^{-3}$M which is by 7 orders of magnitude larger than that being formed in the generator under discussion.

Washing-down of $^{212}$Pb from the collector surface is made by pumping the 0.1M solution of hydrochloric acid, HCl, of the total volume of 10 ml through the helix using a membrane pump, connected separately and in parallel with the first pump pumping air under working conditions.

To ensure minimum fluid losses, helix mounting conditions (helix slope angle, winding density) were very carefully calculated in order to avoid the formation of areas where liquid might get accumulated. It ensured a uniform ascend of the helix along the cylinder surface without sudden discontinuities and artificial waterlocks.

An air humidifier containing about 5 ml of 0.1M diluted hydrochloric acid, HCl, was mounted in front of the helix-shaped collector. In the course of a complete generator working cycle, the humidifier evaporated liquids in the volume of up to 2 ml which allowed the saturated vapor condition to be
sustained and a thin liquid film to be formed on the inner surface of the collector. The latter circumstance has favored an increase of the deposited \(^{212}\text{Pb}\).

Radionuclides \(^{212}\text{Pb}\) and \(^{212}\text{Bi}\) which are produced resulting from \(^{220}\text{Rn}\) decay are deposited on the helix walls, but increased deposition of \(^{212}\text{Pb}\) in view of a liquid film of 0.1M HCl on the walls of the FEP tube used as a collector may be attributed to an affinity of the \(\text{Pb}^{2+}\) formed to aqueous chlorine-containing solution due to its providing for the formation of chloride complexes [16] in addition to the non-volatile nature of \(\text{Pb}^{2+}\) under the normal conditions employed.

2.5. Generator performances and radioactivity measurements

The generator is remotely controlled by a PC-based automatic system. The air flow rate is measured with a flow rate meter (Microbridge Airflow Sensors). Experimental capabilities of the pump prevented gradual variation of the pumping rate, \(Q\), in a wide range, therefore, two \(Q\) values, 270 ml/min and 420 ml/min, were specified. The generator service time is arbitrary, till a hardware fault.

After the accumulation cycle had been finished the pump switched off, and the valves were swapped so that the collector vessel got connected to the rinsing loop. Solution of 0.1M HCl was pumped through the collector tube followed by sampling of a 0.5 ml specimen and taking measurements of the activity for further determination of the activity in the final preparation.

The activity of the radionuclides were determined by the integrals of the photo-peaks of the 239, 583 and 727 keV \(\gamma\)-lines from decays of \(^{212}\text{Pb}\), \(^{208}\text{Tl}\) and \(^{212}\text{Bi}\), respectively, measured with a Ge-semiconductor detector coupled to a multi-channel analyzer (Ortec).

3. Results

3.1. Experiments on generator operation

The 3-day operation of the generator produced the total value of \(^{212}\text{Pb}\) activity of 2.01 MBq with the \(^{228}\text{Th}\) activity of 7.05 MBq (as for July’3 of 2017) and the air flow rates of 414 ml/min totally in the humidifier and the helix-shaped collector. As was experimentally proven, a further increase of the accumulation time, i.e., to 5 days, did not result in an increase of the produced isotope amount.

On reducing the flow rate down to 273 ml/min the activity became 1.73 MBq. Thus, an increase in the flow rate from 270 ml/min to 420 ml/min ensured nearly 15% gain in yield of the isotope. Thus, it is possible to drive at a conclusion that the \(^{212}\text{Pb}\) collection efficiency is at least about 40%.

3.2. Extraction of \(^{212}\text{Pb}\)

After having been pumped through the helix-shaped collector and air humidifier, the solution was supplied into a vial for the product with nearly 1 ml of the rinsing solution remaining in the helix. Pumping during 12 minutes was carried out by the membrane pump; subsequent pump operation gave no decrease of the fluid loss in the helix. The vial with the product is dismounted for further \(^{212}\text{Pb}\) use both for direct application and for the production of alpha-emitting \(^{212}\text{Bi}\). The specific activity of the final preparation is about 200 kBq/ml for the 10-ml volume of eluent and 1-ml volume of losses.

Radiometric measurements of the collector have proven that about 30% of the isotope remain on the walls of the tube. It can be related to the \(^{212}\text{Pb}^{2+}\) sorption on carboxyl groups of the FEP surface. Furthermore, in the case under consideration, an increase or decrease of the acid concentration produced no noticeable effect on the amount of the lead washed-down from the tube which can testify to spatial inaccessibility of the surface-connected cation, \(^{212}\text{Pb}^{2+}\), for the dynamically incoming acid. The total generator efficiency with considering this circumstance achieves, therefore, approximately 30%.

4. Discussion

4.1. Generator performance and prospectives
The collection efficiency increase following air flow rate increase can be explained by growth of resin particles total surface area, contacting with air flow, which provides to carry radon away from reactor volume more effective. The presence of a fluidized bed is an ideal case.

Thus, it is possible to increase the total efficiency by optimal configuration and modernization of the thorium reactor. Aside from the creation of the fluidized bed, cassette design of radon source could be realized, where $^{228}$Th-containing resin could be distributed in a thin (1-2 mm) layer. Investigations with such a reactor type would allow to study humidity impact to radon emanation from the resin. It is also prospectively to investigate the use of different materials in collector vessel, in particular, for study lead deposit mechanism on its walls.

Despite the relative low $^{212}$Pb production efficiency, the proposed design has several advantages. Closed circuit provides lead collection at room temperature, which fundamentally improves an operation process of the generator. Besides, $^{228}$Th-containing resin production is expected to be more technologically and simpler than $^{228}$Th[Ba(C$_{18}$H$_{35}$O$_{2}$)]. Current levels of specific activity (up to 200 kBq/ml) can be used for in vitro experiments, as well as for preclinical trials within certain limits (for example, see [17,18]). For wide $^{212}$Pb-generator use in preclinical trials thorium reactor is assumed to be filled with new $^{228}$Th-containing ion-exchange resin followed by significant specific activity increasing. Simple and cheap generator design provides continuous $^{212}$Pb production for the investigations with synthesis of radio conjugates and its in vivo and in vitro studies.

5. Conclusions
The generator was designed for experimental works aimed at the synthesis of radiopharmaceuticals and in vitro and in vivo trials of the synthesized radiopharmaceuticals; for this reason, the attained activity reaches the level of 2 MBq, and it could be easily significantly increased by resin renewal. The question of applicability of the suggested process for clinical practice which would require an increase of the product activity up to 1 GBq demands further investigations.

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