



A ^{212}Pb generator based on a ^{228}Th source

Sindre Hassfjell

Department of Chemistry, Nuclear Chemistry Section, University of Oslo, POB 1033, Blindern, N-0315 Oslo, Norway

Received 29 August 2000; received in revised form 23 October 2000; accepted 31 October 2000

Abstract

A two-compartment ^{212}Pb generator has been constructed and characterized physically and chemically. It is based on transport by airflow of gaseous ^{220}Rn emanating from thin layers of [^{228}Th]barium stearate. ^{220}Rn is collected in a glass bubbler by extraction into an organic solvent and solidified at temperatures below -72°C . Tracer studies show that the decay product ^{212}Pb can be recovered with approximately 70% yield. It is suggested that this generator design could accommodate therapeutic levels of $^{212}\text{Pb}/^{228}\text{Th}$. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: ^{212}Pb generator; ^{212}Bi ; ^{228}Th ; α -particles; Radionuclide therapy

1. Introduction

Radionuclide therapy with α -particle emitters is emerging as a promising tool in cancer therapy with ^{211}At , ^{212}Bi , ^{213}Bi and ^{212}Pb (in vivo generation of ^{212}Bi) as the most promising radionuclide candidates (Vaidyanathan and Zalutsky, 1996; McDevitt et al., 1998; Sgouros et al., 1999; Fritzberg, 1998). Numerous data from in vitro and in vivo experiments conclude that α -particles are highly cytotoxic, more so than alternative treatment strategies (Kozak et al., 1986; Huneke et al., 1992; Behr et al., 1999; Nikula et al., 1999). It has been shown in vitro that a single α -particle traversal of a cell nucleus has a 20–40% probability of killing the cell (Søyland and Hassfjell, 2000; Hei et al., 1997). ^{211}At needs a cyclotron for production while ^{212}Pb , ^{212}Bi and ^{213}Bi are members of decay chains of the long-lived parents ^{232}Th and ^{235}U , respectively, and can therefore be produced by generators.

For efficient therapeutic use of $^{212}\text{Pb}/^{212}\text{Bi}$ $\sim 10\text{ GBq}$ (0.27 Ci) should be readily available at the treatment site. The current generator principle for producing $^{212}\text{Pb}/^{212}\text{Bi}$ involves elution of a ^{224}Ra -loaded cation-exchanger column with HCl or HI (Atcher et al., 1988). Such generators at source strengths up to 1.0 GBq

(27 mCi) have until recently been available from the University of Chicago. If the ^{224}Ra ($t_{1/2} = 3.6\text{ d}$)-based generator could accommodate radioactivity levels of 10–20 GBq (0.27–0.54 Ci), which still remains to be seen, generator replacement would be needed every 3–6 d. Such frequent generator replacement would be expensive and inconvenient, due to the high-energy γ -rays emitted from the decay of ^{208}Tl . If the longer-lived ^{228}Th ($t_{1/2} = 1.9\text{ yr}$) 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 accomplished. Furthermore, making generators from freshly separated ^{228}Th could diminish the problem with high-energy γ -radiation during shipping.

Previous efforts to construct $^{212}\text{Pb}/^{212}\text{Bi}$ generators based on ^{228}Th have failed to accommodate therapeutic levels of radioactivity due to radiolytic damage of the generator materials (Zucchini and Friedman, 1982; Hassfjell and Hoff, 1994). In this paper a novel ^{228}Th -based generator prototype for the production of $^{212}\text{Pb}/^{212}\text{Bi}$ for clinical applications, is proposed. It is based on the principle of collecting ^{220}Rn emanating from ^{228}Th -doped barium stearate, and accommodates a low radioactivity-to-mass ratio to avoid the destructive effects of radiolysis. The generator performance has been characterized through tracer studies.

E-mail address: s.p.hassfjell@kjemi.uio.no (S. Hassfjell).

2. Materials and methods

2.1. Production of [^{228}Th] barium stearate

All chemicals and solvents were of PA grade. The [^{228}Th]barium stearate was made as previously described by Hassfjell and Hoff (1994) and outlined by Hursh and Lovaas (1967). Briefly, approximately 0.1 MBq (3 μCi) of $^{228}\text{Th}(\text{NO}_3)_4$ (surplus from the last generator) was dissolved in dilute HCl (pH=4) together with a small amount of $^{232}\text{Th}(\text{NO}_3)_4$ (Merck) as carrier and 10.8 g of $\text{BaCl}_2 \cdot 2\text{H}_2\text{O}$ (Merck). This solution was slowly added to a stirred and heated solution of 28.3 g (5% molar excess) sodium stearate [$\text{NaC}_{18}\text{H}_{35}\text{O}_2$] (Merck) in methanol. The Ba(II) and Th(IV) precipitated completely as [$^{232/228}\text{Th}$]barium stearate, from now on referred to as [^{228}Th]barium stearate for convenience. After a few minutes of additional stirring, the precipitate was filtered off and washed thoroughly with methanol, and finally dried over silica gel.

2.2. The generator principle

The generator consists of two major compartments, the ^{228}Th source compartment (Figs. 1B–C, 2) and the radon collector (Fig. 1A). The [^{228}Th]barium stearate is stacked in thin layers (Fig. 2) close together inside a cage (Fig. 1B–C). Dry air is passed continuously through the cage, carrying emanated ^{220}Rn out of the cage and into a glass bubbler (Fig. 1A). The bubbler is filled with an organic solvent at temperatures below -71°C . By breaking up the airflow into numerous small bubbles the radon gas is rapidly extracted into the organic solvent and solidified. In this manner the required decay product ^{212}Pb is entrapped in the bubbler. At the end of a collection period, ^{212}Pb can be recovered in a HNO_3 solution.

2.3. The ^{228}Th source compartment

The ^{228}Th compartment was made by welding 5 mm thick aluminum plates into a rhombic cage open at two ends. The cage has inner dimensions $12.6\text{ cm} \times 13.4\text{ cm} \times 26.0\text{ cm}$, of which the two open ends have the inner dimensions $12.6\text{ cm} \times 13.4\text{ cm}$. Funnels made of perspex were mounted at the two open ends. The funnels were shaped as approximately half spheres with square ends to fit the cage openings, and small tubes of 1 cm diameter as air inlet and outlets. To avoid air leaks, both funnels were tightly fitted to the cage openings with a system of aluminum frames, O-rings and screws. One of these openings was designed for fast disconnection of the funnel to allow for rapid radioactivity measurements of the cage interiors after generator runs.

One of the funnels was designated the air inlet of the generator construction, and was connected to dried

pressurized air by PVC tubing fitted to the opening. The tube of this inlet funnel was elongated into the interior of the funnel. At the inside of the funnel the tube was perforated with small holes of approximately 1 mm diameter. Additionally, this funnel had a perspex plate glued onto the inside close to the square end and vertically to the airflow with similar perforations. These perforated devices were added to the inlet funnel to ensure homogeneous airflow throughout the volume of the cage. The air was supplied from a standard laboratory bench outlet of pressurized air, and dried by bubbling it through methanol at temperatures $<-72^\circ\text{C}$. Before entering the generator the dried air was passed through several meters of PVC tubing to allow for temperature equilibration with the surroundings. The designated outlet funnel was connected tightly through a short piece of PVC tubing to the second compartment of the construction, the radon collector.

Inside the cage 26 parallel tracks were made in each of the two opposite planes of $26.0\text{ cm} \times 13.4\text{ cm}$ and parallel to the air stream. These tracks were 2 mm deep, 4.5 mm wide, and were spaced 0.5–1.0 mm apart. They were made to fit source frames containing the [^{228}Th]barium stearate parallel and close together along the direction of airflow.

The source frame construction is shown in Fig. 2. It was designed and constructed as follows: The [^{228}Th]barium stearate was confined inside a square rubber frame with $11\text{ cm} \times 11\text{ cm}$ inner dimensions, 5 mm width and 2 mm thickness. One $12\text{ cm} \times 12\text{ cm}$ sheet of PTFE filter paper with $0.45\text{ }\mu\text{m}$ pore size (Sartorius, Goettingen) was placed on each side of the rubber frame, thereby enclosing the [^{228}Th]barium stearate. This unit was then confined tightly inside two square steel frames with screws. Each steel frame had outer dimensions of $13\text{ cm} \times 13\text{ cm}$ with 1.0 cm frame width and 2 mm thickness. The outside of each steel frame had a steel mesh of $0.10\text{ mm} \times 0.10\text{ mm}$ with a 0.08 mm thick wire welded onto it, completely covering the inner square.

Each source frame contained approximately 6 g [^{228}Th]barium stearate at a density of 0.25 g/cm^3 . Insufficient source frames were made, to fill all the available tracks in the cage, primarily due to the time and cost of production. Secondly, it was not necessary to fill all the tracks in order to perform tracer studies with the generator. Instead, “dummy frames” of solid perspex plates of the same dimensions as the source frames were made to fill the surplus tracks. These plates were made in two lengths, 13 cm and 26 cm, both having a width of 13 cm and a thickness of 4 mm. The source frames were interchanged with the plates for all possible track positions to establish if there were differences in the emanation yield according to position. When completely filled up with source frames and plates, the free air space inside the cage was restricted to 27 small (0.5–1 mm) parallel slits in the direction of the airflow.

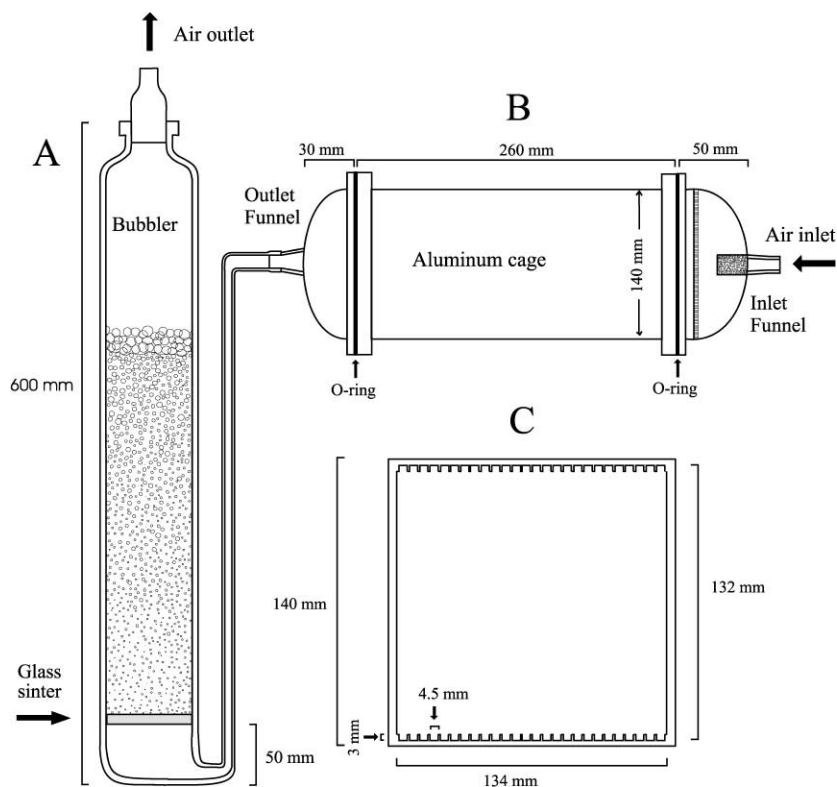


Fig. 1. A drawing of the generator construction. (A): The bubbler where ^{220}Rn is collected. The figure illustrates how the glass sinter disperses the airflow into small bubbles in the extraction solvent. (B): A side view of the aluminum cage and the inlet and outlet funnels. (C): A cross-sectional view of the inside of the aluminum cage, showing the parallel tracks where the source frames were positioned.

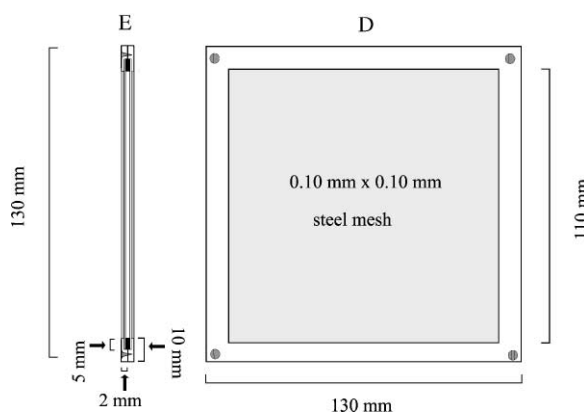


Fig. 2. A drawing of a source frame construction. (D): A cross-sectional view of a source frame showing the steel frame, the steel mesh and the screws in each corner. (E): A side view of a source frame depicting the ^{228}Th barium stearate layer (white) inside the source frame, the rubber frame (black), the filter paper layer (thin lines), the steel mesh (gray) and the screws connecting the steel frames.

2.4. The radon collector

The second compartment was a bubbler, termed the radon collector (Fig. 1A). The bubbler was made from a 60 cm long Pyrex glass tube with 9 cm inner diameter,

and fitted with a sintered glass filter of pore size 2 in the designated bottom end. Underneath the glass sinter the tube was fused tightly to a glass tube of 1 cm inner diameter. The latter tube was bent parallel to (and along the whole length of) the larger glass tube and at the top

it was bent horizontally and connected with a short piece of PVC tubing to the tube of the outlet funnel. The outlet of the bubbler at the top of the larger glass tube was tightly connected to PVC tubing of 1 cm inner diameter. The end of this PVC tubing was either connected to a charcoal filter and a fume hood outlet, or just to a fume hood outlet. Extraction solutions for ^{220}Rn were normal hexane ($n\text{-C}_6\text{H}_{14}$), methanol (CH_3OH), or a mixture thereof, sometimes also with trace amounts of water present. To maintain the acquired collection temperature ($< -71^\circ\text{C}$) the radon collector was immersed into a large reservoir of methanol and dry ice (CO_2 (s)) (-78°C).

2.5. Generator performance experiments and radio-activity measurements

To operate the generator no manipulation was necessary other than turning on the airflow. The generator was tested in continuous operation for periods T up to 2 d at different airflows Q in several experiments. The airflow was calculated by measuring the speed of soap films in a custom-made volume-calibrated glass tube. Pressure differences (ΔP_j) over the different compartments (j) were measured at the PVC tube connections with small (2 mm inner diameter) mercury-filled PVC tubes connected through short three-way glass connectors. Q was varied in the range 1–4 dl/s and ΔP over 70–6000 Pa. The identity, yields and distribution of the radionuclides were determined by the integrals of the photo-peaks of the 239, 583 and 727 keV γ -lines from decays of ^{212}Pb , ^{208}Tl and ^{212}Bi , respectively, measured with a Ge semiconductor detector (EG&Ortec) coupled to a multi-channel analyzer (Canberra). The ratio between the integrals of the 239 keV γ -line from the ^{212}Pb decay and the 241 keV γ -line from the ^{224}Ra decay were also used to quantify ^{212}Pb depletion in the [^{228}Th]barium stearate. During and after operation the outer surfaces of all generator parts were examined for ^{220}Rn leaks with an α -particle-sensitive proportional counter (Canberra).

The effect of varying Q and P on the ^{220}Rn emanation ability was investigated with the ^{228}Th source compartment both connected to and disconnected from the radon collector. Losses of ^{212}Pb to the interior of the aluminum cage and to the inlet and the outlet funnels were also measured. When the radon collector was disconnected, $\Delta P_{\text{source comp}}$ was varied by extra lengths of narrow PVC tubing connected to the outlet funnel. The importance of solvent extraction vs. cryogenic entrapment of ^{220}Rn in the radon collector was investigated by varying the collection temperature, both with and without solvent being present. The distribution of collected ^{212}Pb between the glass surface of the bubbler and the solvent was investigated as a function of the polarity of the solvent. The recovery efficiency was

investigated with different molarity of HNO_3 by solvent extraction and by washing the glass surface of the empty bubbler.

To determine the distribution of ^{212}Pb after a full experimental run the radioactivity of the source frames, the inlet and outlet funnels, the aluminum cage, the plates, the PVC tubing, the charcoal filter, the bubbler, the solvent and the recovered yields of ^{212}Pb were measured. These measurements were decay corrected for the time period between the end of the collection and the measurement. The fractions of the total amount of ^{212}Pb for the actual experimental conditions were calculated by: $k = C_{212-\text{Pb}} / (C_{228-\text{Th}}(1 - e^{-\ln 2 \times T / 10.6h}))$ where $C_{212-\text{Pb}}$ is the count rate of the actual ^{212}Pb source, $C_{228-\text{Th}}$ is the count rate of ^{212}Pb in the source frames in radioactive equilibrium with ^{228}Th and T is the time in hours from onset to the end of the generator run. In Section 3, the k values are presented at the conditions of radioactive equilibrium for the actual generator run, i.e., $T = \infty$.

To correct for differences in geometry, the recovered yield of ^{212}Pb was measured after evaporating the HNO_3 solution containing the ^{212}Pb , to dryness on a glass surface with shape and area similar to those of the source frames. Attenuation of the γ -rays through the source frames and the plates was also measured and corrected for. The distributions of ^{212}Pb in the radon collector were indirectly determined by relating the relative measurements of ^{212}Pb before and after HNO_3 extraction/wash with the measurement of the recovered ^{212}Pb fraction. The yields are presented as a means of 2–3 parallels with standard deviation of the mean from accumulated uncertainties given in parentheses.

3. Results

3.1. Generator performance experiments

The main results of the generator performance experiments may be summarized as follows: Close to optimum yield with this generator prototype was achievable with an airflow of 2.0 dl/s and with 0.8 l hexane in the bubbler. Under these conditions, the emanation yield was 78.5%. If all tracks were filled with source frames 2.5% would be lost as back deposits on source frames and outlet funnel, and 3% would escape the bubbler, leaving 73% of the ^{212}Pb in the radon collector. Finally, the recovered yield would be approximately 70%. No leakage of ^{220}Rn from the generator system during operation could be detected, and no ^{228}Th ($< 10^{-6}$ Bq/Bq) was observed in the collected ^{212}Pb .

The maximum emanation yield of ^{220}Rn was approximately 80% and decreased with increasing ΔP_{total} (for $\Delta P_{\text{total}} > 2.7$ kPa), as expected. For $\Delta P_{\text{total}} < 2.7$ kPa the percentages of total ^{212}Pb left on the source frames were

22.5 (± 0.7)% at $Q = 1.0$ dl/s and 20.5 (± 0.7)% at $Q = 4.0$ dl/s. This slight reduction with increasing Q is most likely explained by decreased back deposits. No difference in emanation effect was observed between source frames close to the cage walls and those in the center of the cage. Deposition of ^{212}Pb onto the plates and the outlet funnel was observed. At $Q = 1.0$ dl/s and $\Delta P_{\text{total}} < 0.07$ kPa deposits on the plates located between the source frames (plates B) and the plates located after the source frames in the direction of the airflow (plates A) were 1.6 (± 0.3)% and 3.5 (± 0.5)%, respectively. At $Q = 2.0$ dl/s and $\Delta P_{\text{total}} = 6.00$ kPa the deposits were found to be 1.5 (± 0.3)% on plates B and 2.2 (± 0.4)% on plates A. The plate deposition decreased with increasing Q and decreasing ΔP_{total} , and the lowest values found were 0.5 (± 0.2)% on plates B and 1.1 (± 0.3)% on plates A at $Q = 4.0$ dl/s and $\Delta P_{\text{total}} = 0.13$ kPa. ^{212}Pb deposits on plates were only detected on the plates facing the same slit as at least one source frame. Only 0.4 (± 0.1)% ^{212}Pb deposits were found on the outlet funnel, showing no significant variation with Q and ΔP_{total} . ^{212}Pb deposits neither were detected on the aluminum cage nor on the inlet funnel ($< 0.05\%$). These observations show that ^{220}Rn did not flow or diffuse backwards to any significant extent. Based on the amount of plate deposits the average back deposits between the source frames was estimated for the case of a complete generator with 26 cm long source frames filling all available tracks.

At large airflows more ^{212}Pb escaped the bubbler, thereby decreasing the amount of collected ^{212}Pb . The cross-sectional area of the bubbler limits its capacity for airflow. When the airflow reaches this limit the $\Delta P_{\text{bubbler}}$ increases dramatically and an excessive elevation of the bubbler solvent surface is evident soon after. Experiments carried out at 2.0 dl/s with 2.0 l (30 cm height) of solvent, allowed approximately 1% of the ^{212}Pb to escape the radon collector. This flow rate was below the capacity limit and resulted in a modest elevation of the solvent surface by approximately 1 cm and a $\Delta P_{\text{bubbler}}$ of 3.6 kPa. At the same airflow the escaped fraction increased to 3% when the solvent volume was reduced to 0.8 l (12 cm height). However, the extra loss was outweighed by increased ^{220}Rn emanation and decreased plate deposits due to reduced $\Delta P_{\text{bubbler}}$ (2.7 kPa). $\Delta P_{\text{source comp}}$ (< 0.07 kPa) was insignificant at these airflow rates.

Hexane and methanol were chosen as solvents because they have freezing points lower than -78°C , low viscosity and relatively high extraction coefficients (D) for radon (Weigel, 1978). Hexane exhibited the highest extraction yields, in agreement with the literature D values (Weigel, 1978), and was therefore the preferred solvent. The extraction efficiency increases with decreasing temperature, but only slightly less extraction efficiency was noted at -50°C vs. temperatures below

-72°C . However, with a dry bubbler at temperatures $< -72^\circ\text{C}$, the collected yield of ^{212}Pb dropped substantially to approximately 10%.

3.2. Recovery of collected ^{212}Pb

The ^{212}Pb was deposited both in the organic solvent and on the glass surface of the bubbler. The distribution between these two media was highly dependent on solvent composition. With pure hexane 98–99% of the collected ^{212}Pb was deposited on the glass surface of the bubbler, mainly in the glass sinter. In a few minutes, $> 98\%$ of the glass-deposited ^{212}Pb could be washed off with 2×50 ml of 1 M HNO_3 . With 0.1 M HNO_3 the extraction efficiency was lowered to approximately 90%, and with > 1 M HNO_3 the yield was close to 100%. With increasing polarity of the solvent increasing amounts of ^{212}Pb were found in the solvent. With an emulsion of a few ml water in a 2.0 l solution of 95% hexane and 5% methanol, as much as 95% of the collected ^{212}Pb was found in the solvent, mainly in the water phase. At these amounts of water neither ice formation nor clogging of the glass sinter was observed during collection. Extraction of ^{212}Pb from the organic solvent was possible with dilute nitric acid. Approximately 94% of the ^{212}Pb in 1.0 l hexane could be extracted with 100 ml 0.1 M HNO_3 . Extraction with dilute nitric acid while evaporating off the hexane resulted in 100% recovery. Recovery of ^{212}Pb from the solvent was more labor intensive and time consuming than washing off glass-deposited ^{212}Pb . Furthermore, a yellow residue was found after evaporating the HNO_3 solvent extract to dryness.

4. Discussion

4.1. Generator performance and design criteria

To minimize the generator size and optimize the ^{212}Pb yields, goals were set to avoid turbulence and to keep the free volume in the cage and in the outlet funnel as small as possible. Turbulent flow can create eddies resulting in increased transportation time of the ^{220}Rn with subsequent reduction in the collected yield of ^{212}Pb . Similarly, the lesser the free volume, the shorter the transportation time for the ^{220}Rn . The results clearly show that rapid transportation of ^{220}Rn from the source frames to the bubbler is essential to diminish loss. The air volumes in the cage (between frames/plates) and the outlet funnel were approximately 1.0 and 0.5 l, respectively. The amount of ^{212}Pb formed during the transportation time to the bubbler was at least twice the amount found deposited on the plates and on the outlet funnel. This shows that the ^{212}Pb formed in the gas phase was also carried to some extent with the

airflow. Furthermore, the low amounts found on the outlet funnel indicate that deposits increase with surface area, as expected. The small reduction in loss achieved by increasing the airflow beyond 2.0 dl/s is outweighed by the need for a larger bubbler, which would make recovery of the ^{212}Pb more troublesome.

To minimize the diffusion time of ^{220}Rn out of the [^{228}Th]barium stearate the layers were kept thin. According to the literature one could expect emanation yields close to 100% for a diffusion distance of 1 mm (Wahl and Daniels, 1958; Gregory and Moorbath, 1951), much higher than the 80% limit found in this study. This discrepancy may be explained by the extra 2 mm thickness of the source frames in addition to the 2 mm thick [^{228}Th]barium stearate layer. Thus, there was a 1 mm broad band of stagnant or more slowly moving air that the ^{220}Rn needed to pass to enter the fast airflow in the center of the slits. Increased back deposits would therefore be anticipated. This anticipation was substantiated by experiments where a source frame was exposed to airflow perpendicular to the [^{228}Th]barium stearate layer, resulting in an increase in the emanation yield to 88%. Thus, improving the frame design and reducing the inter source frame distance would probably both increase the ^{212}Pb yields and make the generator conveniently smaller.

These experiments showed that solvent extraction from gas phase is an efficient way of collecting ^{220}Rn in this generator design, more important than cryogenic entrapment. A finer glass sinter in the bubbler would mean formation of smaller bubbles and possibly more rapid extraction of ^{220}Rn into the liquid phase. A bubbler with glass sinter 4 was tested, but abandoned as it resulted in a very high flow resistance that would have lowered the emanation yield significantly, as well as increased the probability for leakage.

The finding of the collected ^{212}Pb primarily in a polar environment indicates that organic lead compounds were not frequently formed. Formation of $^{212}\text{Pb}^{2+}$ may be attributed to redox reactions with the O_2 gas, with trace levels of water, or perhaps with the glass surface of the bubbler. The results show that pure hexane is a good extraction solvent resulting in high collected yields of ^{220}Rn and allows for easy recovery of ^{212}Pb from the glass surface of the bubbler. Only HNO_3 solutions were investigated for ^{212}Pb recovery; however, other solutions, e.g., HCl , might be better suited, depending on the ^{212}Pb application. By means of ion-exchangers efficient conjugation to carrier molecules with the recovered ^{212}Pb or ^{212}Bi would be possible (Atcher et al., 1988; Korkisch, 1989).

The generator operation was only investigated with tracer levels of radioactivity due to the limited availability and high cost of ^{228}Th . However, an estimate of its potential as a therapeutically useful generator construction has been made. In a previous generator

construct (Hassfjell and Hoff, 1994) it was found that radiolytic damage to the [^{228}Th]barium stearate in 50 MBq/0.09 g packages resulted in decreased emanation efficiency. In later experiments stable ^{220}Rn emanation was found for at least 2 years from [^{228}Th]barium stearate packages with 12 MBq/0.09 g. The limit for stable operation may lie somewhere between these two levels of specific radioactivity. By filling all available tracks with full-length source frames (26 cm long) each source frame would contain approximately 13 g [^{228}Th]barium stearate. By multiplying with the 26 frame positions in the cage, the generator could accommodate a total of 340 g [^{228}Th]barium stearate. When multiplying this number by the radioactivity-to-mass ratio of 133 MBq/g, which allows for stable ^{220}Rn emanation, the generator could accommodate approximately 45 GBq (1.2 Ci) of ^{228}Th . This estimate assumes that the specific radioactivity level found for stable operation can be extrapolated to higher radioactivity levels. With $k=0.70$, such a generator could deliver approximately 25 GBq (0.67 Ci) of ^{212}Pb each day, which would probably be satisfactory for efficient therapeutic use of this radionuclide.

The proposed generator should be viewed more as a prototype showing a useful operation principle for a ^{228}Th -based generator than as a completed generator construction for clinical use. Improvements are therefore suggested. The carrier gas could be run in a closed circuit by a pump, with two bubblers mounted in parallel guided by a remote-controlled switchyard. Furthermore, for easy source frame replacement the cage could be made as a separate unit with vacuum gate valves at both ends. Such improvements would enhance safety, significantly reduce the bulk volume of carrier gas, and allow for continuous collection of ^{212}Pb .

The high radioactivity levels needed for clinical applications necessitate extensive shielding, installation of the generator system in a gas-tight hot cell, and preferably automated production. The simplicity of operation of this generator construct, especially during collection, facilitates automation.

Acknowledgements

The creativity and excellent skills of engineers Manuel Neira and Rune Bjørnstøl and chief engineer Bjørn Dalbakk at the mechanical workshop, and the glass blowers Thore Palving and Terje Hansen, all at the Chemistry Department, the University of Oslo, are greatly appreciated. Without them this project could not have been carried out. The advice during the generator construction and testing, the invaluable discussions and careful reading of this manuscript, all by Christina Søyland Ph.D., are dearly appreciated. This project was funded by the Norwegian Research Council.

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