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Extraction of lutetium (III) from aqueous solutions by employing a single fibre supported liquid membrane

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Abstract

Transport behaviour of Lu(III) across a polypropylene hollow fibre supported liquid membrane (SLM) containing di(2-ethylhexyl)phosphoric acid (DEHPA) in dihexyl-ether as a carrier has been studied. The donor phase was 11 or 2.75 μmol dm^{-3} Lu(III) in the buffer solution consisting of 0.2 mol dm^{-3} sodium acetate at pH 2.5 - 5.0. A miniaturised system with a single hollow fibre has been operated in a batch mode. The concentration of Lu(III) was determined by indirect voltammetric method using Zn-EDTA complex. The effect of pH and volume of the donor phase, DEHPA concentration in the organic (liquid membrane) phase, the time of extraction and the content of the acceptor phase on the Lu(III) extraction and stripping behaviour has been investigated. The results have been discussed in terms of the pertraction and removal efficiency, the recovery, the memory effect and the mean flux of Lu(III). The optimal conditions for the removal of ^{177}Lu(III) from labelled ^{177}Lu-radiopharmaceuticals have been discussed and identified. The removal efficiency of Lu(III) greater than 99% was achieved at pH of the donor phase between 3.5 and 5.0 using DEHPA concentration in the organic phase of 0.47 mol dm^{-3} and the ratio of the donor to the acceptor phase of 182.

Keywords: DEHPA; Lu(III); SLM extraction; radiopharmaceutical

1. Introduction

Radiopharmaceuticals are drugs labelled with radionuclides which can be used in various diagnostic and therapeutic applications in nuclear medicine. Interest in the use of radiolabelled peptides and monoclonal antibodies for therapy is growing in the last decade [1]. Radioactive isotope ^{177}Lu and labelled radiopharmaceuticals are being increasingly used as therapeutic agents in nuclear medicine [2]. ^{177}Lu is ideally suited for radio-diagnostic and radio-therapeutic purposes due to the fact that it has both gamma and beta properties, a shorter radius of penetration than Y-90 and can easily be obtained in a pure form. ^{177}Lu has a half-life of 6.71 days and decays by emission of an electron to form hafnium-177. ^{177}Lu emits a medium energy β^- particle ($E_{\beta max}$ = 497 keV) and has the maximum particle range of ~ 2mm, making it an effective radionuclide for radiotherapeutic applications in smaller tumours and micrometastases. Furthermore, the presence of a γ-photon (E_γ = 208 keV) allows imaging and dosimetry together with radionuclide therapy [2].

The production of radiopharmaceuticals is a complex process involving production of a radionuclide, labelling of the target molecule, purification of the labelled molecule from the free radionuclide, and quality control of intermediate and final products. Although the binding efficiency of the radionuclide to the target molecule is usually very high (~ 98%), there is always a fraction of the free radionuclide left unbound. This is a very important issue in the production of radiopharmaceuticals for radiotherapy. A single dose for radiotherapy can be very high (up to 30 GBq), thus the absolute amount of carrier-free radionuclide can be significant. The free ^{177}Lu(III) accumulates in bones, so it is imperative to remove free ^{177}Lu(III) from the labelled compound. The short half-life of ^{177}Lu is beneficial from the standpoint of quickly decomposing when administered to a patient, but is problematic from the standpoint of requiring prompt purification after incorporation into a radiopharmaceutical product. The most common technique for purification of pharmaceuticals is cation-exchange chromatography. In our previous paper [3], we have proposed the application of flat-sheet SLM system for the removal of free ^{177}Lu(III) from a ^{177}Lu(III) labelled compound.

The first application of supported liquid membrane (SLM) extraction was reported more than twenty years ago [4]. Since its introduction, different approaches and applications of SLM extraction have been described such as analysis of drugs [5], pesticides [6], metal ions [7], organic pollutants [8], etc. There has been a growing interest in the use of SLM extraction in chemical and biochemical separations. Though a large number of successful applications of

SLM extraction for metal-ion separation has been reported [9, 10], very little work has been done on the application of SLM extraction for radionuclide separation [3, 11, 12].

In SLM extraction, also named pertraction [13], target analytes are extracted from an aqueous feed sample, the 'donor phase', into an organic phase entrapped in the micropores of a hydrophobic support membrane, and further transferred into the acceptor phase at the other side of the membrane. Miniaturised SLM extraction has been developed using a flat or hollow fiber membrane and applied to the concentrating of analytes prior to chromatography analysis [14, 15]. Also, SLM extraction has been applied to investigate equilibrium processes called Equilibrium Sampling Through Membrane (ESTM) in biochemical [16] and environmental [17] samples. Recently, SLM extraction concept has been extended to a single hollow fibre immersed directly in the feed solution without using any module to enclose the fibre [18]. SLM extraction in a single hollow fibre has been applied to investigate the equilibrium extraction (ESTM) of organic pollutants from waste waters [18] and for determination of drug-protein binding [19]. In addition to the well-known major benefits of membrane extraction such as large interfacial area per unit volume, low consumption of organic solvents, good opportunity for process automation etc, SLM in a single hollow fibre has several added advantages such as easy to handle approach, no special device to avoid accidental release of radioactive material, and sample volume as low as 1 cm^3. Two-phase MMLLE (microporous membrane liquid liquid extraction) resembles SLM extraction, the only difference being that the acceptor (strip) phase is not involved in the process, e.g. the analytes are extracted from an aqueous donor phase into the organic phase placed inside the lumen of a hollow fibre.

The aim of the present study is to investigate the pertraction of Lu(III) from an aqueous phase by applying miniaturised SLM extraction in a single hollow fibre and the application of this technique for the removal of unbound ^{177}Lu(III) from labelled ^{177}Lu-radiopharmaceutical.

2. Experimental

2.1. Chemicals and materials

$LuCl_3$, di(2-ethylhexyl)phosphoric acid (DEHPA), dihexyl ether (DHE), $ZnCl_2$, ethylenediaminetetraacetic acid (EDTA), tri-n-octylphosphine oxide (TOPO), lauric acid and crown ether (7, 16-didecyl-1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Potassium perchlorate, sodium acetate,

hydrochloric acid and acetic acid were purchased from Lach Ner (Neratovice, Czech Republic). All the chemicals were of the analytical-reagent grade. Deionised water was supplied from a Milli-Q water purification system (Millipore, Bedford, MA, USA). The microporous polypropylene hollow fibre membrane, ACCUREL PP 50/280 (50 μm wall thickness, 280 μm inner diameter, 0.1 μm pore size, 60% porosity), was supplied by Membrana GmbH (Wuppertal, Germany) [20].

The stock solution of $LuCl_3$ (1.1 mmol dm^{-3} Lu) was prepared in water and was stable for months at room temperature. The donor phase containing 11 or 2.75 μmol dm^{-3} Lu(III) in the buffer solution (0.2 mol dm^{-3} sodium acetate at pH ranging from 2.5 to 5.0) was prepared shortly before each experiment. In most of the experiments the acceptor phase was 2 mol dm^{-3} HCl. Also, 4 – 8 mol dm^{-3} HCl, 2 mol dm^{-3} H_2SO_4, 0.5 mol dm^{-3} ammonium carbonate and water were used as the acceptor phase. The organic membrane phase was 0.06–1.24 mol dm^{-3} DEHPA in DHE.

2.2. Measurement procedure

A 797 VA Computrace analyzer (Methrom, Switzerland) was applied for all voltammetric measurements, controlled by 797 VA Computrace software ver. 1.2. A Methrom Multimode mercury electrode, in the hanging mercury drop electrode (HMDE) mode, served as a working electrode. A Pt rod was the auxiliary electrode and an Ag/AgCl/KCl (3 mol dm^{-3}) double function electrode with ceramic diaphragm was the reference electrode.

The indirect voltammetric method using Zn-EDTA complex for determination of lutetium was described earlier [21]. Briefly, prior to electrochemical measurement, dissolved oxygen was removed from the supporting electrolyte (0.86 mol dm^{-3} $KClO_4$, 0.05 mol dm^{-3} sodium acetate buffer pH 5.4 and 0.4 μmol dm^{-3} Zn-EDTA complex) by a 5 minute purge with suprapure nitrogen. A new Hg drop (surface area of 0.30 mm^2) was made and the stirrer was simultaneously switched on (2000 rpm). Zn was deposited at -1.200 V for 90 s. The scanning was initiated with the following parameters: initial potential -1.200 V, termination potential -0.800 V, pulse amplitude 0.050 V, pulse time 0.04 s, and sweep rate 0.010 V s^{-1}. The peak current due to free Zn(II) dissociated from the Zn-EDTA complex was measured as a blank. Then an aliquot of Lu(III) was added, the cell was purged with nitrogen for 120 s, and the new voltammogram measured. Whereas Lu(III) forms a more stable EDTA complex

than Zn(II), adding of Lu(III) liberates an equivalent amount of Zn(II) and allows indirect determination of Lu(III). The concentration of lutetium was determined by using standard addition method.

2.3. Procedure of SLM extraction in a single hollow fibre

The membrane wall was impregnated by soaking it in the organic phase for 30 s followed by rinsing the outer membrane surface with water. The lumen of the hollow fibre was then filled with the acceptor phase using a 1 cm^3 syringe with 0.3 mm thick needle and the ends of the fibre were bent and wrapped with a peace of Al-foil and inserted in a 50 μL limited volume vial (Alltech). The membrane was then dipped in the donor solution placed in a 10 – 50 cm^3 bottle. During the extraction, the bottle was shaken on a shaker (Promax 2020, Heidolph, Schwabach, Germany) at 100 rpm. At regular time intervals, the hollow fibre was taken out from the donor phase and the acceptor phase from the lumen was injected into 1.5 cm^3 eppendorf vial with a 1 cm^3 syringe. The effective volume was calculated after extraction for each hollow fibre separately. Also, the acceptor phase was weighed using an analytical balance. All experiments were conducted in triplicate, and the average value and relative standard deviation were presented as the results. Similar experimental setup was described in more details in [18, 19].

2.4. Calculations

The efficiency of lutetium transfer through the liquid membrane can be evaluated by the several parameters: *P* - pertraction efficiency (%), *E* - removal efficiency (%), *M* - memory effect (%), *R* - recovery (%), and J_m - the mean flux of lutetium across the membrane. *P* is a percent of Lu(III) initially present in the donor phase that is found in the acceptor phase after extraction and can be defined by:

$$P = \frac{n_A}{n_D^{in}} = \frac{C_A V_A}{C_D^{in} V_D} \times 100 \qquad (1)$$

where n_D^{in} is the initial number of moles of lutetium in the donor phase, n_A is the number of moles of lutetium collected in the acceptor phase after the extraction, C_D^{in} is the initial Lu(III) concentration in the donor phase, C_A is the concentration of Lu(III) in the acceptor phase, V_D

and V_A are the donor and acceptor volume, respectively. The removal efficiency is the percent of the initial amount of Lu(III) removed from the donor phase:

$$E = \frac{\left(n_D^{in} - n_D^{w}\right)}{n_D^{in}} \times 100 = \frac{C_D^{in} - C_D^{w}}{C_D^{in}} \times 100 \qquad (2)$$

where n_D^w and C_D^w is the number of moles and concentration of Lu(III) in the donor phase after the extraction, respectively. If the removal of lutetium from the sample is the main objective of the process, *E* is more important parameter for the assessment of process efficiency than *P*. The memory effect is a percent of lutetium initially present in the donor phase that is captured in the organic phase after extraction:

$$M = \frac{n_D^{in} - n_D^{w} - n_A}{n_D^{in}} \times 100 = \frac{\left(C_D^{in} - C_D^{w}\right)V_D - C_A V_A}{C_D^{in} V_D} \times 100 \qquad (3)$$

The memory effect ($M=E-P$) is a result of incomplete transfer of Lu(III) across the membrane and its capture in the organic phase.

In order to quantify the rate of transport of Lu(III) through the membrane, the mean flux of lutetium across the membrane, J_m, is calculated using the equation:

$$J_m = \frac{C_A V_A}{tA} \qquad (4)$$

where *t* is the extraction time and *A* is the effective membrane area.

3. Results and Discussion

Supported liquid membrane extraction of Lu(III) in a single hollow fibre with DEHPA as an extractant and its suitability for separation of free radionuclide ^{177}Lu(III) from the radiopharmaceutical labelled with ^{177}Lu(III) has been investigated in this study. The donor solution in all experiments was $LuCl_3$ in the buffer solution (0.2 mol dm^{-3} sodium acetate at pH from 2.5 to 5.0) that represented a typical condition for radiolabelling of peptides. Lu(III) was first extracted from the donor phase placed outside a microporous hollow fibre into the organic solvent immobilised in the membrane pores. Then, Lu(III) diffused across the membrane and stripped from the other side of the membrane into the aqueous acceptor phase contained inside the hollow fibre.

3.1. Optimization of the SLM extraction parameters

The pertraction and removal efficiency are affected by various factors, such as the composition of the liquid phases, pH of the donor and acceptor phase, the rate of diffusion of the species through the organic phase, the distribution coefficient, the volume ratio of the donor to the acceptor phase, the duration of extraction, etc. [25].

3.1.1. Extraction time

The effect of the extraction time on the amount of Lu(III) extracted in a single hollow fibre is shown in Fig. 1. Lu(III) was extracted from 5 cm^3 of the donor phase (11 μmol dm^{-3} Lu(III) in 0.2 mol dm^{-3} Na-acetate buffer pH 5.0) with 0.16 mol dm^{-3} DEHPA in DHE placed in the pores of a 185-mm-long hollow fibre membrane and then reextracted into the acceptor phase (2 mol dm^{-3} HCl). The extraction time was in the range from 5 min to 24 h and the shaking speed of the sample was 100 rpm to decrease a mass transfer resistance in the donor phase.

As can be seen from Fig. 1, the equilibrium was established after about 100 min of extraction and during this time interval 93% of Lu(III) was removed from the donor phase. After reaching the equilibrium, the removal efficiency (E) remained constant over the time period investigated (24 h), which also indicated good long-term membrane stability. It is evident from Fig. 1 that the transfer of Lu(III) from the donor phase to the organic membrane phase was a fast process and 82% of Lu(III) was extracted in the first 5 min of extraction. It means that after only 5 min the Lu(III) concentration in the donor phase exceeded 88% of its value at the equilibrium. In the production of ^{177}Lu radiopharmaceutical, it is very important to achieve fast removal of free radionuclide due to their relatively short half-life.

The pertraction efficiency, *P*, of Lu(III) was 3.3% after 5 min of extraction and 6.6% at the equilibrium. Therefore, 86% of the Lu(III) removed from the aqueous phase remained in the organic phase entrapped within the pores of the membrane. These results indicate that Lu-DEHPA complex was accumulated in the organic phase, either because there was a high mass transfer resistance in the organic phase or there was the major resistance in the acceptor phase. The similar results for SLM extraction of Lu(III) were obtained using a flat-sheet membrane in continuous cross flow system [3].

Fig. 1 also shows the removal efficiency vs. time for MMLLE of Lu(III) in a single hollow fibre under the same experimental conditions and using the same amount of organic phase as in the pertraction experiments. It is clear that the removal efficiencies of Lu(III)

obtained in the pertraction experiments are higher than those in MMLLE process. Therefore, in the subsequent experiments, only pertraction process has been studied.

3.1.2. The influence of donor pH

The mechanism of extraction in a system with acidic carrier such as DEHPA is a coupled counter-transport type, which is proton driven [22]. In this study, Lu(III) was transferred from the donor to the acceptor side of the membrane, while the protons were transferred in the opposite direction, from the acceptor side to the donor side. The acceptor pH must be at least 2 pH units lower than the donor pH to create driving force for mass transfer.

The influence of pH of the donor solution on Lu(III) extraction was investigated over a donor pH range of 2.5 – 5.0 using the acceptor phase with a constant pH value of - 0.3 (2 mol dm^{-3} HCl). Fig. 2(i) shows the effect of the donor pH on the mean flux of Lu(III) across the organic phase over the time interval from zero to 60 min at a Lu(III) concentration in the donor phase of 11 µmol dm^{-3} and a DEHPA concentration in the organic membrane phase of 0.16 mol dm^{-3}. The mean Lu(III) flux increases with increasing pH to 3.0 and reaches a plateau value in the pH range from 3.0 to 4.0. With further increase of pH from 4.0 to 5.0, J_m sharply decreases.

Lanthanide metals (Ln) can form complexes of different structure with DEHPA depending on pH of the aqueous solution [22, 23]. The flux of lanthanides across SLM depends on the molecular structure of a metal-DEHPA complex, which in turn is affected by pH of the donor phase [23]. Depending on the lanthanide ion and pH of the solution, Ln can form different species with DEHPA such as $LnXA_2(HA)_3$, LnA_32HA and LnA_3HA, where X stands for an anion in the donor solution (e.g. nitrate or chloride anion), and HA and A stand for DEHPA in the molecular and deprotonated form, respectively. As pointed out by Moreno and Valiente [22], $LnXA_2(HA)_3$ is responsible for the transport of lanthanide (Ln) cations through supported liquid membranes and is increasingly dominant form of complex as advancing in the lanthanide series. At pH > 3.5 the dominant complex which is formed between Ln(III) and DEHPA is $LnA_3(HA)_2$ which probably do not take part in lanthanide membrane transport [22]. At pH < 1.5, Lu(III) is present in the aqueous solution in the ionic form as $LuCl^{2+}$ and does not form complexes with DEHPA. It is in agreement with our experimental data (not shown here) that in MMLLE the removal efficiency of Lu(III) was

only 24% at pH 1.5. In addition, at very low pH values, the driving force for the counter-current transfer of H^+ ions is too low.

The pH dependence of lutetium flux through the membrane containing DEHPA (Fig. 2 (i)) agrees with the rate of transfer of lanthanides through the same liquid membrane reported earlier [22, 23]. At lower pH levels (2.5 – 3.5) $LuClA_2(HA)_3$ is responsible for the Lu(III) transport through the liquid membrane and the flux reaches maximum. At pH 4.0, $LuA_3(HA)_2$ complex starts to form in the organic membrane phase and the rate of mass transfer decreases due to lower permeability of $LuA_3(HA)_2$. At pH 5.0 the mean flux is significantly reduced, probably because virtually non-permeable $LuA_3(HA)_2$ complex is predominantly present in the organic phase.

The results shown in Fig. 2(ii) support the conclusion that $LuA_3(HA)_2$ complex is only slightly permeable through the liquid membrane at pH 5. The pertraction of Lu(III) increased from 16.7 to 21% with increasing the pH from 2.5 to 4.0 and then sharply fell to 6.5% at pH 5.0. The removal of Lu(III) from the donor phase increased from 51 to 88% with increasing the donor pH from 2.5 to 5.0. The number of free DEHPA molecules at the donor solution-organic phase interface was high enough to allow the formation of new complex molecules in spite of the fact that re-extraction on the other side of the membrane was poor. It is also evident from Fig. 2 (ii) that the memory effect increased with increasing the donor pH due to forming a non-permeable complex.

The similar results for SLM extraction of Lu(III) were obtained earlier using a flat membrane in a cross-flow system [3]. Also, the accumulation of metal ions (Cu, Zn and Ni) in the organic membrane phase (0.5 mol dm^{-3} di-(2-ethylhexyl) dithiophosphoric acid-activated composite membrane) and low degrees of re-extraction over a prolonged time were observed by Macanás and Muňoz [26].

3.1.3. The influence of DEHPA concentration

The variation of Lu(III) removal with the carrier concentration in the range from 0 to 1.24 mol dm^{-3} DEHPA is shown in Fig. 3. The experiments were carried out at pH 4.0 to obtain maximum removals of Lu(III), as suggested from Fig. 2(ii). The maximum lutetium flux was achieved at the range of DEHPA concentration from 0.16 to 0.47 mol dm^{-3}. At the DEHPA concentration higher than 0.47 mol dm^{-3}, the rate of transfer of Lu(III) across the liquid membrane is lower due to higher viscosity of the organic phase.

Fig. 3(ii) shows the effect of DEHPA concentration on the *P*, *E* and *M* parameters. The removal of Lu(III) increased from 6 to 90% with increasing the DEHPA concentration from 0 to 0.47 mol dm^{-3}, which shows that in the absence of DEHPA the extraction is negligible. In the range of DEHPA concentration between 0.47 and 1.24 mol dm^{-3}, the rate of complexation reaction was independent on the DEHPA concentration due to large excess of DEHPA molecules over Lu(III).

The pertraction efficiency increased from 16 to 22% with increasing the DEHPA concentration from 0.06 to 0.16 mol dm^{-3}, and then remained constant with further increase in the DEHPA concentration to 0.93 mol dm^{-3}. At the highest DEHPA concentration applied (1.24 mol dm^{-3}), *P* was reduced to 10% because the equilibrium in complexation reaction was shifted toward the formation of Lu(III)-DEHPA complex. As a result, *M* reached a maximum value at the highest DEHPA concentration.

3.1.4. The influence of the acceptor phase composition

Different acceptor solutions have been prepared: 0.1 – 8 mol dm^{-3} HCl, 2 mol dm^{-3} H_2SO_4, 0.5 mol dm^{-3} ammonium carbonate and pure water and the efficiency of SLM extraction of Lu(III) was measured (Table 1). Lu(III) was extracted from the 5 cm^3 donor solution (11 μmol dm^{-3} Lu(III) in 0.2 mol dm^{-3} Na-acetate buffer pH 3.5) with 0.16 mol dm^{-3} DEHPA in DHE as the extractant. The effective membrane length was 185 mm. The removal efficiency of Lu(III) from the donor phase was in the range from 74 to 95% for different acceptor phases listed in Table 1. A significant decrease in *E* at 8 mol dm^{-3} HCl as compared with 2 mol dm^{-3} HCl can be explained by an increased transport of H^+ ions from the acceptor to the donor solution followed by the change in pH of the donor phase. A decrease in pH of the donor solution by 0.4 pH units was detected only using 8 mol dm^{-3} HCl as the acceptor phase. It means that the buffer capacity of the donor solution was enough to neutralize the transport of H^+ ions from the acceptor to the donor in all cases except at the highest acid concentration applied. The highest pertraction (18%) of Lu(III) was obtained at 2 mol dm^{-3} HCl or H_2SO_4 in the acceptor phase. On the other hand, the lowest pertraction (0.3 and 0.4%) was obtained for ammonium carbonate and water as the acceptor. It can be concluded that the stripping of Lu(III) from the organic phase is negligible if there is no pH difference between the donor and acceptor phase. Also, if the concentration of H^+ ions is too high (8 mol dm^{-3}

HCl), the transport of H^+ ions to the donor phase causes a reduction in the donor pH and the decrease in the removal efficiency.

3.1.5. The influence of carrier in the organic phase

To try to improve Lu(III) permeation through the liquid membrane, the following carriers in the organic phase have been investigated: a binary mixture of DEHPA and TOPO, a mixture of TOPO and TBP, Lix 84-I, a crown ether and a mixture of crown ether and lauric acid. Lu(III) was extracted from 5 cm^3 of the donor phase (11 μmol dm^{-3} Lu(III) in 0.2 mol dm^{-3} Na-acetate buffer pH 3.5) with different carriers dissolved in DHE. The organic phase was entrapped in the pores of a 185-mm-long hollow fibre membrane. 2 mol dm^{-3} HCl was used as the acceptor phase. The results are shown in Table 2. It is clear that the binary mixture of DEHPA and TOPO yielded a somewhat lower removal efficiency and pertraction than pure DEHPA solution. The use of other well-known metal carriers such as TOPO and TBP, Lix 84-I and crown ethers resulted in significantly lower removal efficiencies as compared to DEHPA solution and no improvement in pertraction efficiency was achieved.

3.1.6. The influence of donor volume, Lu(III) concentration, hollow fibre length and number of extraction stages on SLM extraction

In order to meet the highest requirements regarding the lutetium removal from the donor phase, the influence of the donor volume, hollow fibre length and Lu(III) concentration was investigated and the results are shown in Table 3. Two SLM extraction processes have been studied: (i) one-stage process in which a hollow fibre was in contact with the donor phase for 2 h and (ii) two-stage process, in which the fibre used in the first 60 min of operation was replaced by a freshly prepared fibre and the process was allowed to continue for another 1 h. As can be seen from Table 3, the two-stage process yields much better Lu(III) removals at relatively high initial concentrations of Lu(III) in the donor phase and large donor volumes. As an example, the Lu(III) removal at the initial donor concentration of 55 μmol dm^{-3} was about 66 and 87 % in one-stage and two-stage process, respectively. On the other hand, at 11 μmol dm^{-3} of Lu(III) in the donor, the removal was 95 and 97 % in one-stage and two-stage process, respectively.

In the single-stage process, under the same experimental conditions the pertraction is much more efficient for longer fibres, whereas the Lu (III) removal is only slightly better. At the same number of moles of lu(III) in the donor, the Lu(III) removal and pertraction is higher at the higher donor concentration. The higher the donor concentration, the higher the rate of transfer of Lu(III) through the liquid membrane and the equilibrium is reached sooner. Probably, at the donor concentration of 11 μmol dm^{-3} the equilibrium between the membrane and acceptor phase was not established after 2 h and consequently, the pertraction efficiency was significantly lower.

The effect of donor volume on the Lu(III) removal and pertraction efficiency after 120 min of operation in one-stage process was shown in Fig. 4. The initial Lu(III) concentration in the donor phase was 14.6 μmol dm^{-3} at pH 3.5 and the acceptor volume was constant at 11 μL. It is evident that both the removal and pertraction efficiency can be significantly improved by decreasing the amount of the donor phase. The removal efficiency was as high as 95% when the ratio of the donor volume to acceptor volume was 182.

3.2. The optimal conditions for removal of unbound ^{177}Lu(III) from ^{177}Lu-labeled compound

The optimal conditions for the removal of unbound ^{177}Lu(III) from ^{177}Lu-labeled compound can be established based on the experimental results obtained in this study. The maximum removal efficiency of Lu(III) of 95% was achieved when the V_D/V_A ratio had the lowest value, i.e. when the donor volume was 2 cm^3 (Fig. 4). It can also be seen from Figs. 2 and 3 that the maximum removal was obtained at pH of the donor phase in the range from 3.5 to 5.0 and at the DEHPA concentration of 0.47 mol dm^{-3}. In order to obtain the greatest possible removal efficiency, Lu(III) was extracted under the following conditions: the donor phase was 2 cm^3 of 0.0146 mmol dm^{-3} Lu(III) in 0.2 mol dm^{-3} Na-acetate buffer at pH 3.5, the organic phase was 0.47 mol dm^{-3} DEHPA in dihexyl ether and the acceptor phase was 11 μL of 2 mol dm^{-3} HCl. After 120 minutes of single-stage extraction, 99% of Lu(III) was extracted from the donor solution. When greater volumes of the donor phase should be treated, the similar separation effects can be obtained using either longer fibres or two-stage operation.

4. Conclusion

The obtained results indicate that SLM extraction of Lu(III) in a single hollow fibre is highly suitable technique when working with small-volume samples, since the operation of conventional membrane contactors requires larger feed volumes for recirculation. In particular, miniaturised single hollow fibre membrane device used in this work is highly suitable for purifying radiopharmaceuticals after labelling procedure, because the volumes of labelled compounds are usually very small (1-2 cm^3). Also, the SLM extraction using a single hollow fibre in a batch mode has two additional advantages over conventional SLM devices: first, it is easy to handle, which can be beneficial to avoid radioactive contamination, and secondly, the volume of labelled compound solution remains unchanged.

The transfer of Lu(III) from the donor phase to the organic membrane phase was a fast process and 82% of Lu(III) was extracted from 5 ml of donor in the first 5 min of extraction. The time needed to achieve the equilibrium was 100 min. Regarding the removal of Lu(III), the optimum DEHPA concentration in dihexyl-ether was found to be 0.47 mol dm^{-3} and the optimum pH of the donor phase was in the range from 3.5 to 5.0.

For lutetium (III) extraction from 5 cm^3 donor volume containing 11 μmol dm^{-3} Lu(III), the highest removal efficiency (97%) and pertraction (44.3%) was obtained applying the hollow fibre with an effective length of 370 mm.

Practical application of SLM extraction using a single hollow fibre for purifying ^{177}Lu-labeled compound from the unbound ^{177}Lu(III) primarily depends on the removal efficiency of Lu(III) from the donor phase. The maximum removal efficiency was achieved when the V_D/V_A ratio was the lowest, i.e. for the donor volume of 2 cm^3. Based on the obtained results, one can conclude that SLM extraction of Lu(III) in a single hollow fibre presents a simple and fast method, which can be applied for highly efficient removal of free radionuclide, ^{177}Lu(III), from the ^{177}Lu-labeled compound.

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FIGURE CAPTIONS

Figure 1. The effect of extraction time on the amount Lu(III) extracted in a single hollow fibre. Donor phase: 5 cm^3 11 μmol dm^{-3} Lu(III) in 0.2 mol dm^{-3} Na-acetate buffer pH 5.0; Acceptor phase: 2 mol dm^{-3} HCl; Organic membrane phase: 6 μl of 0.16 mol dm^{-3} DEHPA in dihexyl ether. Legend: ○ – *P*, pertraction efficiency (%); □ – *E*, removal efficiency for pertraction (%); ∆ – *R*, recovery (%);■ – removal efficiency for MMLLE (%).

Figure 2. (i) The effect of donor pH on the mean flux of Lu(III) across the membrane; **(ii)** The effect of donor pH on the separation effects. Donor phase: 5 cm^3 11 μmol dm^{-3} Lu(III) in 0.2 mol dm^{-3} Na-acetate buffer, pH range of 2.5 - 5.0; Acceptor phase: 2 mol dm^{-3} HCl; Organic membrane phase: 0.16 mol dm^{-3} DEHPA in dihexyl ether. The extraction time was 60 min and the average effective membrane length was 185 mm. Legend: ■ – J_m, mean flux (mol m^{-2} s^{-1}); ○ – *P*, pertraction efficiency (%); □ – *E*, removal efficiency (%); ∆ - *M*, memory effect (%).

Figure 3. (i) The effect of the carrier concentration on the mean flux of Lu(III) across the membrane; **(ii)** The influence of DEHPA content in dihexyl ether on Lu(III) extraction in a single hollow fibre. Donor phase: 5cm^3 11 μmol dm^{-3} Lu(III) in 0.2 mol dm^{-3} Na-acetate buffer pH 4.0; Acceptor phase: 2 mol dm^{-3} HCl; Organic membrane phase: 0.06 – 1.24 mol dm^{-3} DEHPA in dihexyl ether. The extraction time was 120 min and the average effective membrane length was 185 mm. Legend: ■ – J_m, mean flux (mol m^{-2} s^{-1}); ○ – *P*, pertraction efficiency (%); □ – *E*, removal efficiency (%); ∆ - *M*, memory effect (%).

Figure 4. The effect of donor volume on the Lu(III) concentration in the donor and acceptor phase after 120 min of extraction. Donor phase: 14.6 μmol dm^{-3} Lu(III) in 0.2 mol dm^{-3} Na-acetate buffer pH 3.5; Acceptor phase: 2 mol dm^{-3} HCl; Organic membrane phase: 0.16 mol dm^{-3} DEHPA in dihexyl ether. The extraction time was 120 min and the average effective membrane length was 185 mm. Legend: ○ – *P*, pertraction efficiency (%); □ – *E*, removal efficiency (%).

Table 1. The influence of the acceptor phase composition on the efficiency of SLM extraction

Acceptor	*E*,%	*P*,%	*M*,%
0.1 mol dm^{-3} HCl	94.7	17.9	76.8
1 mol dm^{-3} HCl	93.7	18.2	75.5
2 mol dm^{-3} HCl	94.6	18.7	75.9
4 mol dm^{-3} HCl	91.6	8.1	83.5
8 mol dm^{-3} HCl	74.0	6.4	67.6
2 mol dm^{-3} H_2SO_4	90.6	17.9	72.7
0.5 mol dm^{-3} $(NH_4)_2CO_3$	90.3	0.3	90.0
Milli-Q water	83.4	0.4	83.0

Table 2. The influence of different carriers in the organic phase on the efficiency of Lu(III) pertraction

Extractant	E,%	P,%	M,%
0.16 M* DEHPA	94.6	18.7	75.9
0.16 M DEHPA + 8.6 mM lauric acid	94.1	4.9	89.2
0.16 M DEHPA + 0.32 M TOPO	91.1	15.7	75.4
0.32 M TOPO + 0.93 M TBP	32.7	1.6	31.1
60% Lix 84-I	29.8	0.8	29.0
0.007 M crown ether	0.8	-	-
0.007 M crown ether + 0.009 M lauric acid	4.5	-	-

*M is mol dm^{-3}

Table 3. Comparison between one-stage and two-stage SLM extraction of Lu(III): Donor solution: 5 or 20 cm^3 Lu(III) in 0.2 mol dm^{-3} Na-acetate buffer at pH 3.5 or 5.0; Acceptor phase: 2 mol dm^{-3} HCl; Organic membrane phase: 0.16 mol dm^{-3} DEHPA in DHE; the extraction time was 120 min. In two-stage process, after 1 h of operation the hollow fibre used for extraction in the first stage was replaced by another one freshly prepared.

V_D, cm^3	pH	C_D^{in}, µmol dm^{-3}	Hollow fibre length, mm	Type of SLM extraction	*E*, %	*P*, %	*M*, %
5	3.5	11	185	One-stage	94.6	18.7	75.9
5	3.5	11	370	One-stage	97	38.3	58.7
5	3.5	55	185	One-stage	66.5	13.6	52.9
5	3.5	55	185	Two-stage	87.4	16.1	75.4
5	5.0	11	185	One-stage	93	6	87
5	5.0	11	185	Two-stage	96.7	11	85.7
20	3.5	2.75	185	One-stage	84.7	9.1	75.6
20	3.5	2.75	370	One-stage	90.8	19.2	71.6
20	3.5	2.75	185	Two-stage	92.9	15.3	77.6

Fig. 1

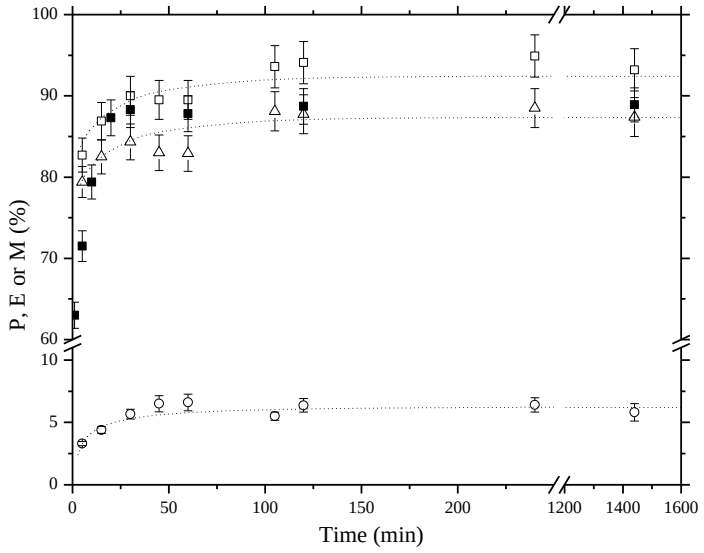


Fig. 2

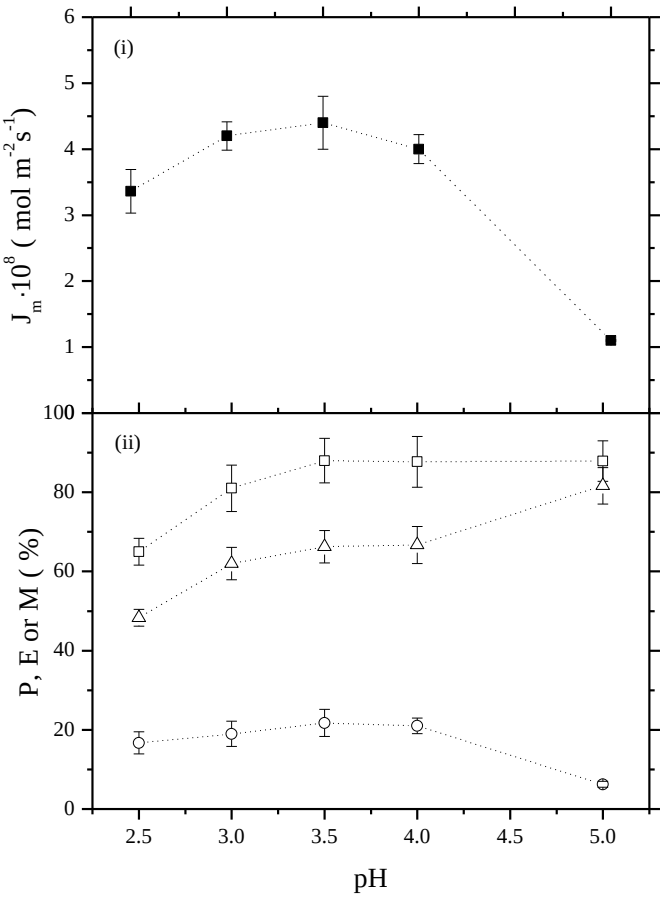


Fig. 3

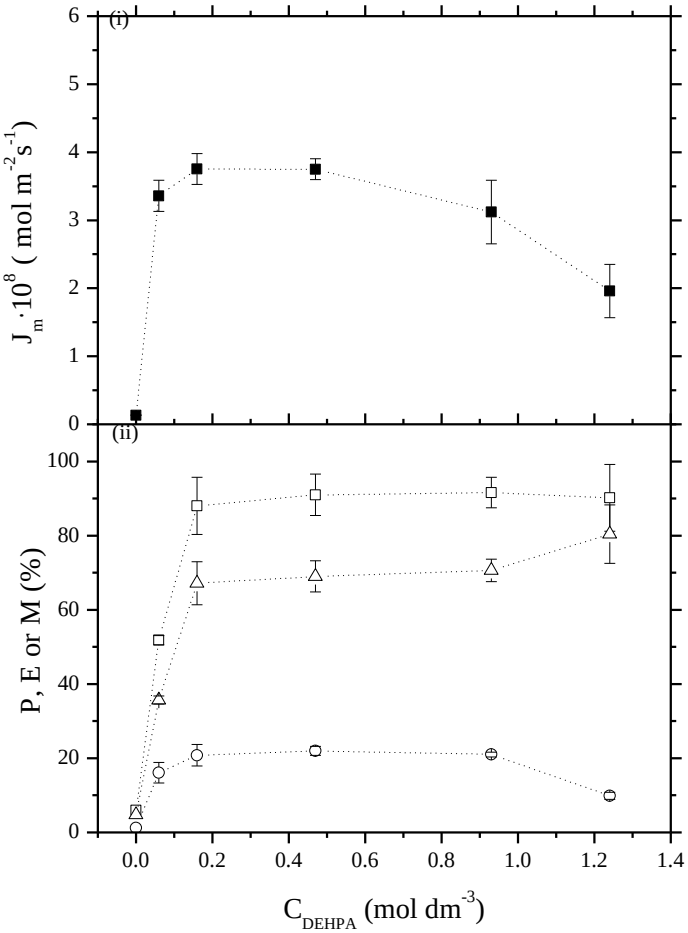
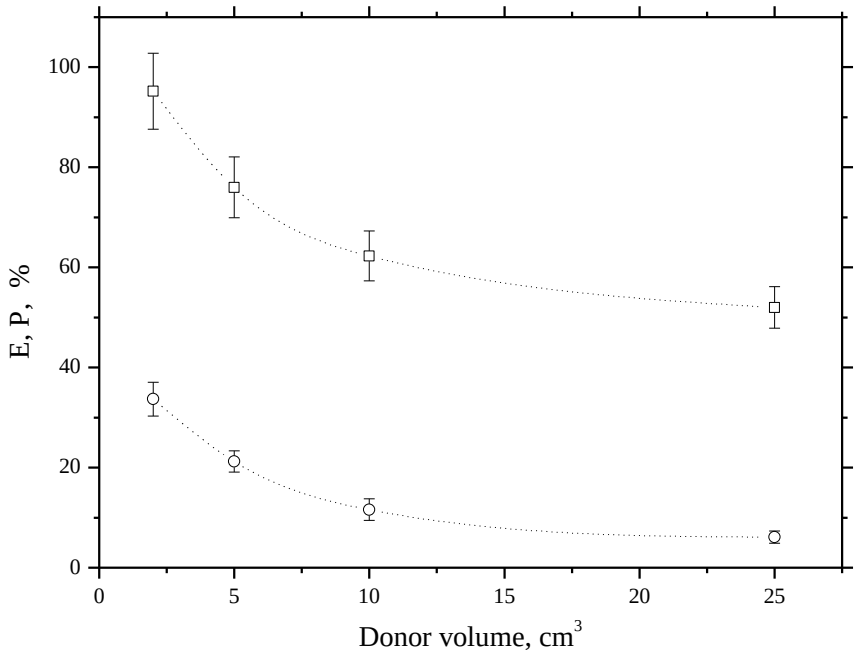

(i)
(ii)
$J_m \cdot 10^8$ (mol m^{-2} s^{-1})
P, E or M (%)
C_{DEHPA} (mol dm^{-3})

Fig. 4


E, P, %
Donor volume, cm^3