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OPTIMATION OF RHENIUM-OXO-GLUCONATE SYNTHESIS AS A PRECURSOR FOR SYNTHESIS OF RHENIUM (V)-TETROFOSMIN

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ABSTRACT

OPTIMATION OF RHENIUM-OXO-GLUCONATE SYNTHESIS AS A PRECURSOR FOR SYNTHESIS OF RHENIUM(V)-TETROFOSMIN. Rhenium-188 or Rhenium-186 labeled compounds have been widely used as therapeutic radiopharmaceutical for cancer. Most of rhenium (Re) radiopharmaceuticals involve Re with oxidation state of 5, one of which is Re-dioxo-tetrofosmin. Complexes of Re(V)-ligand can be generated from Re(V)-oxo-gluconate through ligand exchange process. Optimation of rhenium-oxo-gluconate synthesis was carried out by varying mole ratio of gluconate to perrhenate and reaction time, in which ^{188}Re was added to perrhenate solution as radiotracer. Stability study of Re-oxo-gluconate at room temperature and elevating temperature was carried out by measuring its radiochemical purity within several hours. Radiochemical purity was analysed using 2 systems of paper chromatography with Whatman-3 paper as solid phase, and acetone and saline as mobile phases, respectively. Highest yield was obtained using mole ratio of 6000, i.e 87.43% (SD=3.01%), and the optimum reaction time was 1 hour. Storage at room temperature and elevating temperature resulted in the decrease of radiochemical purity of 10% (within 3 hrs) and 30% (within 1 hour), respectively. Re-dioxo-tetrofosmin which was used as a model of Re(V)-ligand, was obtained through ligand exchange reaction with the yield of 92.1%. The result showed that Re-oxo-gluconate can be successfully synthesized in high yield but low stability.

Keywords: Re-oxo-gluconate, Rhenium-188, Synthesis, Radiochemical purity, Tetrofosmin

ABSTRAK

OPTIMASI SINTESIS RENIUM-OKSO-GLUKONAT SEBAGAI PREKURSOR UNTUK SINTESIS RENIUM (V)-TETROFOSMIN. Senyawa bertanda Renium-188 atau Renium-186 sudah digunakan secara luas sebagai radiofarmaka terapi kanker. Sebagian besar radiofarmaka bertanda renium (Re) melibatkan Re dengan bilangan oksidasi 5, antara lain Re-diokso-tetrofosmin. Reaksi kompleksasi Re(V)-ligan dapat diturunkan dari Re(V)-okso-glukonat melalui proses pertukaran ligan. Telah dilakukan optimasi sintesis renium-okso-glukonat dengan memvariasikan perbandingan mol glukonat terhadap perrenat dan memvariasikan waktu reaksi, dengan menambahkan ^{188}Re kedalam larutan perrenat sebagai perunut. Studi kestabilan Re-okso-glukonat pada suhu kamar dan suhu yang dinaikkan dilakukan dengan mengukur kemurnian radiokimianya selama beberapa jam. Kemurnian radiokimia Re-okso-glukonat dianalisis dengan 2 sistem kromatografi menggunakan kertas Whatman-3 sebagai fasa diam, dengan fasa gerak berturut-turut aseton dan salin (larutan natrium klorida 0,9%). Perbandingan mol 6000 : 1 menghasilkan senyawa kompleks dengan tingkat kemurnian radiokimia tertinggi yaitu 87,43% (SD=3,01%), serta waktu reaksi optimum pada 1 jam. Penyimpanan senyawa kompleks pada suhu kamar dan suhu yang dinaikkan menyebabkan penurunan kemurnian radiokimia berturut-turut sebanyak 10% (dalam waktu 3 jam) dan 30% (dalam waktu 1 jam). Re-diokso-tetrofosmin yang digunakan sebagai model dari senyawa kompleks Re(V)-ligan, berhasil diperoleh melalui reaksi pertukaran ligan dengan kemurnian radiokimia 92,1%. Dari percobaan ini disimpulkan bahwa Re-okso-glukonat telah berhasil disintesis dengan rendemen yang tinggi namun kestabilannya rendah.

Kata kunci: Re-okso-glukonat, Renium-188, Sintesis, Kemurnian radiokimia, Tetrofosmin

INTRODUCTION

Radiopharmaceuticals for detecting heart disease and tumor are commonly used in nuclear medicine in Indonesia, two of them are technetium-99m sestamibi (^{99m}Tc-MIBI) and ^{99m}Tc-tetrofosmin [1-7]. In-vivo stability of ^{99m}Tc radiopharmaceuticals can be predicted through biodistribution during the use, but ideally it has been studied previously. Radiochemical stability of ^{99m}Tc-tetrofosmin can be studied rather than chemical stability, because it can only be obtained in a very small concentration which making it impossible to be analysed using chemical instruments. Molecular structure of Re-tetrofosmin is assumed to be the same as that of Tc-tetrofosmin, so Re-tetrofosmin can be used as a model to study in-vitro stability of Tc-tetrofosmin since Re-tetrofosmin can be synthesized in micro scale without using radioactive rhenium [8-9].

Rhenium and technetium have similar chemical properties since they belong to VIIB group in periodic table known as transition metals, so they have similarity especially in terms of the ability to form complex compounds with ligands. Non radioactive rhenium is available in nature rather than technetium, so that chemical properties and stability of rhenium tetrofosmin can be studied using chemical instruments. Therefore rhenium can be used as a model to study and predict the behavior of technetium radiopharmaceutical in-vivo [8-9].

Rhenium-ligand complexes have been widely used as therapeutic radiopharmaceuticals for cancer, accordingly literatures related with the development of rhenium radiopharmaceuticals can be easily obtained [10-15].

Rhenium and technetium in the reduced state are relatively unstable and easily reoxidised by oxygen in the air or solution, so the interference of oxygen has to be minimized. Reducing agent such as stannous chloride is required in higher amounts and the addition of antioxidant such as ascorbic acid is sometimes required. As of technetium, rhenium has oxidation state of 0, +1, +2, +4, +6 and +7, from which the most stable state is 7 and the most widely used is 5. Molecular structure of Re-tetrofosmin is assumed to be the same as that of Tc-tetrofosmin (Figure 1), which is called Re-dioxo-tetrofosmin since two oxygen atoms are attached to Re [16-17].

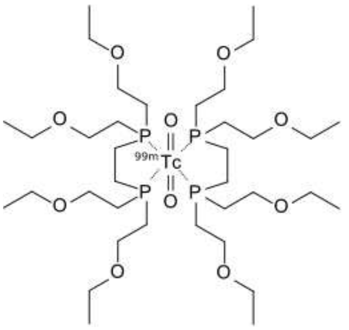

Figure 1. Molecular structure of ^{99m}Tc-dioxo-tetrofosmin.

Rhenium has higher potential of oxidation than technetium, making it more difficult to reduce its oxidation state proceed with the formation of Rhenium complex compound. To accomplish the reaction, stannous chloride as reducing agent is required in higher amount and the reaction is carried out in an atmosphere of nitrogen or argon to avoid the presence of oxygen which can oxidize Sn (2+) and reoxidize Re (5+) to Re (7+). Complexation of Tc(V)-dioxo- tetrofosmin or trans-diokso Tc (V) diphosphine is usually slow and unstable but can be accelerated and stabilised by the addition of co-ligand that serves as transchelator such as sodium D-gluconate, then the process of ligand exchange (gluconate will be replaced by tetrofosmin) can be accelerated by increasing the concentration of tetrofosmin or heating [16-19].

Protocol for synthesizing Tc-tetrofosmin is available in several journals but it can not be applied to Re-tetrofosmin, so for this purpose it needs another approach. Re-oxo-gluconate is commonly used as a precursor for synthesising Rhenium complex compound with oxidation state of 5. Since oxidation state of Re in the compound of Tc-tetrofosmin is also 5 so the reaction of Re with tetrofosmin can be carried out using Re-oxo-gluconate pathway. For this purpose radioactive rhenium either ^{186}Re or ^{188}Re can be added as a tracer [16-19].

Study and preparation of carrier free ^{188}Re-oxo-gluconate was reported with radiochemical purity of over 90% but the stability is low [18-19]. The term carrier means an isotope (usually non-radioactive) that is added to the radioactive atoms to facilitate the reaction, for example non radioactive ^{185}Re that is added to ^{188}Re in the labeling process or synthesis of radiolabeled compound.

As in Tc-tetrofosmin complex compounds, prior to formation of Re-tetrofosmin previously oxidation state of Re has to be reduced from 7 to 5 through the establishment of Re-oxo-gluconate as an intermediate complex/chelate which takes 1-2 hours at pH 5. To accomplish the reaction, stannous chloride as reducing agent is required in higher amount and the reaction is carried out in an atmosphere of nitrogen or argon to avoid the presence of oxygen which can oxidize Sn (2+) and reoxidize Re (5+) to Re (7+) as can be seen in the equation (1) and (2) [16-22].

$$[ReO_4]^- + Sn^{+2} + \text{Na-gluc.} \rightarrow [ReO(\text{gluc.})_2]^- + Sn^{+4} \quad \text{..} \quad (1)$$

$$[ReO(\text{gluc.})_2]^- + \text{tetrofosm.} \rightarrow [ReO_2\,(\text{tetrofosm.})_2]^+ + \text{Na-gluc.} \quad \text{..............} \quad (2)$$

The yield of synthesis is represented by percentage of radiochemical purity or radiolabeling yield which is used as test parameter. The radiochemical purity of both Re-oxo-gluconate and Re-dioxo-tetrofosmin was analysed using paper chromatography, thin layer chromatography and Sep-Pak C18 column [23-25].

Based on literature searching, the research regarding carrier added $^{186/188}$Re-tetrofosmin synthesis nor the study of physico-chemical characteristics of non radioactive rhenium tetrofosmin has not been done anywhere, so approach has been made through the route of carrier-added ^{188}Re-oxo-gluconate synthesis which also has not been reported anywhere. To synthesize carrier-added ^{188}Re-oxo-gluconate, optimation of several reaction parameters need to be conducted.

This experiment was carried out to obtain optimum condition in synthesizing rhenium-oxo-gluconate in micro scale to be used as precursor for rhenium-dioxo-tetrofosmin synthesis. Non radioactive rhenium-dioxo-tetrofosmin will then be used to study in-vitro stability of ^{99m}Tc-tetrofosmin in blood serum. The aim of this study is to support the development of technetium-99m tetrofosmin radiopharmaceutical in PTRR-BATAN in the last 3 years.

EXPERIMENTAL METHOD

Material and Equipment

The material used are tetrofosmin (ABX), sodium D-gluconate (Sigma-Aldrich), stannous chloride dihydrate (Sigma-Aldrich), glacial acetic acid (Merck), sodium acetate (Merck), nitrogen gas (high purity, medical grade) , ammonium perrhenate (Merck), a solution of perrhenate ^{188}Re obtained from ^{188}W / ^{188}Re generator (PTRR-Batan), acetone, methylene chloride, physiological NaCl solution (saline) and other materials.

The equipment used are chromatography chamber supported with Whatman-3 paper strips (Merck), TLC-SG strips (Merck), gamma management system (DPC), TLC scanner (Bioscan), glassware and other equipment.

Methods

Synthesis method used was referred to the synthesis method of rhenium gluconate which serves as precursors to the formation of complex compounds based on rhenium (V) oxo ligand [16-19]. Synthesis of rhenium tetrofosmin was carried out by transchelation process in which gluconate was replaced or substituted by tetrofosmin. Re-gluconate synthesis was performed by reacting sodium gluconate 0.5 M (in 0.2 M sodium acetate solution) with 0.04 mg of potassium perrhenate (solution of 1 mg/mL in water) added with ^{188}Re of 0,1 mCi and 0.1 mL of solution $SnCl_2$ dihydrate (solution of 20 mg/mL in 10% acetic acid) for 1-2 hours [7]. The reaction was carried out in a sealed container with a nitrogen gas atmosphere for 15 minutes and then the atmosphere containing N_2 gas was maintained by covering the container with a balloon that was developed with N_2 gas as can be seen in Figure 2.

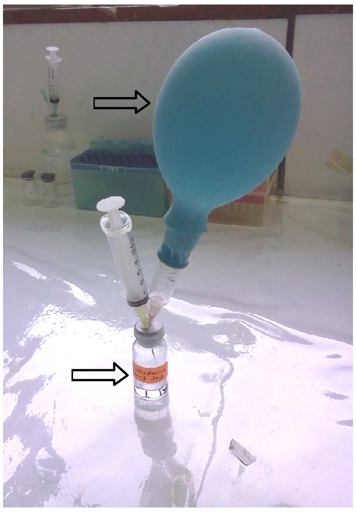

Figure 2. Ilustration of synthesis process of Re-oxogluconate

Re-oxogluconate formation was identified by paper chromatography using Whatman-3 paper as stationary phase eluted with acetone (system 1) and saline (system 2). In system 1 Re-oxogluconate and Re oxide (rhenium colloid) retained at the base (Rf 0) while perrhenate eluted to the front at Rf 1. In system 2 Re-oxogluconate and perrhenate (free perrhenate) eluted to the front at Rf 0.8 while ReO_2 colloids retained at the base at Rf 0 [16-19].

Radioactivity of the product in the chromatograms was measured by Gamma Management System (GMS) and TLC scanner (Bioscan). Radiochemical purity of the product was analysed using paper chromatography detected by radiochromatography scanner with in-line gamma detector (Bioscan), alternatively, Gamma Management System (GMS) was also used as a routine application when the radioactivity was getting low (less than 1 mCi). Optimation of the synthesis was done by varying the amount of gluconate and reaction time, whereas the stability of the complex compound was observed within several hours both with and without heating.

Transchelation process or formation of Re-dioxo tetrofosmin was carried out by adding 0.3 mL of Re-oxogluconate into 0.1 mL of an aqueous solution containing 1 mg of tetrofosmin, heating at 95°C for 15 minutes and allowed to stand for 30 minutes.

The yield was measured by thin-layer chromatography using TLC-SG strips as stationary phase and mixture of acetone-dichloromethane (35: 65) as mobile phase, in which Re oxide colloid retained at the base at Rf 0 while perrhenate or free Re eluted at Rf 1 and Re-dioxo tetrofosmin eluted to the middle of the strips at Rf 0.5.

RESULTS AND DISCUSSION

Synthesis of ^{188}Re-oxo-gluconate using no-carrier-added ^{188}Re (not containing non-radioactive Re) resulted in a low yield of ^{188}Re-oxo gluconate of 68.5%, but the yield increased to 92.4% after using twice amount of stannous chloride. It conformed the result according to Noll et al. [18-19] that the yield is around 80-90%. Radiochemical purity of the product was analysed using paper chromatography detected by radiochromatography scanner with in-line gamma detector, and the performance of radiochromatogram was as in Figure 3.

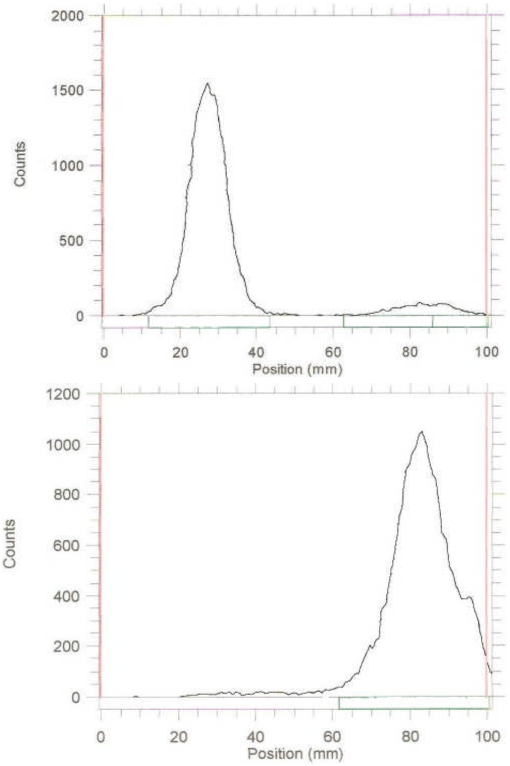

Figure 3. Peak of ^{188}Re-oxo gluconate in chromatography system with acetone as eluant (top) and peak of ^{188}Re-oxo gluconate in system with saline as eluant (bottom)

The reaction pH required for the complexation of Re-oxo gluconate as well as Re-dioxo tetrofosmin was 4-5 in contrast to the alkaline pH required for the complexation of ^{99m}Tc-tetrofosmin. Increasing the amount of reducing agent to a certain extent can improve the yield of Re-oxo gluconate and reduced the perrhenate as impurity.

In the formation of ^{188}Re-gluconate with addition of carrier or non-radioactive perrhenate resulted a low radiochemical purity product of 39.3% which perrhenate and Re colloid impurity of 15% and 45.7% respectively. The addition of non-radioactive perrhenate to the reaction mixture lowered radiochemical purity, this is due to the insufficiency of ligand in this case was gluconate which resulted the hydrolysis of reduced perrhenate into Re oxides colloid and reoxidation small part of reduced perrhenate to perrhenate. Addition of sodium gluconate 2.5 times folded to the reaction increased radiochemical purity significantly from 39.3% to 87.43% (SD = 3.01%, n = 3) in which the impurity is perrhenate (12.6%). This indicates that most of perrhenate reduced to Re (V) forming complexes of Re (V) oxo gluconate.

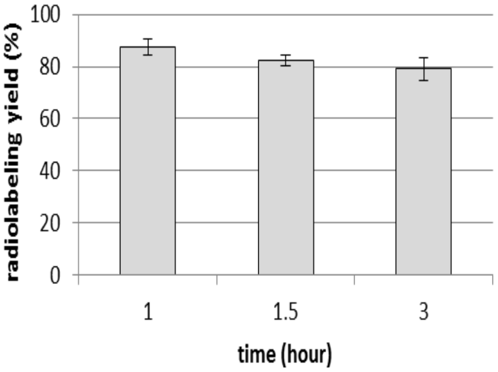

Figure 4. The stability of Re-oxogluconate observed within 3 hours.

In the same experiment in which the reaction time was varied at 1, 1.5 and 3 hours, resulting in radiochemical purity of Re-oxogluconate with no significant difference between reaction time of 1 and 1.5 hours, i.e 82.28% (SD=2), but using reaction time of 3 hours the radiochemical purity decreased slightly to 79.14% (SD=4.35%), as can be seen in Figure 4.

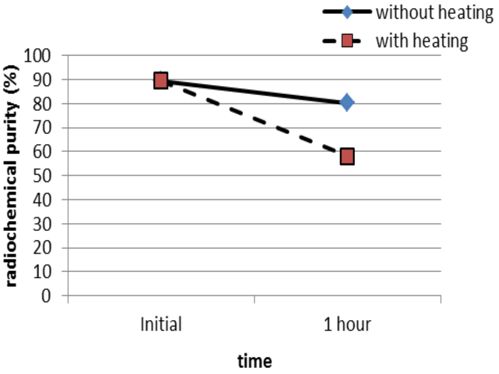

Figure 5. Stability decrease of Re-oxogluconate with and without heating.

The slight decline in the radiolabeling yield of Re-gluconate indicated that the addition of reaction time did not lead to an increase in the yield but even lowered the stability of complex. This suggests that Re-gluconate compound has relatively low stability, so that Re (V) was reoxidized back to Re (VII). Thus the optimal reaction time for the synthesis of Re-gluconate is 1 hour.

Instability of Re-oxogluconate was also observed when the reaction mixture was heated at 95°C for 15 minutes and then incubated up to 1 hour, in which the radiochemical purity decreased from 89.26% to 59.5% (Figure 5). This was caused by disruption of the stability of the complex by heat so that a small portion of Re (V) was reoxidized into Re (VII) or perrhenate.

The same experiment using carrier added ^{186}Re (perrhenate Re-186 solution which contained non-radioactive Re by an amount equal to the previous experiment) resulted in a high yield of Re-oxogluconate i.e 96.1% radiochemical purity with 3.9% of perrhenate impurity. The use of carrier-added ^{186}Re which contained

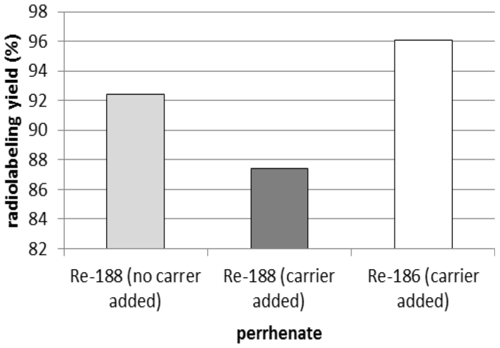

Figure 6. Radiolabeling yield of Re-oxogluconate using various rhenium.

15 mg/ ml of non radioactive Re in a volume of 0.7 ml provided higher yield compare with that using ^{188}Re which total volume was 1.6 ml, this was due to the more concentrated reaction mixture which cause sufficient contact between reactant molecules resulting in a greater probability of reaction.

The experiment using no carrier-added ^{188}Re showed slightly lower yield compared with that of ^{186}Re, because of moderate volume of reaction mixture (Figure 6).

Re-oxogluconate obtained from the optimised condition of reaction was used to synthesise Re-dioxo tetrofosmin, resulted in 92.4% (SD=2.06, n=3) yield of Re-dioxo tetrofosmin. Tetrofosmin required for the reaction was in excess with mole ratio of 2000 times to the mole of potassium perrhenate used. The process was carried out by heating the reaction mixture in 15 minutes followed by incubating for 30 minutes in room temperature.

CONCLUSION

Formation of Re-oxogluconate resulted with high yield in 1 hour, but the stability is low. The amount of sodium D-gluconate as ligand should be in excess due to the slow reaction. Due to the low stability of Re-oxogluconate, it is unlikely to characterize it using chemical instruments. For the next experiment it is suggested to add an antioxidant such as ascorbic acid to increase the stability of Re-oxogluconate.

Re-dioxotetrofosmin can be synthesised in high yield from transchelation process of Re-oxogluconate, in which the amount of tetrofosmin as the main ligand has to be in excess. It can be concluded that Re-oxogluconate synthesis pathway can be used to synthesize Re-dioxo-tetrofosmin.

It is suggested to use this method in the development of other Re(V)-ligand complexes for therapeutic radiopharmaceuticals.

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