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Review Article

^{188}W/^{188}Re Generator System and Its Therapeutic Applications

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The ^{188}Re radioisotope represents a useful radioisotope for the preparation of radiopharmaceuticals for therapeutic applications, particularly because of its favorable nuclear properties. The nuclide decay pattern is through the emission of a principle beta particle having 2.12 MeV maximum energy, which is enough to penetrate and destroy abnormal tissues, and principle gamma rays (E_γ = 155 keV), which can efficiently be used for imaging and calculations of radiation dose. ^{188}Re may be conveniently produced by ^{188}W/^{188}Re generator systems. The challenges related to the double neutron capture reaction route to provide only modest yield of the parent ^{188}W radionuclide indeed have been one of the major issues about the use of ^{188}Re in nuclear medicine. Since the specific activity of ^{188}W used in the generator is relatively low (<185 GBq/g), the eluted $^{188}ReO_4^-$ can have a low radioactive concentration, often ineffective for radiopharmaceutical preparation. However, several efficient postelution concentration techniques have been developed, which yield clinically useful $^{188}ReO_4^-$ solutions. This review summarizes the technologies developed for the preparation of ^{188}W/^{188}Re generators, postelution concentration of the ^{188}Re perrhenate eluate, and a brief discussion of new chemical strategies available for the very high yield preparation of ^{188}Re radiopharmaceuticals.

1. Introduction

Rhenium-188 is currently considered a very attractive candidate for a wide variety of therapeutic applications. Its properties include emission of a high energy beta particle with a maximum energy of 2.12 MeV, a 155 keV (15%) gamma photon for imaging, and versatile chemistry for attachment to a variety of targeting molecules, which make ^{188}Re an important candidate for applications where deep tissue penetration is a benefit. Emission of gamma photons, which can be readily imaged, is an added benefit that permits evaluation of biodistribution, pharmacokinetics, and dosimetry. Rhenium-188 is a Rhenium-186 radioisotope, which was the first rhenium radioisotope applied in nuclear medicine, owing to its $E_{\beta\,\max}$ of 1.07 MeV and E_γ of 137 keV (very close to the 140 keV of ^{99m}Tc).

Rhenium-188 of modest specific activity can be produced by direct activation in a nuclear reactor. Irradiation of natural rhenium element inside a fission-reactor-driven and high-flux neutron field yields a mixture of ^{186}Re and ^{188}Re [1], being the relative contribution of each radioisotope dependent on the irradiation time and postbombardment decay [2]. Both ^{186}Re and ^{188}Re under radionuclidic purity form may instead be prepared by irradiating the highly enriched targets, ^{185}Re and ^{187}Re, respectively, in research reactors. Direct production using isotopically enriched targets inside reactors often yields carrier-added (CA) radioisotopes, having specific activity values high enough for the preparation of selected radiopharmaceuticals useful for bone pain palliation therapy, hepatocarcinoma, radiosynovectomy, and intravascular radionuclide therapy (IVRNT). However, the specific activities of (n, γ) produced ^{186}Re and ^{188}Re are not adequate

Table 1: Examples of nuclear constants for nuclides in the ^{188}W production chain.

Nuclide	Decay constant, λ (s^{-1})	Cross-section, σ (b)	Values for resonance integral, I (b)
^{186}W	—	37.9	485
^{187}W	8.09×10^{-6}	64.0	2760; 10
^{188}W	1.16×10^{-7}	12	0; 50 000; 1.4
^{187}Re	—	76.4	300
^{188}Re	1.13×10^{-5}	<2	—

for radiolabelling molecules such as peptides and antibodies which seek low density targets such as receptors and tumour antigens.

The production method of choice for ^{188}Re is by the decay of the longer lived ^{188}W parent ($t_{1/2}$, 69.4 d), which is produced through a double neutron capture reaction on ^{186}W. Preparation of ^{188}Re from a ^{188}W/^{188}Re generator is instead quite interesting, as it provides a long-term source for no-carrier-added (NCA) ^{188}Re at the nuclear medicine departments [3–5]. Depending upon the specific activity of ^{188}W, chromatography based on alumina or a gel type generator can be performed. In both cases, no-carrier-added (NCA) ^{188}Re is eluted with saline solution in the form of sodium perrhenate. The chromatographic generator with alumina is suitable for high specific activity ^{188}W, and the technology is similar to that used for ^{99}Mo/ ^{99m}Tc generators assembled with fission produced ^{99}Mo. The 24 h postgenerator ^{188}Re elution in-growth of 62% and high elution yields (75–85%) result in daily yields of about 50%, with consistently low ^{188}W parent breakthrough ($<10^{-6}$) [6, 7]. Simple postelution concentration methods have been developed to provide very high radioactive concentration solutions of ^{188}Re for radiolabelling (>25,9 GBq/mL saline from a 37 GBq generator) [4–8]. A postelution concentration step can be used to concentrate the perrhenate solution to very high radioactive concentration. Gels and polymers containing zirconium or titanium can be used. The reported advantages of these systems are the ability to use low specific activity of ^{188}W and the possibility to obtain high radioactive concentration suitable for radiopharmaceutical applications.

This paper reviews the availability and use of ^{188}Re including reactor production of ^{188}W,the development of techniques for the preparation ^{188}W/^{188}Re generators and concentration systems, and the most important chemical strategies development in the last years for the preparation of ^{188}Re radiopharmaceuticals.

2. Reactor Production of ^{188}W

Tungsten-188 is a key example where very high thermal neutron flux is required for production of sufficient specific activity for practical use for the adsorption-based ^{188}W/^{188}Re generator [4, 9–14]. Because of the double neutron capture reaction step, modest thermal cross-section values (Table 1), and product burn-up, the ^{188}W is reactor produced with relatively low specific activity [11]. For example, 24 d irradiation even at high thermal flux level of $\Phi_{th} > 10^{15}$ $cm^{-2}s^{-1}$ yields ^{188}W with a specific activity of only 148–185 GBq/g [9]. Use of this relatively low specific activity ^{188}W requires larger amounts of alumina for the generator column, thus increasing the eluent volume and decreasing the ^{188}Re concentration (activity/volume (MBq/mL)) [4, 5]. The increase in specific activity using very high flux reactors is dramatically illustrated for the production of ^{188}W from enriched ^{186}W by the ^{186}W(n,γ) ^{187}W(n,γ) ^{188}W pathway (Figure 1). The modest ^{186}W and ^{187}W neutron capture cross-sections (Figure 1), the competing burn-up of the ^{188}W product [13], and the significant self-shielding that has been observed [11, 12] are factors that decrease the ^{188}W specific activity.

At the Oak Ridge National Laboratory (ORNL, Oak Ridge, Tennessee, USA), the high flux isotope reactor (HFIR), production of ^{188}W from both ^{186}W-enriched metal and oxide tungsten targets, has been evaluated over the past several years [4, 8–11]. Tungsten-188 having adequate specific activity suitable for the production of ^{188}W/^{188}Re generators can be accomplished also in only a limited number of the research reactors, that is, SM Reactor, RIAR, Dimitrovgrad, Russian Federation, and BR2 Reactor, Belgium.

2.1. Availability of Enriched ^{186}W Target Material. Ideally, ^{188}W should be produced by neutron irradiation of enriched ^{186}W targets, especially for the subsequent preparation of high activity ^{188}W/^{188}Re generators. The use of enriched targets is also required to minimize co-production of other radioactive species. In addition, the use of enriched targets reduces the target volume considerably, since the W targets are quite large because of the modest ^{188}W production yields. Furthermore, because of the relatively low specific activity of ^{188}W produced by the double neutron capture process, even at very high thermal flux, the highest specific activity ^{188}W is generally sought to minimize the amount of adsorbent required for loading of the traditional aluminium oxide adsorption type generator. The irradiation of high purity natural W results in much lower specific activity and requires even higher levels of the alumina adsorbent [14]. Although large electromagnetically separated quantities of highly enriched ^{186}W are available on the world market and mechanical-driven (i.e.,) centrifuge enrichment method has also been demonstrated on a small scale, another strategy has been demonstrated feasility, that is the recovery of nonactivated ^{186}W from used generators, since only a small fraction of ^{186}W is transmuted to ^{188}W during the reactor irradiation process. By increasing the pH of the generator eluent, salts of tungstic acid can be readily removed [15]. The use of ammonium hydroxide with peroxide, for instance, can remove >95% of the available W from the alumina column. Subsequent precipitation with nitric acid (chloride complexes have limited solubility), recovery by centrifugation and then heating at high temperature, readily converts the W to the oxide, which could then conceivably be used for preparation of additional targets for neutron irradiation. Although long

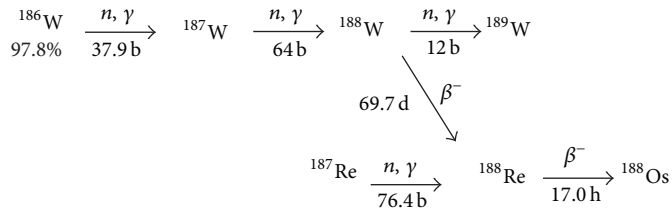

Figure 1: Scheme for reactor production of ^{188}W.

decay periods would be expected to reduce the activity of the residual radioactivity to manageable levels, this recovered W would still be radioactive with longer lived contaminants. Target fabrication with this material would thus probably require special handling. Nonetheless, this approach could represent a possible method for recovery of the ^{186}W target material.

A strategy currently used at ORNL [12, 14] involves the use of enriched metallic ^{186}W targets that are pressed into pellets and subsequently sintered at high temperature prior to neutron irradiation. This approach dramatically increases the target density and thus the loading and ^{188}W production capability per target, and about 5 g of these discs (8–10/target) can be loaded into one HFIR hydraulic tube target assembly. The issue of self-shielding may need to be taken into account, as this decreases the specific activity compared with the use of granular/powder targets [10]. Although the total ^{188}W activity produced per target is higher with the pressed targets, since significantly more target material can be used per target holder, the ^{188}W specific activity decreases as the mass of the enriched ^{186}W increases. Although the key factors leading to such a discrepancy are still not well understood, the specific activity of the irradiated ^{186}W-enriched pellets is considerably less (20–25%) than the specific activity of the irradiated granular/powder enriched ^{186}W target [9].

3. Processing of ^{188}W

3.1. Tungsten Metal and Tungsten Oxide Targets. Although a variety of postirradiation processing strategies are possible, processing of ^{188}W has usually involved postirradiation basic dissolution of ^{186}W oxide targets and/or high temperature oxidative processing of metallic enriched ^{186}W targets [8–10]. Relatively large enriched ^{186}W targets are required to produce multicurie levels of ^{188}W. Use of granular/powder oxide targets can simplify the processing, since dissolution in sodium hydroxide solution with heating is straightforward. Enriched ^{186}W targets under powder form are routinely used for production of ^{188}W at the SM reactor at the Research Institute of Atomic Reactors (RIAR) in Dimitrovgrad, Russia. However, although powder metal of oxide targets was routinely used for ^{188}W production in the ORNL HFIR for many years [12–14], transition to use of the highly enriched ^{186}W pressed and sintered targeted geometry was originally explored as a strategy to increase the ^{186}W mass per target [11]. More recently, the pressed discs have become the target

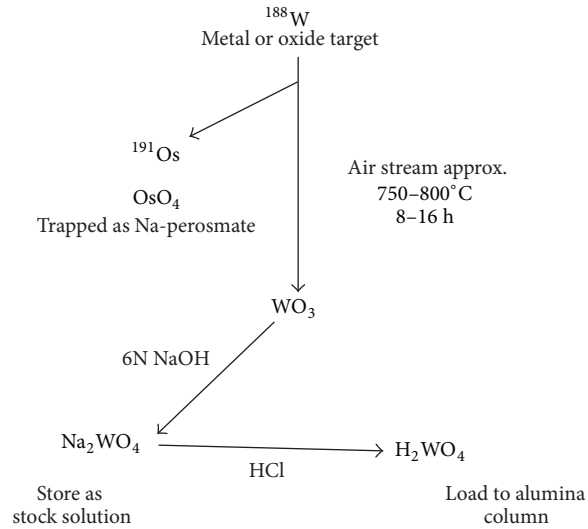

Figure 2: ORNL postirradiation processing scheme for pressed/sintered enriched ^{186}W metal targets [16].

of choice at ORNL because of the requirements for use of available hot cells and the need to minimize hot cell contamination resulting from potential release of the highly radioactive powder. Subsequent removal of any radionuclide impurities is possible, such as with ion exchange chromatography as is used at RIAR [16]. The purification procedure is based on treating the sodium tungstate solution in a mixture of acetic acid and hydrogen peroxide, with subsequent passage through cation exchange resin [17]. To perform this procedure, the sodium tungstate basic solution is evaporated to moist salts, and the residue is dissolved in acetic acid solution containing 3–5 vol.% hydrogen peroxide. The solution is passed through the column filled with the KU-2 cation exchanger (an analogue of Dowex-50). Tungsten forms anionic peroxide complexes that are not retained by the resin, whereas many other metals, unable to produce anionic acetate or peroxide complexes, are retained in cationic form and have distribution ratios higher than 10^2. The tungsten peroxide complexes are destroyed by heating of the purified solution to 60–80°C, with precipitation of tungstic acid. If metallic granular/powder or pressed/sintered enriched ^{186}W targets are used, as at ORNL, the irradiated target material is first heated to 750–800°C in a quartz furnace while a stream of air is passed over the target material for conversion to tungsten oxide for subsequent dissolution in base, as shown in Figures 2 and 3. In this case, the contaminating levels of

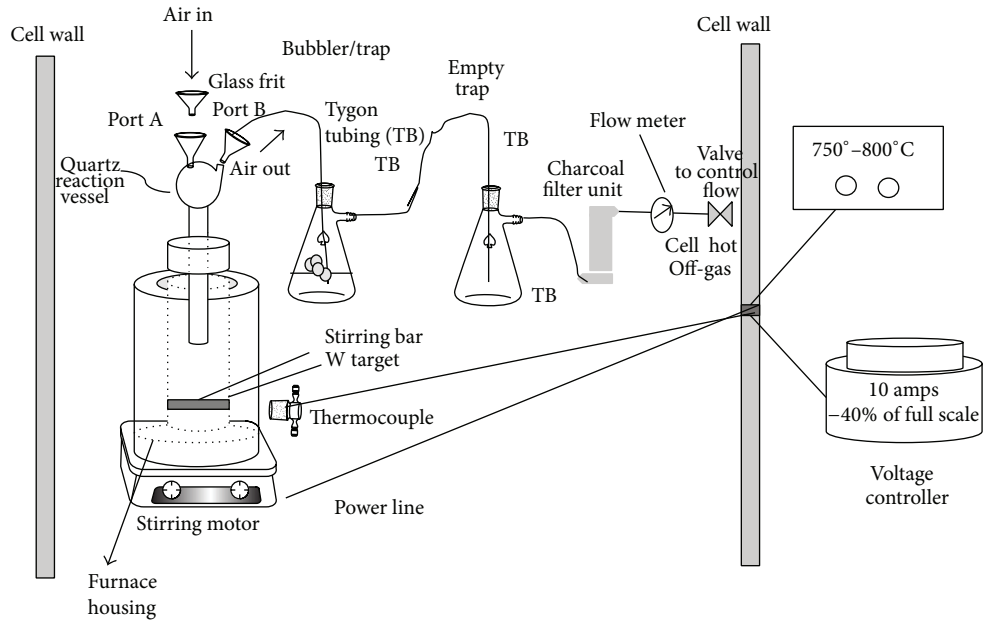

Figure 3: Apparatus used at ORNL for postirradiation conversion of metallic enriched ^{186}W targets to tungsten oxide [16].

most of the ^{191}Os radionuclidic impurities are also swept away from the target for subsequent trapping in base. At ORNL, the resulting sodium tungstate stock solution is not purified further, since the possible presence of low amounts of the ^{191}Os and ^{192}Ir impurities present in the ^{188}Re generator eluents used for radiopharmaceuticals preparation has been shown to be without consequences.

3.2. Radionuclide Impurities. Both ^{191}Os ($t_{1/2}$ = 15.4 d, gamma emission at 129.42 KeV, 29%) and ^{192}Ir ($t_{1/2}$ = 73.8 d, gamma emission at 316.51 KeV, 83%) radionuclides are produced during irradiation of ^{186}W targets; the levels are produced depending upon the irradiation parameters. Although not yet documented in detail, it can be assumed that these two impurities are coproduced by a series of transformations coming from the decay of ^{190}Os that is formed during neutron irradiation of enriched ^{186}W [16]. However, at secular equilibrium, these two radionuclide impurities usually are not detected in the gamma spectrum of ^{188}W and ^{188}Re because of the intensity of the 159 keV gamma photon emitted from ^{188}Re.

The presence of ^{60}Co in decayed samples of the ^{188}Re eluate from ^{188}W/^{188}Re generators probably results from activation of the low levels of natural cobalt (^{59}Co) present in the Al material used to construct the hydraulic tube units. It is assumed that, after irradiation, small amounts of the Al base material probably accompany the irradiated ^{186}W material, which is removed after opening the hydraulic tube assembly. Most of the ^{191}Os is removed during the oxidative conversion of the metallic W target to tungsten oxide, and any remaining ^{191}Os and ^{192}Ir is generally only detected in small amounts by gamma spectroscopy following decay of ^{188}Re in the saline eluted bolus. These impurities are slowly eluted from the generators in only very small amounts. If the tandem cation/anion postconcentration system is used, as in the general practice in most clinical centres, essentially all the ^{192}Ir is trapped on the column during concentration.

Tungsten-188 breakthrough can be also present in ^{188}Re eluates (with values typically in the 10^{-6} range). However, any ^{188}W breakthrough can be effectively removed by subsequent postelution process by passage of the bolus through a small, commercially available alumina QMA Sep-Pak column [18].

4. The ^{188}W/^{188}Re Generator System

4.1. Alumina Based ^{188}W/^{188}Re Generators. Alumina based chromatographic generator systems, similar to those available for ^{99m}Tc, are prepared for obtaining ^{188}Re. At ORNL, active acidic aluminium oxide is used to prepare the columns. Tungsten-188 with a maxima specific activity of 185 GBq per gram of tungsten as sodium tungstate in 0.26 mol L^{-1} of NaOH, with a concentration of 7.6 GBq per millilitre, can be used. The pH level of the Na_2 $^{188}WO_4$ solution (0.26 mol L^{-1} of NaOH) has to be adjusted to 2-3 with 0.1 mol L^{-1} HCl, and the required amount of activity is loaded onto the column under controlled vacuum pressure (flow rate: 1 mL/min.). The column, placed in shielded housing and handled inside appropriate facilities, is washed with 100 mL of 0.9% NaCl solution (normal saline) and, after allowing growth of the ^{188}Re, eluted with 10 mL of saline. Table 2 summarizes the characteristics of the commercial ^{188}W/^{188}Re generators available in the world market.

Rhenium-188 having very high radionuclidic and radiochemical purity (>99%) can be eluted from the alumina based generator with high elution efficiency (>80%). Nonetheless,

Table 2: The characteristics of the commercial $^{188}W/^{188}Re$ generators.

Institution/suppliers	Strength	Column material	Specific activity of W-188	Remarks
ORNL, TN, USA	9.25 GBq (250 mCi) to 111 GBq (3 Ci) cGMP system	Alumina	148–185 GBq (4-5 Ci)/g	>500 generators since 1986.
Dimitrovgrad, Russia	3.7–111 GBq (0.1–3 Ci) Sterile cGMP system	Alumina	185 GBq (5 Ci)/g	Regular production and supply.
IRE, Belgium	Up to 55.4 GBq (1.5 Ci)	Alumina	185 GBq (5 Ci)/g	Generator is available with an automatic concentration module.
ITM AG, Germany	Unknown	Alumina	185 GBq (5 Ci)/g	Regular production and supply.
Polatom, Poland	18.5 GBq (500 mCi) cGMP system	Use of $^{99}Mo/^{99m}Tc$ column system	185 GBq (5 Ci)/g	Regular production and supply.
IDB, Holland	3.7–18.5 GBq (100–500 mCi)	Alumina	Unknown	Regular production and supply.

most often the ^{188}Re eluted from an alumina column chromatography generator is not suitable for the direct formulation of radiopharmaceuticals; a postelution concentration of the generator eluent solution is essential to obtain $^{188}Re\,O_4^-$ having radioactive concentration sufficient for radiopharmaceutical formulation.

4.1.1. Postelution Concentration of ^{188}Re Perrhenate from the Generator. The use of low specific activity ^{188}W and of old generators results in low radioactivity concentrations of the eluted ^{188}Re perrhenate, which is often not suitable for radiolabelling of biomolecules. Postelution concentration is essential in such cases. Reports in the literature [7, 18–20] on effective postelution concentration of ^{188}Re using tandem ion exchange columns prompted an exploration of possible means of postelution concentration of the ^{188}Re perrhenate eluate. Postelution concentration of no-carrier-added ^{188}Re perrhenate is based on its selective retention on a tiny anion exchange column and subsequent recovery in a small volume of suitable eluent. This concentration of perrhenate is possible only when the ^{188}Re eluate is free of any other macroscopic anionic species. Three different methods of postelution concentration can be used, as described below.

Use of IC-Ag and Sep-Pak Accell Plus QMA Anion Exchanger Column. The technology developed at ORNL uses a Maxi-Clean IC-Ag; Ag^+ form cation exchanger cartridge (Alltech Associates, USA) and a Sep-Pak Accell Plus QMA anion exchange cartridge (Waters Corporation, Milford, USA) was used in the first method of postelution concentration, as reported by Guhlke et al. [18–20]. The Maxi-Clean IC-Ag cartridge was conditioned with 5 mL of deionized water. Rhenium-188 eluate obtained from a $^{188}W/^{188}Re$ generator in 10 mL of normal saline solution was freed of macroscopic Cl^- ions as AgCl precipitate by passage through an Alltech IC-Ag^+ cation exchange cartridge. This ^{188}Re perrhenate eluate free of chloride anion was then passed through the small Sep-Pak Accell Plus QMA anion exchange cartridge (130 mg) to retain the perrhenate and was subsequently reeluted with a very small volume (1 mL) of normal saline. The effluent from the IC-Ag cartridge and a few mL of deionized water used for washing were measured to assess any loss of ^{188}Re activity in the concentration process. Using this method, ^{188}Re yield of $79 \pm 3\%$ was obtained, with a concentration factor of about 10. The ^{188}W breakthrough was well below $10^{-4}\%$ and at times was undetectable. In Figure 4 a schematic drawn of ^{188}Re generator and concentration system with IC-Ag and Sep-Pak Accell Plus QMA anion exchanger column is reported. The complete generator setup consists of an attachment for the generator effluent for flow through an alumina QMA SepPak, which effectively removes low levels of any ^{188}W breakthrough and then through a tandem silver-cation/QMA anion column for concentration of the ^{188}Re eluate to usable radioactive concentration.

Use of Dowex 1X8 and AgCl Column. A Dowex 1X8 anion exchanger (Cl-form, 200–400 mesh) with a capacity of 3–5 meq/g (Sigma Chemicals) and extra pure AgCl were used in this method of postelution concentration [21]. Between 10 and 12 mg of Dowex 1X8 resin was taken in a 2 mL syringe and placed in a polypropylene tube (~8 mm × 1 mm) with a few millilitres of water. The other end of the tube was packed with glass wool. Both ends of the tube were fitted with miniature barbed polypropylene fittings. Ten millilitres of normal saline solution was passed through the resin column and washed with 5 mL of water (~5 bed volumes of the resin column). Between 1 and 1.5 g of commercial AgCl salt was taken in a glass column (12 mm × 8 mm) with a sintered disc (G-2), closed with a silicon rubber septum, washed with a few millilitres of deionized water, and used. Between 20 and 40 mL of ^{188}Re eluate in normal saline obtained from the generator was passed through the Dowex 1X8 anion exchange column (placed in appropriate shielding) at a flow rate of 2-3 mL/min using controlled vacuum pressure. The activities in the effluent from the Dowex 1 column and in the subsequent washings with a few millilitres of deionized water were measured to assess the adsorption of the perrhenate. These were treated as radioactive waste and appropriately disposed of. The no-carrier-added ^{188}Re perrhenate adsorbed on the tiny anion exchange column was reeluted with 5-6 mL of 0.2 mol dm^{-3} NaI solution and passed through the AgCl column (1 g, 12 mm × 8 mm) placed in proper shielding (6-7 mm of lead). The effluent of ^{188}Re perrhenate obtained by

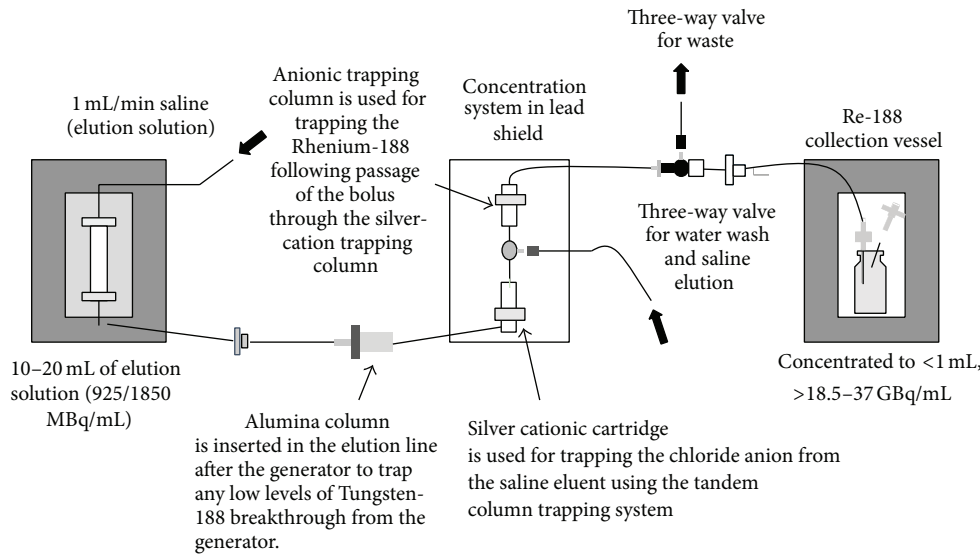

Figure 4: Schematic drawn of ^{188}Re generator and concentration system with of IC-Ag and Sep-Pak Accell Plus QMA anion exchanger column [19].

washing the column with 1.5–1.8 mL of deionized water was collected in a 10 mL vial. This ^{188}Re perrhenate was free of iodide (removed as AgI precipitate) and isotonic with normal saline. In this system, there was a loss of ^{188}Re activity (6–12% in the case of 20 mL primary eluate volume and 17–25% in the case of 40 mL primary eluate volume) and the yield of ^{188}Re was about 72.4 ± 12%. However, the ^{188}W breakthrough was below 10^{-4}%. The presence of Ag on ^{188}Re eluate was not determined. However Chattopadhyay et al. [22] demonstrated that the quality of the [^{99m}Tc]$NaTcO_4$ concentrated with this procedure complies with the specifications applicable for radiopharmaceutical use.

Use of a Single Column of DEAE Cellulose. The third method devised for postelution concentration involved the construction of a generator bed free of chloride ions and elution of the ^{188}Re perrhenate in acetate buffer. This method was based on earlier work with ^{99m}Tc pertechnetate [23, 24]. The ^{188}Re perrhenate eluted was then trapped on a DEAE cellulose column and eluted in a small volume of saline. Briefly, the generator was washed initially with approximately 200 mL of 1 : 1 vol./vol. 0.025 mol dm^{-3} NH_4OAc: 0.7 mol dm^{-3} AcOH at ~pH 3, to remove the chloride (Cl^-) ions. The effluents were checked for the absence of chloride ions by $AgNO_3$ testing. The generator was then set aside to allow for the growth of ^{188}Re. The ^{188}W/^{188}Re generator was then eluted with 20–25 mL of acidic ammonium acetate [17] and passed through a small anion exchange column of DEAE cellulose (300 mg, 10 mm × 8 mm) to trap ^{188}Re perrhenate. Subsequently, ^{188}Re was recovered in 4 mL of normal saline. The mean practical yield of ^{188}Re in this method was 72.9 ± 2.3% (n = 11). The time required for the concentration process was 15–20 min. The DEAE cellulose column was flushed with 5-6 mL of deionized water to keep the system ready for the next elution.

4.2. Novel Materials for Column Matrix for Use in Radionuclide Generators. Materials with a higher capacity for tungsten adsorption are of great interest owing to the low specific activities of ^{188}W, which necessitates the use of large alumina columns, which in turn leads to low radioactive concentration or to tungsten breakthrough. Dadachov et al. [25] proposed a new concept in which ^{188}W obtained by (n, γ) reaction of natural tungsten can be incorporated into a titanium tungstate based gel. Brodskaya et al. [26] have reported a method for chromatographic separation of tungsten and rhenium using organophosphorus resins. A major disadvantage of this process is the radiation degradation of the resin, which is sensitive to radiation damage. Another alternative approach is emerging from research being conducted in Japan [27, 28] in which reactor irradiated molybdenum (i.e., low specific activity) was adsorbed into a zirconium polymer, with higher uptake capacity for ^{99}Mo than for alumina. Chakravarty et al. [29] used nanocrystalline zirconia, a high capacity sorbent material tested for its utility in the preparation of ^{188}W/^{188}Re generators. The structural investigation of the material was carried out using X-ray diffraction, surface area determination, FTIR, and TEM micrograph analysis. Various experimental parameters were optimized to separate ^{188}Re from ^{188}W. The capacity of the material was found to be ~325 mg W/g at the optimum pH. A chromatographic ^{188}W/^{188}Re generator was developed using this material from which >80% of ^{188}Re generated could be eluted with 0.9% saline solution, with high radionuclidic, radiochemical, and chemical purity and appreciably high radioactive concentration suitable for radiopharmaceutical applications. Application of titanium polymer prepared by the polymerization reaction of $TiCl_4$ with isopropyl alcohol for the preparation of a ^{188}W/^{188}Re generator and the elution characteristics of ^{188}Re were studied by Venkatesh et al. [30].

For the synthesis of the polymeric titaniumadsorbent, titanium tetrachloride was mixed with isopropyl alcohol in the ratio of 1 : 2 in a beaker with vigorous stirring. The material obtained was water soluble. To make this into an insoluble polymer, it was heated for 2 h at 150°C. This product was insoluble in water and in most of the mineral acids and alkaline. Thedried cake was ground to a fine powder and sieved with a 25–50 mesh sieve. The distribution ratio (K_d) of ^{188}W in 0.1 mol dm^{-3} HNO_3 was determined at different time intervals and the results indicated that about 45 min is required to reach the equilibration. In all subsequent experiments, the polymer was adsorbed with the ^{188}W activity for 45 min. It was observed that the maximum adsorption of ^{188}W as tungstate on thetitanium polymer occurred at pH 5-6. While both ^{188}W-tungstate and ^{188}Re asperrhenate were adsorbed, when eluted with saline, perrhenate exhibited farless affinity (approximately 600-fold lower) for the matrix. In order to estimate the saturation capacity of the titanium polymer and the concentration at which breakthrough begins, adsorption of ^{188}W on the titanium polymer was determined under dynamic conditions using an ion exchange chromatographic column in the presence of different carrier concentrations of tungsten in the feed. The breakthrough capacity and saturation capacity of tungsten were found to be 62 and 120 mg/g, respectively, indicating that approximately 62 mg of tungsten per gram of titanium polymer can be loaded without any breakthrough being observed. A process demonstration run was carried out with this adsorbent using 1 mCi of ^{188}W, and the elution behavior of the ^{188}Re was studied. It was observed that only about 60–70% of the ^{188}Re on the column could be eluted with saline, but that approximately 92% of this was eluted in the first 3–5 mL. Further study of this material is needed and will be done as the next step in generator development.

Monroy-Guzman et al. [31] prepared ^{188}W/^{188}Re generators based on ^{188}W-tungstates and hydroxyapatite. The titanium tungstate gels were synthesized from tetrabutyl orthotitanate and sodium ^{188}W-tungstate solutions. Gels were prepared using ^{188}W-tungstate solutions of four different pH values (in the range of 1.95–12) at a Ti : W molar ratio of 1 : 1. The gels were stirred and dried for 2.5 h at 80°C and then placed on polyethylene columns. The zirconium tungstate gels were prepared from zirconium ethoxide solutions and sodium ^{188}W-tungstate solutions following the process described above. Gels were prepared using ^{188}W-tungstate solutions of four different pH values at a Zr : W molar ratio of 1 : 1. The columns were washed with 50 mL of 0.9% NaCl and were eluted every three days for a period of three months. They found that the pH level of the ^{188}W-tungstate solution used for the preparation of the titanium and zirconium ^{188}W-tungstate based generators influence the efficiency and the ^{188}W breakthrough of the generators. Both parameters decreased when the gels were synthesized with more acidic ^{188}W-tungstate solutions. The best ^{188}Re elution efficiency (~73%) was obtained from the titanium ^{188}W-tungstate based generators; however, the lowest ^{188}W breakthrough (0.3%) was obtained from the zirconium ^{188}W-tungstate based generators. The ^{188}Re radiochemical purity obtained from both types of generator is less in the gels prepared with basic ^{188}W-tungstate solutions (83–87%) than in those prepared with acidic ^{188}W-tungstate solution, which had a ^{188}Re radiochemical purity of 100%.

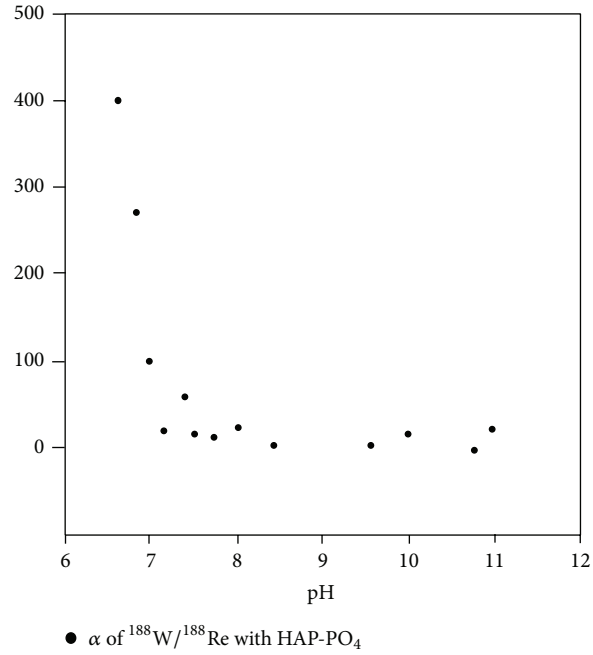

Figure 5: Separation factors of tungsten and rhenium ($\alpha_{W/Re}$) on hydroxyapatite [31].

The $\alpha_{W/Re}$ separation factors shown in Figure 5 indicate that tungsten and rhenium can be readily separated with 0.9% NaCl solutions at pH levels below 7.5. Based on these data, hydroxyapatite based generators were constructed using four 0.9% NaCl solutions at pH 5.5, 6.0, 6.3, and 6.5 (series A), and using hydroxyapatite particles of three sizes (series B). Results on the performance of these generators are shown in Figures 6 and 7. For all the ^{188}Re eluates obtained in both series, the pH was 6.5, the phosphate concentration was greater than 1000 ppm, and the radiochemical purity was greater than 90%. The lowest ^{188}W breakthrough and highest average elution volumes were obtained in the generators eluted with 0.9% NaCl solution at pH 6.5 and with hydroxyapatite particles between 38 and 75 μm in size. The efficiency of the ^{188}W/^{188}Re generators decreased with the pH value of the NaCl solution, but the particle size of the hydroxyapatite appeared to have no significant effect. The mean efficiencies obtained were about 65%, whereas the elution volumes and ^{188}W breakthrough values decreased with a decrease of the hydroxyapatite particle size and with an increase of the pH value of the NaCl solution. The generators in series A and B showed that phosphate ions are released during the elution of ^{188}Re, leading to the proposal to wash the generators after elution with 0.9% NaCl solutions, using 0.01 mol dm^{-3} $CaCl_2$ or 0.004 mol dm^{-3} NaH_2PO_4 solutions, in order to avoid the dissolution of hydroxyapatite.

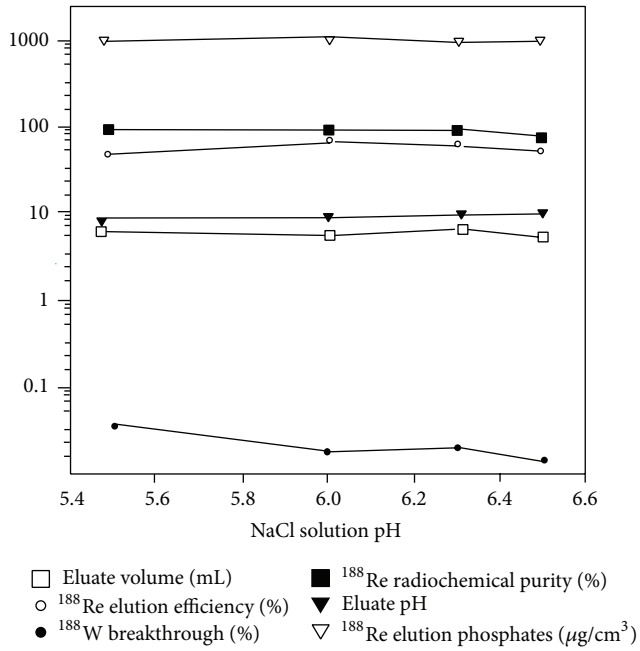

FIGURE 6: Performance of the hydroxyapatite based $^{188}W/^{188}Re$ generators as a function of the 0.9% NaCl solution pH (series A) [31].

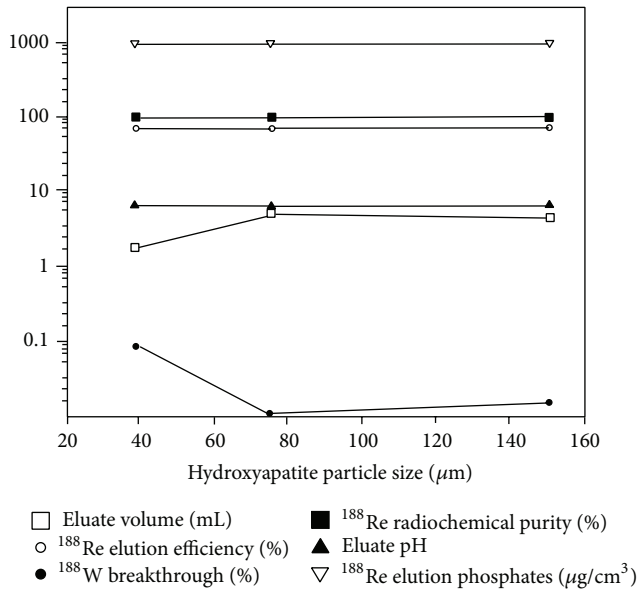

FIGURE 7: Performance of the hydroxyapatite based $^{188}W/^{188}Re$ generators as a function of the hydroxyapatite particle size (series B) [31].

A third series of generators (series C) was then fabricated and evaluated using the method previously described. The performance of these generators as a function of the eluent is shown in Figure 8. Washing the generators with 0.01 mol dm^{-3} $CaCl_2$ or 0.004 mol dm^{-3} NaH_2PO_4 solutions

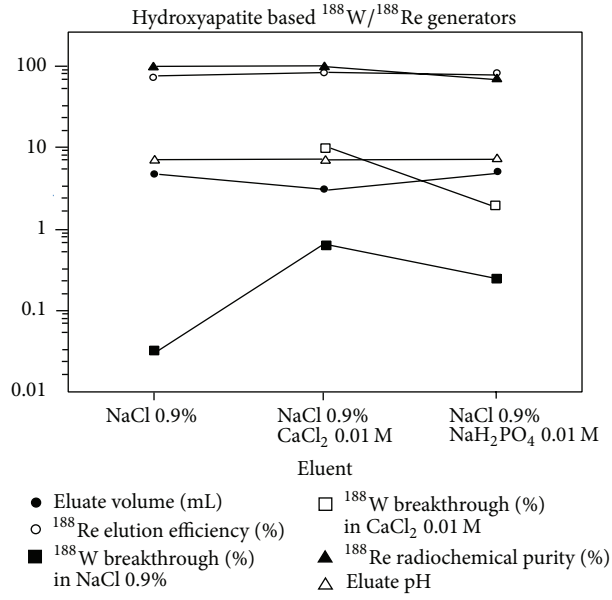

FIGURE 8: Performance of the hydroxyapatite based $^{188}W/^{188}Re$ generators as a function of the eluent (series C) [31].

after elution with 0.9% NaCl solutions caused an increase of the ^{188}W breakthrough in the ^{188}Re eluate.

However, there was no apparent effect on the ^{188}Re elution efficiency, the eluate pH, or the radiochemical purity. The presence of phosphate ions in the ^{188}Re eluates shows that the hydroxyapatite continues to dissolve.

5. ^{188}Re-Radiopharmaceuticals

5.1. Reduction of the Tetraoxo Rhenium-188 Anion. Rhenium-188 is a β-emitting nuclide that is currently attracting much interest as a potential candidate for therapeutic applications because of its useful nuclear properties and availability. Another important advantage of employing ^{188}Re-radiopharmaceuticals comes from the easy availability of this radionuclide, which is produced through a transportable generator system under the chemical form of the tetraoxo perrhenate anion $[^{188}ReO_4]^-$ in physiological solution. This situation, therefore, parallels completely that of the nuclide ^{99m}Tc, which is obtained through the $^{99}Mo/^{99m}Tc$ generator system in the form of $[^{99m}TcO_4]^-$, which always constitutes the starting compound for preparing ^{99m}Tc-radiopharmaceuticals. Likewise $[^{188}ReO_4]^-$ is the ubiquitous starting compound for the preparation of ^{188}Re-radiopharmaceuticals. However, since technetium and rhenium belong to the same group 7 of the transition series, the similarities between ^{99m}Tc and ^{188}Re radiopharmaceuticals are even more pronounced. In fact, owing to lanthanide contraction, technetium and rhenium have almost identical ionic radii. This indicates that, when these two elements form analogous complexes having exactly the same chemical structure and stability and differ only in the metal center, these species

should exhibit the same "*in vivo*" biological behavior. Despite this, there exists a fundamental difference between the values of the standard reduction potentials of the redox reactions involving technetium and rhenium compounds. On average, E° of a technetium process is 200 mV higher than that of the corresponding rhenium process. This implies that reduction of $[^{188}ReO_4]^-$ should be much more difficult than that of $[^{99m}TcO_4]^-$. As a consequence, the methods utilized for the preparation of ^{188}Re-radiopharmaceuticals cannot simply follow routes employed for obtaining ^{99m}Tc complexes, and usually more drastic conditions are required [32].

This fact always constitutes a fundamental obstacle for the development of new ^{188}Re-radiopharmaceuticals. A solution to this problem has been proposed [33]. This approach was inspired by a general phenomenon in coordination chemistry that goes under the name of "expansion of the coordination sphere." This phenomenon indicates a redox process in which the metal undergoes a concomitant expansion of its coordination arrangement in going from the initial to the final oxidation state. For instance, in all radiopharmaceutical preparations involving $[^{188}ReO_4]^-$, the starting Re(VII) center should be converted from the tetraoxo anion to the final complex which, usually, has a five- or six-coordination arrangement. The molecular geometry, therefore, should undergo a sudden change from tetrahedral to a more expanded square pyramidal or octahedral geometry. This geometrical process has a great impact on the standard reduction potential of the redox reaction and, generally, its effect determines a decrease of the E° value. It follows, therefore, that if the reduction process was accomplished without the occurrence of such dramatic, geometrical changes, their detrimental influence on E° would be completely cancelled. This result could be easily achieved by first transforming the tetrahedral perrhenate anion into some intermediate Re(VII) complex having a more expanded coordination sphere, by simple substitution of the oxo-groups with some suitable ligand, but without changing the starting metal oxidation state. In this way, the reduction process yielding the final product would take place between this intermediate Re(VII) compound, and not from the tetraoxo anion. It was found that oxalate ions ($C_2O_4^{2-}$) were excellent ligands for producing intermediate Re(VII) complexes possessing an expanded octahedral geometry [34].

Consequently, addition of this species in preparations involving the reaction of $[^{188}ReO_4]^-$ with $SnCl_2$, in the presence of some appropriate coordinating ligand, dramatically improved the yield of formation of the final radiopharmaceutical.

The first application of the above mentioned strategy was carried out for preparing the complex $[^{188}ReO(DMSA)_2]$ (DMSA = dianionic dimercaptosuccinic acid) [33]. This complex had been previously obtained under strong conditions, by heating $[^{188}ReO_4]^-$ at high temperature for a prolonged time, and in the presence of a large amount of $SnCl_2$ as a reductant. Such conditions are completely unsuitable for any "*in vivo*" clinical study in humans. However, addition of oxalate ions changed dramatically the course of this reaction.

5.2. Nitrido Rhenium-188 Complexes. The oxalate-based approach has been subsequently utilized to develop the first efficient procedure for producing the $[^{188}Re{\equiv}N]^{2+}$ core from $[^{188}ReO_4]^-$, at tracer level and under physiological conditions [34]. For this purpose, the method originally developed for the tracer-level preparation of the analogous $[^{99m}Tc{\equiv}N]^{2+}$ was employed [35]. This method was based on the reaction of $[^{99m}TcO_4]^-$ with DTCZ and $SnCl_2$ to afford a mixture of intermediate ^{99m}Tc complexes all characterized by the presence of a terminal Tc≡N group. In this procedure, the species DTCZ played the role of an efficient donor of nitrido nitrogen groups (N^{3-}), and $SnCl_2$ was used as reducing agent. After addition of a suitable dithiocarbamate ligand (L), the intermediate mixture was suddenly converted into a single product corresponding to the complex $[^{99m}Tc(N)(L)_2]$ [36]. When a similar procedure was applied to the preparation of the analogous nitrido ^{188}Re complexes starting from generator-produced $[^{188}ReO_4]^-$, no formation of the final products was obtained. This finding was in close agreement with results obtained in a similar attempt to prepare ^{186}Re nitrido complexes using various derivatives of DTCZ and other sources of N^{3-} groups, which completely failed to give the desired compounds [37]. However, addition of sodium oxalate dramatically changed the outcome of the reaction, and the complexes $[^{188}Re(N)(L)_2]$ were obtained with a final yield > 95%. These results clearly suggest that the key step in the production of the compounds $[^{188}Re(N)(L)_2]$ was the reduction of the ^{188}Re perrhenate anion. Biological experiments carried out in rats showed that the biodistribution of $[^{188}Re(N)(L)_2]$ complexes parallels exactly that observed for the analogous ^{99m}Tc complexes $[^{99m}Tc(N)(L)_2]$. In particular, heart was one of the most important target organs. This fact clearly demonstrates that, inside a matching pair of technetium complexes possessing identical molecular structure and stability toward "*in vivo*" redox reactions, the corresponding radiocompounds always exhibit the same biological behavior.

5.3. Rhenium-188 Lipiodol. Various attempts at labelling lipiodol for the treatment of hepatocellular carcinoma (HCC) [38] with ^{188}Re have been proposed, but most are exceedingly complicated and difficult to apply under controlled conditions. A simple and elegant approach involves the dissolution of a strongly lipophilic ^{188}Re compound into lipiodol, which constitutes a highly hydrophobic material [39].

Using this strategy, ^{188}Re would remain tightly retained as a consequence of the strong hydrophobic interaction between the lipophilic metal complex and the fatty oil. A key requirement of this approach is the need to produce, in high yield, a ^{188}Re complex that possesses sufficient stability to be dissolved in lipiodol and sufficient lipophilicity to remain firmly trapped in this substance. An example of the application of this labelling method has been reported [40–45]. A series of oxo-complexes of ^{188}Re was prepared by reacting $[^{188}ReO_4]^-$ with derivatives of the tetradentate ligand 3,3,10,10-tetramethyl-1,2-dithia-5,8-diazacyclodecane and then mixed with lipiodol. However, the final labelling

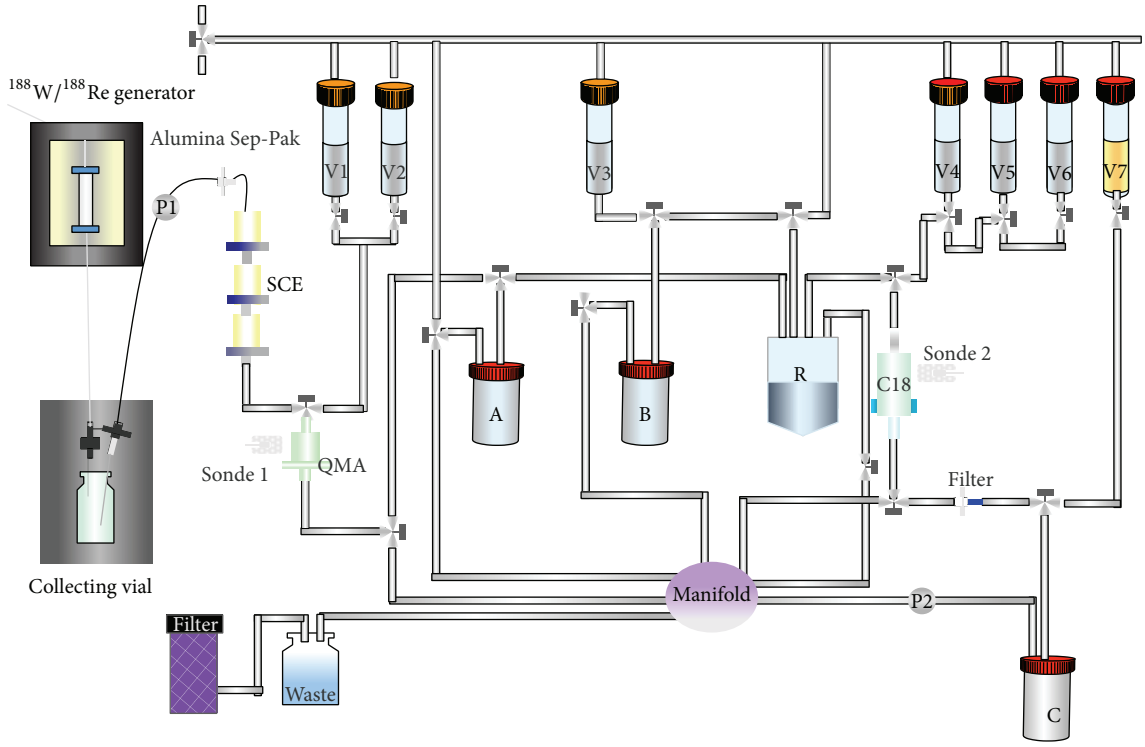

Figure 9: Flowchart illustrating the automated system for the preparation of ^{188}Re-lipiodol [46].

yield was low and the ^{188}Re complex was not stably retained in hepatoma. This result reflects the difficulty in obtaining ^{188}Re complexes in satisfactory yield and the intrinsic instability of oxo-rhenium complexes. Following the same labelling strategy, an efficient procedure for labelling lipiodol with ^{188}Re, at tracer level and under sterile and pyrogen-free conditions was developed, and the resulting radiolabelled product has been successfully employed in the treatment of a number of HCC patients [38]. This labelling procedure was based on the preliminary preparation of the highly lipophilic complex bis(diethyldithiocarbamato) nitrido [^{188}Re] rhenium (^{188}ReN-DEDC) carried out using a two-vial, freeze-dried kit formulation. This complex was, subsequently, mixed with lipiodol to yield the final radiopharmaceutical. The whole preparation involves different steps and complex manipulation of high-activity samples that dramatically increases radiation exposure of the operator, particularly in routine treatment of HCC patients. To overcome this problem, an automated system for the remote controlled preparation of ^{188}Re-lipiodol using this labeling method had been developed. This synthesis module [46] (Figure 9) was designed to accommodate the two-vial kit formulation developed previously for manually conducting the preparation of ^{188}Re-lipiodol in a hospital radiopharmacy. Through this procedure, the hydrophobic lipiodol was used as a solvent for solubilising the highly lipophilic radiocompound ^{188}ReN-DEDC that, in turn, remained strongly trapped into the organic phase. Specifically, the two-vial kit formulation allowed the high-activity preparation of ^{188}ReN-DEDC. The freeze-dried kit was, successively, produced at the Institute of Isotopes in Budapest, Hungary, following current regulatory requirements. The preparation of the complex ^{188}ReN-DEDC was relatively simple as it involved mixing of $[^{188}ReO_4]^-$ with reagents in vial A and glacial acetic acid to yield the intermediate $[^{188}Re{\equiv}N]^{2+}$ core. This group was, then, converted into the final complex ^{188}ReN-DEDC by addition of the content of vial B to vial A. Results showed that this preparation afforded ^{188}ReN-DEDC in high yield (>95%). However, the critical step exposing the operator to the highest radiation burden is when withdrawal of the supernatant aqueous layer was performed by means of a syringe. As this operation had to be carried out after labelling, it required the manipulation of highly radioactive samples. It was found that the automated process was an ideal solution to overcome this important drawback. In the automated system, the content of reconstituted vials A and B were transferred to a reactor vial (R) where the preparation of the final complex ^{188}ReN-DEDC was obtained by heating at 80°C. Most importantly, the manual separation was replaced by a chromatographic procedure carried out by passing the reaction solution pumped out of vial A through a C18 Sep-Pak cartridge onto which the complex ^{188}ReN-DEDC was quantitatively retained. This allowed the elimination of the aqueous solvent and of any residual [^{188}Re] perrhenate. Since $[^{188}ReO_4]^-$ is a highly hydrophilic substance that cannot be dissolved by nonpolar solvents, it constitutes an undesired contaminant in the final radiopharmaceutical that may cause release of activity from the target and uptake in other

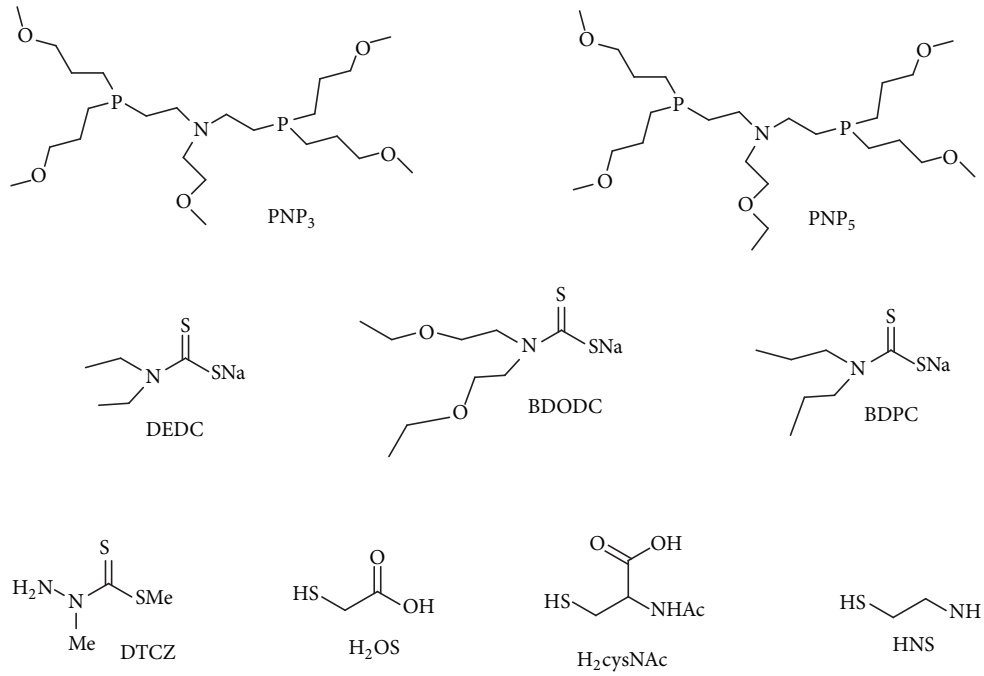

Figure 10: Chemical structure of PNP, L, and B ligands [47].

nontarget organs, particularly in the thyroid gland. Even if the complex ^{188}ReN-DEDC formed with high RCP, the purification step always ensures that all polar radioactive impurities can be efficiently separated from the reaction bulk. Thus, their complete removal appears as a sharp improvement with respect to the nonautomated preparation. The lipophilic complex was, subsequently, recovered by eluting the cartridge with absolute ethanol and then sterilized by passing the resulting solution through a 0.22 μm filter before collecting it into the final recovering vial C. Lipiodol was finally introduced into vial C after evaporating ethanol by short heating under a nitrogen stream, thus causing the complete dissolution of the radioactive complex. The radiochemical yield and chemical identity of ^{188}ReN-DEDC were checked by HPLC chromatography after preparation in the reactor vial R, and after evaporation of ethanol from vial C (Figure 9). Results showed that the complex was produced in high yield (>95%) and that it was recovered unaltered from vial C. Current advantages include a reduced operator assistance during the production process with a concomitant dramatic reduction of radiation exposure, and the possibility to afford high activity samples of ^{188}Re-lipiodol (>5 GBq), thus allowing the daily treatment of a relatively large number of HCC patients. Whole-body γ-imaging of HCC patients within 1–4 h of intrahepatic arterial administration of ^{188}Re-labeled lipiodol demonstrated excellent uptake in the lesion without significant activity in the gut and lungs [33]. Stable retention of activity in hepatoma was revealed at 20 h after administration with minimal increase in colonic activity and some uptake in the spleen. In particular, no lung activity was observed in any patient as opposed to treatment of hepatocellular carcinoma with ^{131}I-lipiodol where lung uptake approaches 35% of administrated activity.

5.4. New Methods for the Preparation of Rhenium-188 Nitride Radiopharmaceuticals. Recently a novel procedure for the preparation of nitride ^{188}ReN radiopharmaceuticals was reported [47]. The novel HO_2C-PEG600-DTCZ nitrido nitrogen atom donor for the preparation of ^{188}Re radiopharmaceuticals containing a metal nitrogen-multiple bond HO_2C-PEG600-DTCZ was obtained by conjugation of *N*-methyl-*S*-methyl dithiocarbazate [H_2N–N (CH_3)–C(=S)SCH_3, HDTCZ] with polyethylene glycol 600 (PEG600). Asymmetrical heterocomplexes of the type [^{188}Re(N)(PNP)(B)]$^{0/+}$ (PNP = diphosphine ligands, B = DBODC, DEDC, NSH, H2OS, CysNAc, HDTCZ) and symmetrical nitride compounds of the type [^{188}Re (N)(L)2] (L = DEDC, DPDC) have been prepared in high yield by using the newly designed nitride nitrogen atom donor HO_2C-PEG600-DTCZ. In Figure 10 is reported the chemical structure of PNP, L, and B ligands. A two-step procedure was applied for preparing the above symmetrical and asymmetrical complexes. The first step involved the preliminary formation of a mixture of nitride ^{188}Re precursors, which contained the [^{188}Re≡N]$^{2+}$ core, through reduction of generator eluted ^{188}Re-perrhenate with tin(II) chloride in the presence of HO_2C-PEG600-DTCZ. In the second step, the intermediate mixture was converted in either the final mixed asymmetrical complex by the simultaneous addition of diphosphine ligand and the suitable bidentate ligand B, or in the final symmetrical complex by the only addition of the bidentate ligand L.

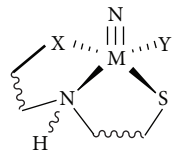

Figure 11: Schematic drawing of the molecular structure of "3 + 1" nitrido complexes (X = S, N; Y = monodentate ligand; M = ^{99m}Tc, ^{188}Re) [48].

It was also demonstrated that the novel water soluble nitride nitrogen atom donor HO_2C-PEG600-DTCZ did not show coordinating properties toward the ^{188}Re≡N core.

More recently [48] a new molecular metallic fragment for labeling biologically active molecules with ^{99m}Tc and ^{188}Re is described. This system is composed of a combination of tridentate π-donor and monodentate π-acceptor ligands bound to a $[M{\equiv}N]^{2+}$ group (M = ^{99m}Tc, ^{188}Re) in a pseudo square-pyramidal geometry (Figure 11). A simple structural model of the new metallic fragment was obtained by reacting the ligand 2,2′-iminodiethanethiol [H_2NS_2 = NH ($CH_2CH_2SH)_2$] and monodentate tertiary phosphines with the $[M{\equiv}N]^{2+}$ group (M = ^{99m}Tc, ^{188}Re). In the resulting complexes (dubbed "3 + 1 complexes"), the tridentate ligand binds the $[M{\equiv}N]^{2+}$ core through the two deprotonated, negatively charged, thiol sulfur atoms, and the neutral, protonated, amine nitrogen atom. The residual fourth position of the five-coordinated arrangement is occupied by a phosphine ligand. The chemical identity of these models ^{99m}Tc and ^{188}Re compounds was established by comparison with the chromatographic properties of the corresponding complexes obtained at the macroscopic level with the long-lived ^{99g}Tc and natural Re isotopes. The investigation was further extended to comprise a series of ligands formed by simple combinations of two basic amino acids or pseudoamino acids to yield potential tridentate chelating systems having [S, N, S] and [N, N, S] as sets of π-donor atoms. Labeling yields and *in vitro* stability were investigated using different ancillary ligands [48]. Results showed that SNS-type ligands afforded the highest labeling yields and the most robust 3 + 1 nitrido complexes with both ^{99m}Tc and ^{188}Re. Thus, this new chelating system can be conveniently employed for labeling peptides and other biomolecules with the $[M{\equiv}N]^{2+}$ group.

6. Conclusion

The availability of ^{188}W/^{188}Re generators and the use of high specific activity ^{188}Re for a variety of important therapeutic applications in nuclear medicine and oncology still continues to be of widespread interest. The attractive radionuclidic and chemical properties of ^{188}Re, and the possibility of obtaining ^{188}Re in-house and on demand make this generator system ideal for many applications. Therefore the development of new chemical strategies allows to obtain in very high yield and in physiological condition ^{188}Re-radiopharmaceutical which gives a new attractive prospective to the development of new Radiopharmaceuticals for therapy.

Conflict of Interests

The authors declare that they have no conflict of interests.

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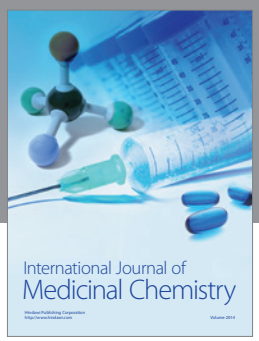

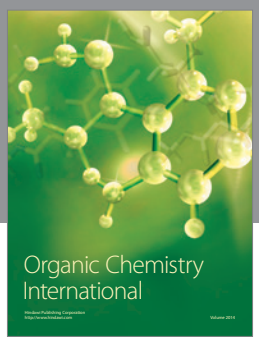

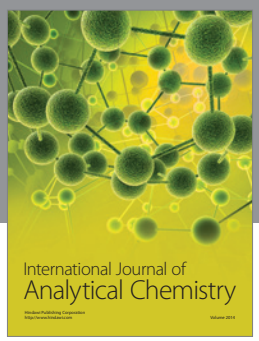

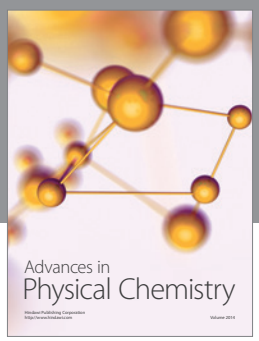

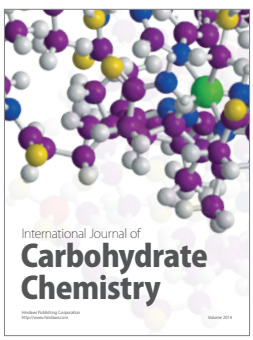

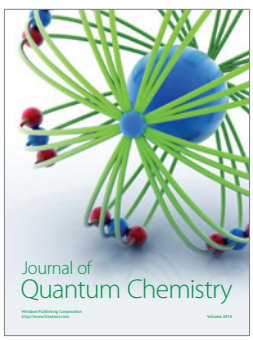

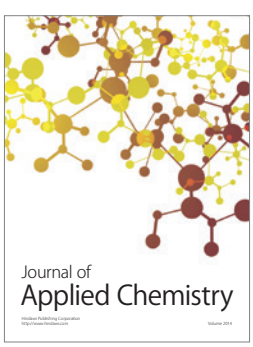

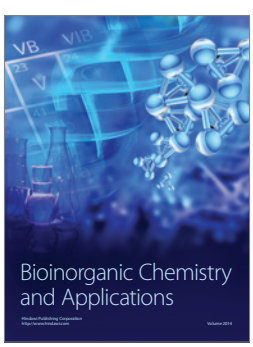

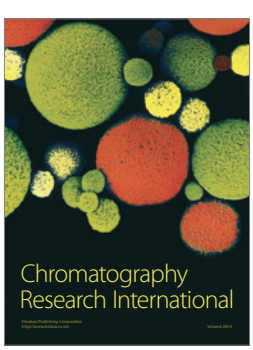

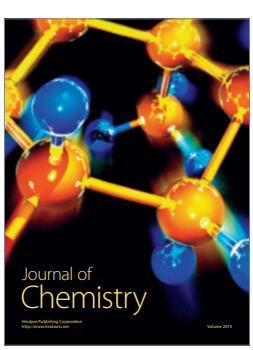

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