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Optimization of Natural Rhenium Irradiation Time to Produce Compositional Radiopharmaceutical

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ABSTRACT

Introduction: Previously, ^{186}Re and ^{188}Re radioisotopes have been produced through appropriate activities, and each of them has been used for therapeutic applications. The ^{186}Re and ^{188}Re have unique properties, which make them proper for the treatment of tumors in different sizes. The long-range ^{188}Re, is suitable for the annihilation of large tumors. In contrast, the short-range ^{186}Re is desirable for the destruction of small tumors. The aim of this study was to find the suitable time for rhenium irradiation in order to simultaneously produce radionuclides with both appropriate and identical activities.

Material and Methods: To reach ^{186}Re and ^{188}Re with appropriate activities to produce compositional radiopharmaceutical, we have investigated natural rhenium irradiation at different times to produce ^{186}Re and ^{188}Re simultaneously with appropriate and identical activities to reach compositional radiopharmaceutical. In this regard, the simultaneous production of ^{186}Re and ^{188}Re with appropriate activities were investigated analytically through natural rhenium irradiation in a reactor. The irradiation was assessed at different time intervals in order to reach appropriate activities for compositional radiopharmaceuticals.

Results: On the basis of the findings, ^{186}Re and ^{188}Re could be produced simultaneously with suitable and almost equal activities with irradiating natural rhenium for 4 days and considering 1 day for cooling. Moreover, the obtained results of this study revealed that the generated impurities were negligible.

Conclusion: The optimization of natural rhenium irradiation time can help the simultaneous production of ^{186}Re and ^{188}Re with appropriate activities for compositional radiopharmaceuticals.

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Introduction

So far, most of the preclinical and clinical investigations have been made to utilize β-producing radionuclides, such as ^{131}I, ^{90}Y, ^{153}Sm, ^{186}Re and ^{188}Re [1-3].

Among commonly used beta emitters in medical treatment, two radioisotopes of rhenium, namely ^{186}Re and ^{188}Re, have important because apart from the therapeutic uses provided by their beta particles emission, gamma radiation emitted by them allows imaging during treatment. Table 1 indicates the properties of ^{186}Re and ^{188}Re [4, 5].

Table 1. Some properties of ^{186}Re and ^{188}Re

Isotope	Half-life (h)	Max β^- energy (MeV)	Range in tissue (mm)	γ-Energy (MeV)
^{186}Re	90	1.07 (70.99%)	5	137 (9%)
^{188}Re	17	2.1 (71.12%)	11	155 (15%)

The ^{188}Re has high energy β^- particles as well as long penetration range to tissues. Considering the fact that these features can lead to high dose delivery to large tumors, it is expected that ^{188}Re shows more efficiency in the treatment of large tumors. The ^{186}Re with a lower energy β^- particles and short penetration range transfer most of its energy to small tumors, and accordingly ^{186}Re is appropriate to destroy small regions.

Regarding the fact that the radioisotope ^{186}Re is more durable due to its longer half-life, it will take more time to convey a similar dosage like that of ^{188}Re. Accordingly, a powerful strategy to destroy all tumors in patients with tumors of different sizes is to deliver the desired dose of a mixture of radionuclides or cocktail. [6, 7]. This distinct and advantageous way can lead to the most efficient results.

It should be mentioned that the separate use of these radioisotopes cannot be effective in the complete destruction of large tumors since the radiation emission of a radionuclide with a shorter half-life, including ^{188}Re, is short. On the other hand, the application of long-life radionuclides, such as ^{186}Re, leads to some difficulties for patients since it takes time to start irradiating and damaging tumors. The combination of radionuclides with complementary properties, specially

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^{186}Re and ^{188}Re, upon the termination of short-lived radionuclide ^{188}Re radiation, leads to the continuation of irradiation to larger tumors with the radiation emission of long-lived radionuclide ^{186}Re. Therefore, the production of both these radioisotopes with appropriate activities is an important step to reach combined radiopharmaceuticals.

Natural rhenium contains two isotopes of ^{185}Re and ^{187}Re. The ^{185}Re is a stable radioisotope of rhenium and ^{187}Re is also a stable radioisotope of rhenium with a long half-life (nearly 4.33×10^{10} years). The abundances of ^{185}Re and ^{187}Re in natural rhenium are 37.4% and 62.6%, respectively. As can be seen in Figure 1, ^{185}Re and ^{187}Re have large cross sections for neutrons ($\sigma = 112.05$ and 76.46 barns, respectively) [8].

Therefore, the irradiation of natural rhenium produces a mixture of ^{186}Re and ^{188}Re [9].

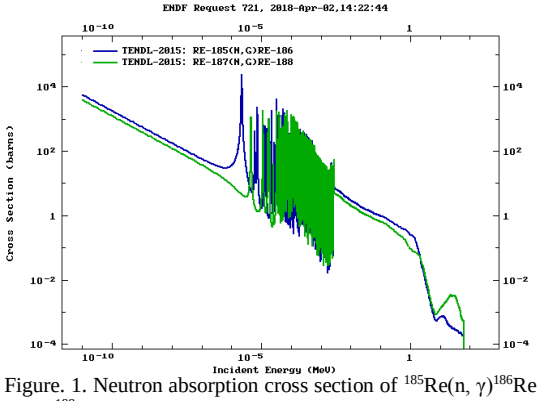


Figure. 1. Neutron absorption cross section of ^{185}Re(n, γ)^{186}Re and ^{187}Re(n, γ)^{188}Re reactions

Previous studies produced these medically applicable radioisotopes in reactors with different ratios due to various parameters, such as irradiation time, cooling time, and neutron flux amount [10-16] . Some of these studies spent even a 4-day cooling to produce a mixture of ^{186}Re and ^{188}Re. It should be noted that the amount of ^{188}Re is negligible after 4 days due to its half-life and the major part of the mixture must be ^{186}R [15]. On the other hand, some other studies suggested a 7-day irradiation and a 1-day cooling [13, 14].

Another important parameter in the production of medically applicable radionuclide is the high purity of radionuclides. Undesirable radionuclides can be produced through the activation of pollutions and impurities in the target radionuclide or by the side reactions to the target material. Moreover, the process followed by irradiation can lead to some chemical impurities to the product.

Radioisotopic impurities created by neutron irradiation technique affect its final use for therapeutic applications. The impurities produced by neutron irradiation can lead to high unnecessary doses in therapeutic applications. Short-lived impurities with the half-lives of several days deliver the unnecessary radiation dose to patients [17]. On the other hand, radionuclides with long half-lives are problematic, particularly the waste disposals at hospitals involving many therapeutic activities [18].

The aim of this study was to find the suitable time for rhenium irradiation in order to produce both ^{186}Re and ^{188}Re with simultaneously appropriate and identical activities and small impurities to reach compositional radiopharmaceuticals.

Materials and Methods

As mentioned, the irradiation of natural rhenium can produce both ^{186}Re and ^{188}Re. This means that this strategy leads to the simultaneous production of these two radioisotopes following compositional radiopharmaceuticals.

Figure 2 illustrates the irradiation of natural rhenium, including two isotopes of ^{185}Re and ^{187}Re and related reactions in reactors. As can be seen, capturing neutron by ^{185}Re lead to the production of one main product, namely ^{186}Re, through which ^{186}Os and ^{186}W are produced by its beta disintegration and electron capture, respectively.

About ^{188}Re production chain, with absorbing one neutron by ^{187}Re this radioisotope is produced. As it was mentioned ^{187}Re is originally present in the natural rhenium chemical composition. Also in the reaction chain, the absorption of a neutron by ^{186}Re produces ^{187}Re. Besides that the beta decay of ^{187}W can increase ^{187}Re amount too. All these produced ^{187}Re with absorbing neutron produces ^{188}Re and these reactions will continue.

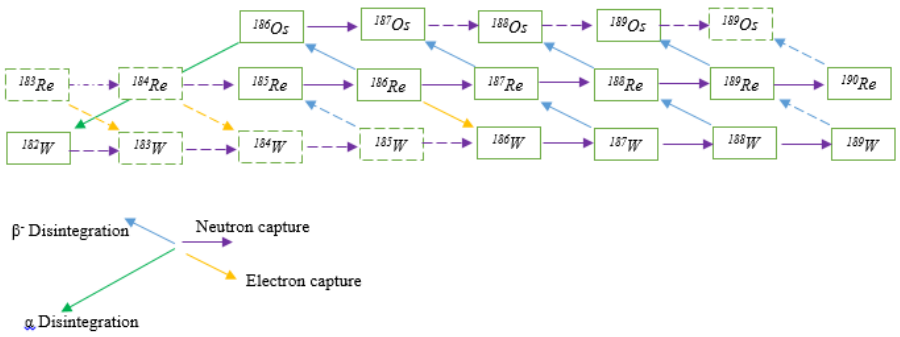


Figure 2. Irradiation of natural rhenium and production of main products and impurities scheme. (To show the general scheme of significant reactions and isotopes in the given calculations, the isotopes with minor importance due to their long half-lives were shown too.. These isotopes were illustrated with dash line squares and their reactions were shown by dash line arrows.)

The analytical calculation of radionuclide activities is an essential part of its production. In every production process, there is a possibility of produced impurities along with the main products. The evaluation of the theoretical results helps us to predict all aspects of production before the experimental production. It should be noted that although the activities of radioisotopes changes with irradiation conditions, the ratio of the produced activities and impurities does not change. Furthermore, with changing irradiating situations like neutron flux, amount of initial matter ,…the optimal time, that is the time to achieve equal amounts of ^{188}Re and ^{186}Re simultaneously, stays unaltered which achieving it is the main purpose of this work. These issues remain stable with the change of irradiation conditions.

The change of nuclide densities as the function of time arises from activation and transmutation can be calculated in the following equation [19]:

$$\frac{dN_i(r,t)}{dt} = \varphi(r,t)\sum_j N_j(r,t)\sigma_{j\to i}(r) + \sum_k N_k(r,t)\lambda_{k\to i}(r) - (1)\varphi(r,t)N_i(r,t$$

Where, $N_i(r,t)$ refers to the number density of nuclide (i) at position (r) and time (t). The $\varphi(r,t)$ denotes total flux at the position of r and time of t, and $\sigma_{n\to m}(r)$ is microscopic cross section to change nuclide (n) into nuclide (m) at the position of r. Moreover, $\lambda_{n\to m}$ signifies decay constant for nuclide (n) changing into nuclide (m). The initial conditions are

$N_i(r,0) = N_{i0}(r)$.

Equation 1 is a set of simultaneous first-order ordinary differential equations, which is homogeneous equation system and can be written into a general matrix (where the spatial variable has been suppressed):

$$\frac{d\mathbf{N}}{dt} = \mathbf{AN}$$

Where, **N** refers to nuclide density vector = $[N_1, N_2, \ldots . N_N]^T$, and A is a transition matrix containing coefficients for decay and transmutation = $\{a_{ij}\}$.

$$a_{ij} = -(\sigma_i^D\varphi + \lambda_i)\delta_{ij} + (\sigma_{j\to i}^F\varphi + \lambda_j c_{j\to i})$$

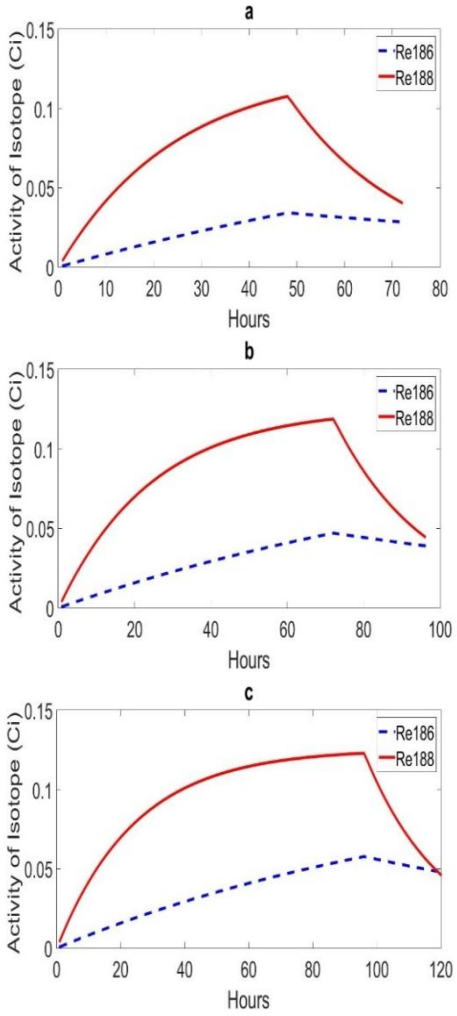
The σ_i^D signifies destruction microscopic cross section of nuclide (i), $\sigma_{j\to i}^F$ refers to production microscopic cross section of nuclide (j) forming nuclide (i), and λ_i is the decay constant of nuclide (i). Moreover, $c_{j\to i}$ is the branching ratio of a decay from nuclide (j) to nuclide (i) and δ_{ij} refers to the Kronecker delta.

The MATLAB 2015a software was used to measure the radionuclides activities, which were produced in the reactor. Finally, $\mathbf{A} = \lambda\mathbf{N}$ equation reached us to activities.

Results

To calculate the activities of radionuclides produced in the production and decay process precisely, the MATLAB program was used in this study. Theoretical methods and computational software were used to estimate the activities of radionuclides at different time intervals of irradiation and also as a function of some parameters, such as neutron fluxes during irradiation time. Furthermore, we can calculate the decay rate of the main radioisotopes and impurities after the irradiation or at any time of the subsequent chemical process. Therefore, the purity of radioisotopes can also be investigated at different time intervals after the irradiation process was performed. These calculations can be useful to estimate radionuclides activity in the experimental process after radioisotopes production.

To reach reasonable and equal activities of rhenium radioisotopes, the activities of ^{186}Re and ^{188}Re were calculated at different time intervals after irradiation. Furthermore, it was considered that the cooling process would take a day to complete. The calculated activities of ^{186}Rhenium and ^{188}Rhenium at different irradiation time intervals are presented in Figure 3.



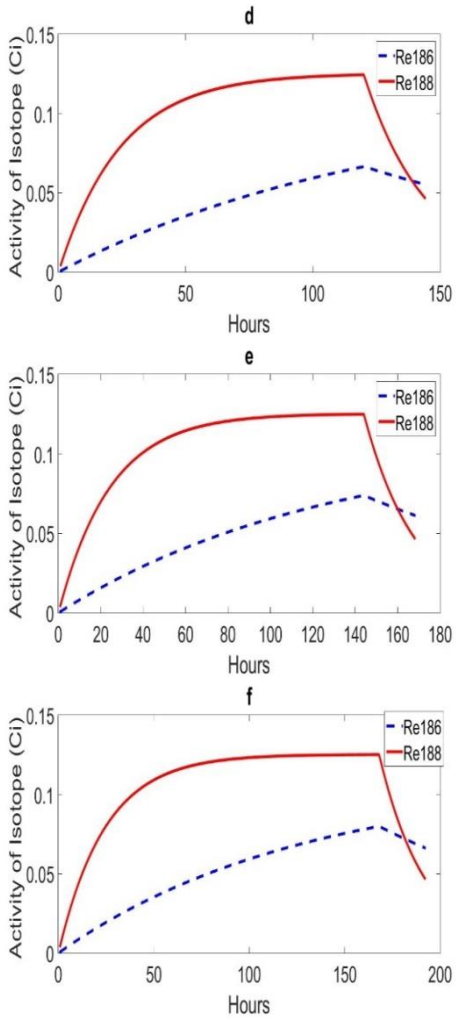


Figure 3. Activity as a function of irradiation time and considering 1 day for cooling a) a 2-day irradiation b) a 3-day irradiation c) a 4-day irradiation d) a 5-day irradiation e) a 6-day irradiation f) a 7-day irradiation

In these calculations, it is considered that 1 mg natural rhenium target was irradiated by thermal neutron flux 3×10^{13} n/(cm^2 s) in the reactor at different irradiation time intervals. As can be seen in Figure 3, the activities of ^{186}Re and ^{188}Re raise in the course of time, meaning that there is a relationship between the time and the activities of ^{186}Re and ^{188}Re. When irradiation time finished, the target was in the cooling process for 24 h during which the activities decreased. As Figure 3 indicates the short-lived ^{188}Re has higher range activity than ^{186}Re during irradiation time. Aside from the shorter half-life, the higher range of ^{188}Re activity is due to the fact that ^{188}Re has been produced from not only by the primary ^{187}Re which was existed in natural rhenium (62%), but also from ^{187}Re that has been generated in the chain started by ^{185}Re.

Table 2 tabulates the values related to the calculation of ^{186}Re and ^{188}Re activities. As can be seen in Table 2, the activities of ^{188}Re and ^{186}Re are so close to each other on a 4-day irradiation with regard to a 1-day cooling.

Radionuclidic Purity

In order to provide precise investigation and high purity, other radionuclides production situation were also investigated in this study. To avoid delivering unnecessary doses to patients, considering the production rate of impurities which might be generated, is a very crucial step in producing radiopharmaceuticals. It is clear that the impurities which might be produced and remained in the irradiated target will stay with main radioisotopes and ultimately exist in producing radiopharmaceutical and causes the delivery of unnecessary doses to the patients.

The exact activities of impurities were calculated and shown in Table 3.

As Table 3 shows, the impurities are so smaller on a 4-day irradiation and a 1-day cooling, compared to a 7-day irradiation and a 1-day cooling. This finding was in line with the obtained results of some other studies.

Table 2. Activities of ^{186}Re and ^{188}Re at the end of different irradiation times and a 1-day cooling

Radionuclide		Irradiation time (Day)					
		2	3	4	5	6	7
^{186}Re	Activity (Ci)	2.839×10^{-2}	3.906×10^{-2}	4.791×10^{-2}	5.525×10^{-2}	6.134×10^{-2}	6.638×10^{-2}
^{188}Re		4.058×10^{-2}	4.473×10^{-2}	4.628×10^{-2}	4.685×10^{-2}	4.706×10^{-2}	4.713×10^{-2}

Table 3. Activities of impurities at the end of different irradiation times and a 1-day cooling

Radionuclide		Irradiation time (Day)					
		2	3	4	5	6	7
^{189}Re	Activity (Ci)	1.613×10^{-7}	2.329×10^{-7}	2.777×10^{-7}	3.036×10^{-7}	3.178×10^{-7}	3.254×10^{-7}
^{187}W		4.574×10^{-8}	1.284×10^{-7}	2.559×10^{-7}	4.248×10^{-7}	6.302×10^{-7}	8.667×10^{-7}
^{187}Re		2.775×10^{-11}	2.774×10^{-11}	2.774×10^{-11}	2.773×10^{-11}	2.772×10^{-11}	2.772×10^{-11}
^{188}W		1.023×10^{-11}	4.458×10^{-11}	1.222×10^{-10}	2.606×10^{-10}	4.753×10^{-10}	7.797×10^{-10}
^{186}Os		5.915×10^{-20}	1.052×10^{-19}	1.599×10^{-19}	2.216×10^{-19}	2.892×10^{-19}	3.616×10^{-19}

Discussion

As Figure 3 shows, (a) and (b) subfigures, ^{186}Re and ^{188}Re neither intersect each other nor reach identical activities. In (d), (e), and (f) subfigures the intersection point of charts are during the cooling process. Accordingly, at the end of cooling time, the produced ^{188}Re and ^{186}Re have different activities again.

Figure 3 illustrates in (c) subfigure approximately at end of the cooling process two charts intersect each other and reach to the almost identical activities, which are useful for compositional radiopharmaceutical.

Previous studies produced these medically applicable radioisotopes in a reactor with different ratios according to various parameters, such as irradiation time, cooling time, and neutron flux amount [10-16]. Some of these studies used 4 days for cooling to produce a mixture of ^{186}Re and ^{188}Re. As was mentioned, after 4 days the amount of ^{188}Re is negligible and the major part of the mixture must be ^{186}Re [15] . A review of the literature revealed that some studies suggested a 7-day irradiation and a 1-day cooling to reach the desired result [13, 14]. It is worth noting that different time intervals for irradiating and cooling natural rhenium in previous studies led to the production of ^{186}Re and a low amount of ^{188}Re. In the present study, the investigation and selection of the appropriate irradiation time lead to the equal activities of ^{188}Re and ^{186}Re.

Generally, the activities of long half-life radioisotopes, such as ^{187}Re (4.33×10^{10} y), ^{188}W (69.8 d), ^{186}Os (2×10^{15} y), can be neglected due to their small range, compared to the main products of ^{188}Re (17h) and ^{186}Re (90h). The two remaining impurities, (i.e. ^{189}Re [24.3 h] and ^{187}W [24 h]) have half-lives near to the investigated main products. However, this issue leads to their production, which was comparatively more than other impurities in the process time. On the other hand, their activities are negligible, compared to those of the main products.

These impurities can be ignored since the activities of ^{189}Re and ^{187}W were in the order of 10^{-7}, which was too small in comparison with the main products (Table 3). However, as can be seen in Table 3, the amount of these impurities will decrease more in the process of radioisotope delivery to the patient after chemical processes.

As mentioned ion the literature, the significant amounts of the impurities lead to high delivery dose in patients, which is considered as polluting influence and separation is essential. In the current study, the obtained results show that the activities of impurities were insignificant and negligible. To produce compositional rhenium radiopharmaceuticals via the irradiation of natural rhenium in the optimized time (a 4-day irradiation and a 1-day cooling), there is no need for separation. Moreover, impurities were not detected even in the gamma spectrum of the irradiated sample.

Conclusion

This study aimed to investigate the simultaneous production of ^{186}Re and ^{188}Re radioisotopes for medical purposes via the irradiation of natural rhenium target. In this regard, a theoretical method was applied at different irradiation intervals (2-7 days along with a 1-day cooling) to reach appropriate activities. The calculations include the activity estimation of all impurities, including both significant and insignificant ones. The former led to higher activities and the latter resulted in a smaller range of activities.

Considering the significant activities, ^{189}Re and ^{187}W had the highest activities, compared to all the investigated impurities with the optimal time of a 4-day irradiation and a 1-day cooling. However, their activities were in a smaller range, compared to those of other studies in which irradiation was performed for 7 days plus a day of cooling. Accordingly, these impurities are negligible compared to our main products. it can then be concluded that the produced impurities in this procedure will not affect the final resultant radiopharmaceuticals and there is no need for the separation process. The evaluation of the results revealed the beneficial power of the investigated theoretical method, which could address all aspects of production in advance.

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