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EXTRACTION CENTRIFUGAL W-188/RE-188 GENERATOR FOR RADIOTHERAPEUTIC APPLICATIONS

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Abstract

^{188}Re extraction generator for medical purposes development results are presented. The main advantage of such generator is the possibility to use as starting material the tungsten oxide of natural isotope composition irradiated in reactor with mean neutron flux ($1.0–1.4\cdot10^{14}$ $n\cdot cm^{-2}\cdot s^{-1}$). The parent (^{188}W) and daughter radionuclides were separated using centrifugal semicounter-current extractor developed at Physical Chemistry and Electrochemistry Institute under RAS (Russian Acedemy of Sciences). In the course of simulated solution experiments, optimal operating conditions were established for ^{188}Re production process. For this purpose, it is proposed to recover ^{188}Re by methylethylketone from alkaline solution (2.5 M KOH + 2.5 M K_2CO_3) containing up to 200 g/l of W element. Methylethylketone is subsequently evaporated to dryness and residue is dissolved in isotonic solution of NaCl. An extraction generator model was built in hot cell; the process developed was then tested on radioactive solutions. The test has shown that the yield is 89% in the average and the radiochemical purity of ^{188}Re solution is ~ 97%. The activity of ^{188}W was less than $1\cdot10^{-3}$ relative to that of ^{188}Re. Activity of other radioisotopes was below $1\cdot10^{-4}$. The content of inorganic impurities in ^{188}Re solution is determined only by the purity of aqueous solutions used for ^{188}Re dissolution. The generator model may be recommended as a basis for creation of commercial prototype of ^{188}Re extraction generator.

Key words: *extraction, generator, methylethylketone, radiopharmaceutical, metastases, preclinical research.*

Nuclear medicine offers arguably the widest prospect for radioactive isotopes' commercial usage. Many radioisotopes including ^{99m}Tc, ^{123}I and others are primarily used for various health conditions diagnostics [1]. A wide scale of research works is now in progress internationally to develop therapeutic radiopharmaceuticals, primarily ones for oncology conditions. ^{188}Re radioisotope should be considered as one of most important and promising isotopes in the field. Radiopharmaceuticals labeled with ^{188}Re, have a therapeutic effect, which significantly reduce (or even completely eliminated) pain from skeletal metastases. Only in Russia tens of thousands of patients is need this treatment and whose treatment will require 300 - 400 Ku ^{188}Re. Skeletal metastatic lesions are detected in more than 60% of patients with breast, lung, prostate, colon, thyroid gland. Traditional methods of bone metastases treatment are external irradiation and amputation of pathological sites of bone. However, because of the high radiation dose to the vital organs at some localization of metastases, external irradiation often cannot be applied. Amputation of the affected parts of the skeleton are also often cannot be implemented because of their location. To solve this problem it is necessary the direct engagement of the radiation dose to the tumor for therapeutic effect with the aim of its reducing or completely destroyed. This can be achieved by using the radiopharmaceutical, which has as a therapeutic agent - a radionuclide with non-penetrating component of radiation (beta-, Auger electrons, characteristic X-rays and low-energy gamma rays) in a chemical form that can selectively accumulate in rapidly growing areas of bone and have less accumulation in normal bone and surrounding soft tissues. In the laboratory FMBC for this purpose have been developed radiopharmaceutical – “Phosphoren, ^{188}Re”. In the Moscow Institute of Rentgenoradiology successfully passed clinical trials of this drug and the results sent to the Ministry of Health of the Russian Federation to obtain permission for medical use. It is routinely obtained as ^{188}W beta decay daughter product. One important property for ^{188}Re as compared to other therapeutic beta emitters (f.i. ^{89}Sr) is its soft (155 keV, 15% yield) decay produced gamma line. This line can be conveniently used as ^{188}Re propagation marker for tissues and organs, thus allowing more accurate therapeutic dose calculation.

^{188}Re centrifugal extraction generator reviewed here is based from technology standpoint on the well-known commercial ^{99m}Tc extraction generator. [4] Said ^{99m}Tc generators typically use Uranium decay produced ^{99}Mo, its specific activity reaching hundreds of kCi (kiloCurie) per gram.

It wouldn't be feasible to produce ^{188}W at this specific activity given its production channel is ^{186}W neutron activation. ^{188}W is produced by double neutron capture, thus even highest neutron flux reactors (Oak Ridge or Dimitrovgrad) enriched ^{186}W target irradiation would yield ^{188}W specific activity below 10 Ci/g. This also leads to inevitably high production cost.

One possible approach to a cheaper and more efficient ^{188}Re generator is extraction technology use to create a regional distribution center for ^{188}Re based on an extraction generator. Khlopin Radium Institute, St. Petersburg, has earned significant expertise in this approach with centralized distribution generator for ^{99m}Tc isotope. For over 20 years, centrifugal extractor based ^{99m}Tc extraction generator has been fully covering the diagnostic needs of St.Petersburg city. Worth mentioning here that ^{188}W half-life of 69 days is much longer than that of ^{99}Mo. This would allow creating a ^{188}Re generator where same ^{188}W batch would yield ^{188}Re batches for an extended period of time (up to 2-4 months depending on the initial ^{188}W generator load). Longer daughter product (^{188}Re) half-life would also allow wider distribution area than just St.Petersburg city.

Viewed as an alternative to conventional adsorption ^{188}Re generator, central distribution extraction generator has a number of advantages over it, including the following:

- any initial specific activity ^{188}W can be used, yielding required ^{188}Re specific activity;

- only the required Re(VII) chemical form of Rhenium isotope is extracted, that is usable for labeled compound synthesis; other Rhenium forms remain in the aqueous mother solution.

- higher ^{188}Re specific activity solutions can be obtained, as the metylethylketone dry residue product form can then be dissolved in small solvent volumes;

- high ^{188}Re purity from inorganic pollutants.

Other important specific property for the extraction generator is that it is of course only operable by qualified radiochemistry lab personnel in the adequate lab environment, and cannot be installed in clinics directly.

As mentioned above, low specific activity (1 Ci/g and below) mother isotope (^{188}W in this case) can be used for extraction generator. This specific activity level is well feasible to achieve by Tungsten oxide irradiation in medium neutron flux reactor (1.0 to $1.4 \cdot 10^{14}$ $n*cm^{-2}*s^{-1}$), f.i. in VVER-M reactor available in SPINP (St.Petersburg Institute of Nuclear Physics). This will drive down the ready ^{188}Re product cost down significantly, likely to the level comparable to ^{99m}Tc isotope.

Considering the reactor neutron energy spectrum, ^{188}W generation curve calculations for VVER-M reactor have shown a feasible maximum specific activity for ^{188}W when irradiating natural tungsten isotope mixture to be 0.3 Ci/g, or 0.5 Ci/g after 2-week irradiation cycle. Thus, a 2-week irradiation cycle for a 20 gram tungsten target will yield ^{188}W activity of 1 Ci, an amount fully sufficient to load a central ^{188}Re distribution generator.

It's also possible to use both metallic tungsten and tungsten trioxide targets to produce ^{188}W isotope. Metallic form would yield more compact targets due to higher tungsten metal density. Metallic target however stands for a more complicated and effort consuming target dissolution process involving nitric and hydrofluoric acid mixture. The solution obtained also requires subsequent multi-stage evaporation to remove fluorine and nitrate ions. Tungsten trioxide targets on the contrary can be dissolved directly in an alkaline solution then used to extract the ^{188}Re from. This makes tungsten trioxide targets a preferred choice for use with the extraction generator.

Worth mentioning here that Mo/Tc system is chemically very similar to W/Re system. Hence the vast experience gained with the ^{99m}Tc central distribution generator can be largely reused in building the ^{188}Re generator. The same methylethylketone (MEK further on) extracting agent was therefore chosen to separate rhenium from tungsten.

Based on other studies data on tungsten [2] and molybdenum [3] extraction as well as Khlopin Radium Institute ^{99m}Tc extractor operation experience, a mixture of alkaline metal (sodium or potassium) hydroxide and carbonate is the most sensible media to extract rhenium or technetium from. This media (alkaline solution + MEK) features a number of advantages including:

- tungsten trioxide high solubility in alkaline media;

- low distribution coefficient for tungsten and virtually any other heavy metal;

- rhenium only extracted from the aqueous solution in the Re(VII) form that is further used to synthesize the radiopharmaceuticals. Other rhenium forms remain unextracted in the alkaline solution.

- MEK high volatility and relatively low boiling point. This allows simply evaporating MEK rather than reextracting rhenium from it, with dry residue subsequent dissolution in the proper solution required for further radiopharmaceutical synthesis. The latter is commonly 0.9% NaCl aqueous solution.

Hydroxide is required for higher tungsten solubility. Carbonate ions presence in the aqueous phase yields several important factors:

- extracted ion (perrhenate) distribution coefficient rises (carbonate ions in this case act as a salinating agent);

- decreases both extracting agent (MEK) solubility in the aqueous phase, and water solubility in the organic phase;

- helps faster phase separation during extraction.

Rhenium distribution coefficient is also increased by tungsten presence in the aqueous phase, the latter acting here as a virtual salinating agent as well.

Published data [3] suggests rhenium distribution coefficients during its extraction from sodium containing solutions to be nearly twice higher than in similar solutions containing potassium. Sodium solutions use therefore appeared a more promising approach initially. It was found in preparation however that for sodium hydroxide and carbonate mixture aqueous solutions sodium tungstate solubility decreases substantially as compared to water solubility. While sodium tungstate water solubility at 20oC is 422 g/L, the highest concentration we were able to achieve was 1.6 mol/L NaOH + 1.8 mol/L Na_2CO_3 + 97.5 g/L of W. This tungsten concentration in the solution is too low to be used in the rhenium generator.

The sodium based system was therefore rejected as impractical. All further developments were carried out with potassium solutions.

Table 1 lists experimental data on rhenium distribution coefficients during extraction from different solutions. Aqueous to organic phase ratio was always 1 to 1.

Table 1: Rhenium distribution coefficients (K_p) when extracted by MEK from different composition solutions

#	Aqueous phase components' concentration			K_p
	KOH, mol/L	K_2CO_3, mol/L	W, g/L	
1	1.0	1.0	-	9.7
2	2.0	2.0	-	19.7
3	2.5	2.5	-	20.0
4	2.5	2.5	100	22.5
5	2.5	2.5	200	27.0
6	1.7	2.5	300	16.6

Table 1 data illustrates the effect of potassium carbonate and tungsten as salinating agents. Distribution coefficient decrease in the maximum tungsten concentration run can be caused by lower potassium hydroxide concentration in the aqueous phase. Certain dip in distribution coefficients during highest tungsten content in the aqueous phase can be attributed to Re(VII) ionic associations dehydration causing solvate decomposition.

Apart from rhenium, tungsten distribution in the systems studied was analyzed. However, the measurement error in tungsten measurement in the organic phase was found to be too high. It can only be stated at this point that tungsten distribution coefficient is at or below 0.01.

For organic extracting agent based extractors, the organic compound radiolysis products appearance should be a primary consideration. The underlying factor is that a fraction of extracting agent volume that was under a relatively long radioactive exposure (over 24 hours in ^{188}Re case) remains above the high-activity aqueous solution. Knowing the typical radiolysis products in the ready product can be useful when synthesizing radiochemicals based on it.

It was earlier shown in [4] that ^{99m}Tc extraction generator features 5-oxy-5-methylheptane-3-OH and 4-oxy-3.4-dimethylhexane-2-OH dimers as primary MEK radiolysis products having boiling point higher than that of the initial substance. Low boiling point radiolysis products naturally escape the ready material along with MEK during the evaporation phase thus causing no effect on the ready material purity.

In order to evaluate radiolysis products output in ^{188}Re generator, an absorbed doses calculation was initially carried out for the organic phase at two ^{188}W aqueous phase volume activity levels, 10 Ci/L, and 5 Ci/L. This corresponds to two ^{188}Re generator loads, 1 Ci, and 0.5 Ci. Model presented in [5] was used for calculation.

It was found that maximum absorbed dose after a 2-month generator work term at 1 Ci and 0.5 Ci load of ^{188}W can be at $1.2 \cdot 10^6$ rad, and $0.6 \cdot 10^6$ rad respectively.

Two MEK samples contacting (2.5 M K_2CO_3 + 2.5 M KOH) alkaline solution were irradiated by Khlopin Radium Institute cobalt gun for 11 hours in order to simulate the dose. One of the samples was placed into a lead container to simulate twice lower dose. An equal period of time was allowed for MEK contact with the alkaline solution without the radiation field. MEK was separated from the aqueous phase immediately after the irradiation. The three MEK samples were then studied in VNIIM (Mendeleev Institute of Metrology). Study results are shown in Table 2.

Table 2: Dimer content after MEK contact with alkaline solution without radiation and after cobalt gun irradiation

Compound	Dimer content		
	No irradiation	Simulated aqueous solution volume activity 5 Ci/L	Simulated aqueous solution volume activity 10 Ci/L
5-oxy-5-methylheptane-3-OH	0.108%	0.0004	0.0032%
4-oxy-3.4-dimethylhexane-2-OH	0.00005%	0.0020	0.0014%

It was found fully in agreement with [4] that two primary compounds are produced in the MEK+aqueous solution system that possess boiling points higher than that of MEK, both being MEK dimers. The data presented leads us to the conclusion that 4-oxy-3.4-dimethylhexane-2-OH is primarily produced by irradiation effect on MEK. The other dimer, 5-oxy-5-methylheptane-3-OH, is produced by MEK contact with the alkaline solution, with its concentration decreasing under irradiation. Cumulative concentration for the two dimers decreases significantly with absorbed dose, likely attributable to radiolysis of the dimers themselves.

Generator main unit is a semi-countercurrent two-stage centrifugal extractor developed by Frumkin Institute for Physical Chemistry and Radiochemistry. Extractor stages are mounted on a single rotation axis, with its case attached to electric motor spindle. ^{188}Re extract from second stage is fed to MEK collection chamber to be accumulated and drained after extraction cycle completion through a collection tube. Extractor schematics is shown in Fig.1.

^{188}Re production unit block diagram is shown in Fig. 2.

Tungsten trioxide dissolved in 2.5 mol/L KOH + 2.5 mol/L K_2CO_3 alkaline solution is loaded into the extractor first stage. 2.5 mol/L K_2CO_3 (flush solution) is fed to its second chamber. Aqueous phase volumes are defined by the extractor build. Given that ^{188}Re can be extracted from ^{188}W solution repeatedly, the initial solution can be used multiple times (up to 2 months) as ^{188}Re builds up in the solution. The flush solution is always used once only.

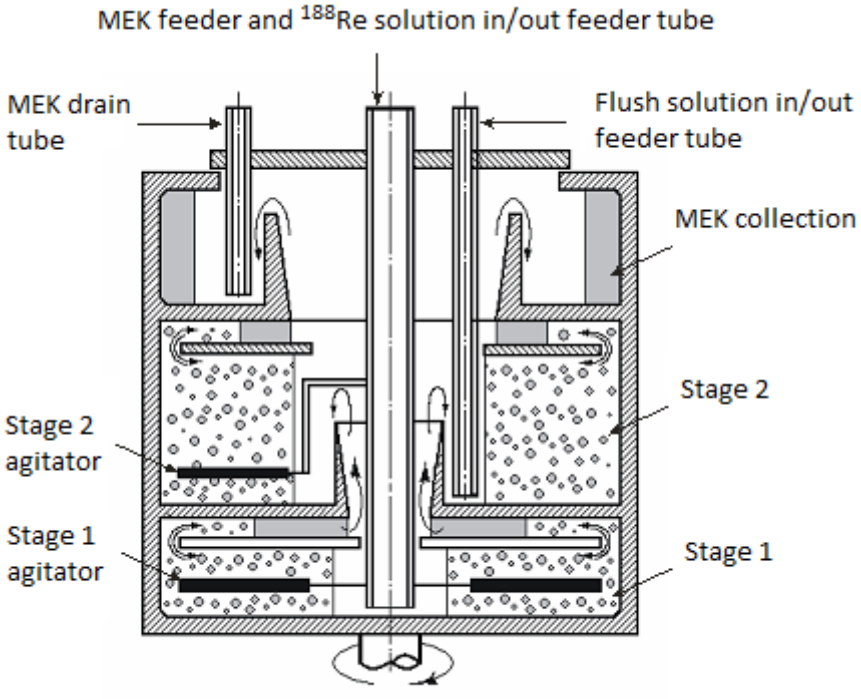


Fig.1. Extraction Centrifugal Generator.

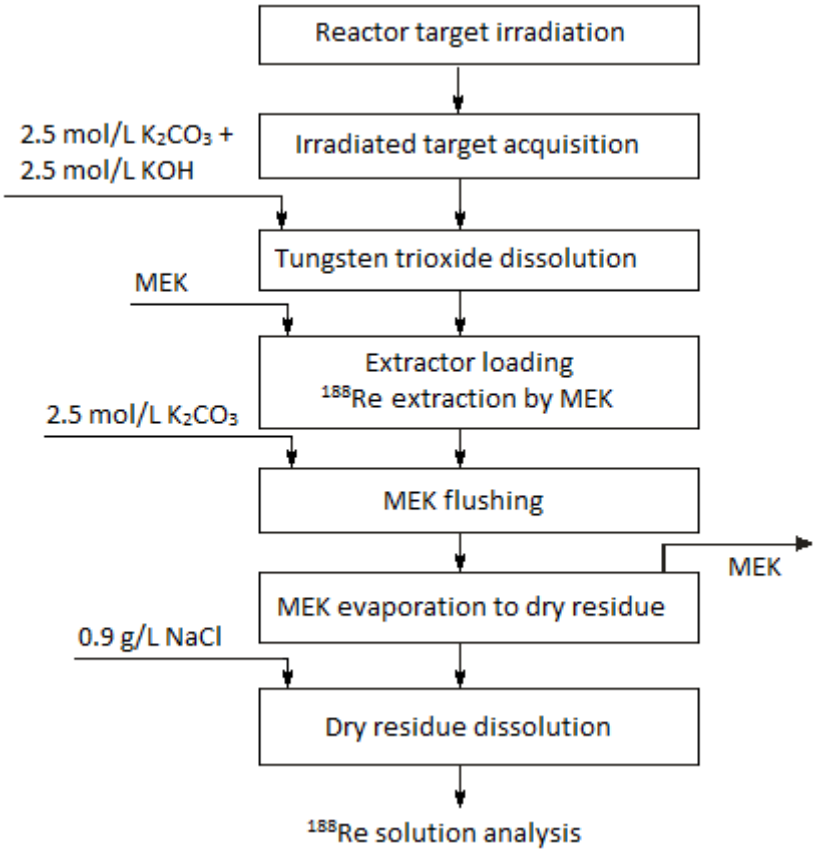


Fig.2. ^{188}Re based radiopharmaceuticals production unit block diagram

Table 3: MEK output vs. extractor rotation rate

Extractor RPM	MEK output, mL
1600	43
2000	42
2400	30

The engine is then started, and the extracting agent is fed to the first chamber. MEK extracts rhenium from the aqueous phase kept in the first extractor stage, and rises to the second stage. Additional ready component cleansing from inorganic pollutants happens here. MEK is then drawn by centrifugal force to the exit chamber. From the exit chamber, MEK feeds to evaporation unit, and is evaporated dry. The dry residue obtained can now be dissolved in any required NaCl 0.9% isotonic solution amount.

Certain extractor operation modes required for proper extraction process were studied on inactive solutions prior. We should mention here that the extractor body gets significantly heated primarily by extractor motor heating, and, at much lower scale, by the internal processes. This may cause MEK output decrease, causing ready isotope yield decline. A series of experiments were ran to study MEK output influencing factors during the extraction. Initial extracting agent volume was always 50 mL.

Table 3 shows extractor MEK output as function of its rotation rate.

Hence based on the data collected we can conclude the optimal rotation rate to be 2000 RPM or below, which corresponds to motor feeding power of about 20 V. Minimum RPM used in the study was 1600, as lower rotation rate would lead to phase separation suffering.

Another variable during the extraction process is MEK inflow rate. Using higher MEK feed rates at the same initial total amount, one can reduce the process time. This lowers the extractor body heating and raises MEK output. However, this may lead to extractor capacity overrun, thus reducing its main quality of aqueous and organic phases separation. Table 4 lists the data on MEK feed rate impact on its output, and aqueous solution residue pH after MEK evaporation.

Our finding based on the data presented is 10 mL/min being the optimal MEK feed rate for the extraction process.

The tests above were carried out on inactive solutions only.

Table 4: MEK feed rate impact on its output and aqueous solution pH after MEK evaporation

MEK feed rate, mL/min	pH	MEK output, mL
5	7.4	42
10	6.9	45
16	11.3	51

Next set of tests was run on active solutions in order to evaluate the optimal MEK volume required for the product extraction. Data for both Re and ^{99m}Tc were collected as a comparison material, the entire set presented in Table 5.

Table 5: Re and Tc output to separate extraction fractions

#	MEK volume	% relative to initial solution fraction volume	
	mL	Re	Tc
1	20	63.3	48.6
2	10	15.0	23.3
3	10	7.9	15.6
4	10	4.4	6.8
5	10	2.9	2.9
6	10	1.8	1.9
7	10		0.9

The data presented shows the optimal MEK volume to be 50 mL (fractions 1-4) yielding total product extraction of over 94%. Larger MEK volume only increases process time, and adds MEK contained pollutants and MEK radiolysis/alkaline media effect decay products to the ready product. One cannot observe significant differences during Re and ^{99m}Tc extraction from aqueous solution. This confirms the elements behavior similarity in the system studied.

^{188}Re yield was also studied during a series of consecutive runs. MEK initial volume was always 50 mL. Experiments data and aqueous solution pH values are presented in Table 6.

Table 6: ^{188}Re yield and aqueous solution pH value

# #	^{188}Re yield, %	pH
1	94	6.52
2	92	6.10
3	78	7.34
4	83	6.52
5	89	6.48
6	86	6.37

^{188}Re yield in the tests was 89% on the average. Solution pH values indicate good phase separation in the extractor and, consequently, good daughter isotope separation from the mother nuclide. ^{188}W activity was found to be below $1 \cdot 10^{-3}$ relative to ^{188}Re activity. Other radioisotopes cumulative activity was below $1 \cdot 10^{-4}$.

Radiochemical purity (RCP) is one of the major properties for radioisotope use in radiopharmaceutics, as it is of primary importance for synthesis to have the radioisotope in proper chemical form. This property directly affects the radiopharmaceutical distribution across human body. This is particularly important for therapeutic pharmaceuticals. Hence the RCP was studied for several solutions obtained. The test results are shown in Table 7.

Table 7: Perrhenate aqueous solution in NaCl radiochemical purity

#	R_f									
batch	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
1	2.3	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	96.9
2	1.4	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	97.7
3	3.9	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	95.2
4	1.6	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	97.6

RCP was 97% on the average, which is satisfactory.

High ^{188}Re hot cell generator solution purity was further confirmed by ICP MS analysis of inorganic solution pollutants. It was shown that inorganic pollutants content in the ^{188}Re solution is defined entirely by purity of the water solution used to dissolve the ^{188}Re material.

Based on several experiments aimed at technology and build validation for the ^{188}Re generator developed it has been proven that the following operation modes:

source solution aqueous phase composition

(extractor first stage) - 2.5 mol/L K_2CO_3 + 2.5 mol/L KOH;

flush solution aqueous phase composition

(extractor second stage) - 2.5 mol/L K_2CO_3;

MEK feed rate 6 - 10 mL/min;

motor rotation rate 2000 RPM;

MEK volume 50-60 mL;

are the optimal ones yielding high quality ^{188}Re material, and thus the unit developed can be recommended as the base setup for commercial ^{188}Re generator creation.

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