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Membrane-assisted liquid phase extraction of Lu(III) in U-shaped contactor with a single hollow fibre membrane

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ABSTRACT

Extraction of Lu(III) from an aqueous LuCl_3 solution at pH 3.5 into an organic phase containing 5% (v/v) di(2-ethylhexyl)phosphoric acid (DEHPA) in di-n-hexyl ether (DHE) immobilized within a polypropylene hollow fibre membrane and a simultaneous back-extraction of Lu(III) into 2 mol dm^{-3}

HCl solution has been investigated using two miniaturized supported liquid membrane (SLM) systems: (i) a single hollow fibre membrane, with stagnant acceptor phase in the lumen, immersed into a donor phase reservoir; (ii) U-shaped module containing a single hollow fibre membrane with a closed-loop recirculation of aqueous phases through the module. In the stagnant SLM system, the maximum extraction efficiency was 8.8% due to limited acceptor volume and absence of flow within the lumen. In recirculating SLM system, after 80 min of operation at the donor phase flow rate of $5.3 \text{ cm}^3 \text{ min}^{-1}$, the acceptor phase flow rate of $0.4 \text{ cm}^3 \text{ min}^{-1}$ and the donor-to-acceptor phase volume ratio of 6.7, the equilibrium removal efficiency of Lu(III) reached 88% and less than 5% of Lu(III) extracted from the feed solution was kept in the organic phase. For shell side flow of the donor phase at the Reynolds number of 3–34, the overall mass transfer coefficient was proportional to the donor flow rate raised to the power of 0.63 and increased from 2.3 to $8.8 \times 10^{-5} \text{ m s}^{-1}$. The rate-limiting step was the mass transfer of Lu(III) within the boundary layer of the donor phase adjacent to the outer wall of the hollow fibre.

Keywords: membrane extraction, supported liquid membrane, radiopharmaceuticals, Lu(III), DEHPA

1. INTRODUCTION

Membrane-assisted liquid-phase extraction (LPE) processes have been applied to the separation of a wide range of analytes including biological molecules¹⁻³, metal ions⁴⁻⁸, organic pollutants⁹⁻¹³ and radionuclides¹⁴⁻¹⁶. Supported liquid membrane (SLM) extraction is a LPE technique that involves simultaneous extraction and re-extraction using either flat sheet or hollow fibre hydrophobic membranes. The organic phase (extractant) is immobilized by capillary forces in the membrane pores, while the aqueous feed (donor) and the stripping (acceptor) solutions are placed on opposite sides of the membrane. Mass transfer in SLM extraction comprises diffusion of the analyte of interest from the bulk of the donor phase to the donor/organic phase interface, partitioning of the analyte between the donor

phase and the organic phase, diffusion of the analyte through the organic phase immobilized within the pores and the analyte re-extraction into the acceptor phase.

In recent years, membrane-assisted liquid-phase microextraction (LPME) has emerged as a convenient alternative to conventional sample pretreatment methods. The concept of LPME is based on the SLM extraction principle and allows simultaneous extraction and enrichment of analytes due to the high donor (up to 1 L) to acceptor (at μL level) phase volume ratio^{17,18}. Due to reduced consumption of hazardous organic solvents, very efficient sample clean-up, pre-concentration, easy automation and on-line coupling to the analytical instruments, primarily chromatographic, membrane-assisted LPME systems have broad application potential within areas such as biochemical, environmental and pharmaceutical analyses¹⁹.

Membrane-assisted LPME have been performed in two classes of miniaturized SLM extraction systems: (i) flat-sheet SLM in flow systems, demonstrated by Jönsson et al.²⁰ and (ii) hollow fiber SLM in stagnant systems also known as hollow fiber liquid-phase microextraction (HF-LPME), introduced by Pedersen-Bjergaard and Rasmussen²¹. The volume of the acceptor solution in miniaturized SLM extraction systems is typically in the range of 2-30 μL . Both SLM configurations have their own advantages and limitations: HF-LPME employs inexpensive membranes which are normally discarded after use, equipment is very simple but the automation of the extraction step is difficult; flat-sheet SLM contactor normally reuse the membrane, with a consequent risk of carryover effects, equipment is more complex than for HF-LPME but well suited to on-line hyphenation with chromatographic techniques²². The choice of adequate SLM configuration primarily depends on particular analytical application.

Miniaturized SLM extraction systems are convenient to use when working with small volume samples, such as biological samples (blood, plasma, serum, etc.) or radiopharmaceutical formulations. In our previous work^{23,24}, we have investigated the application of two miniaturized SLM extraction systems to the removal of the free $^{177}\text{Lu}(\text{III})$ from the $^{177}\text{Lu}(\text{III})$ -labelled compound: (i) dynamic, continuous-flow flat-sheet membrane contactor and (ii) static (batch) liquid-phase microextraction system in a single hollow fibre. Radionuclide ^{177}Lu possesses favorable radiophysical characteristics for

therapeutic applications in nuclear medicine, hence a large number of radiochemistry and radiopharmacy investigations were orientated toward the potential ^{177}Lu -radiopharmaceutical production and its application in endoradiotherapy of malignant tumors²⁵⁻²⁸. One of the main steps in the production process of ^{177}Lu labeled radiopharmaceuticals for human *in vivo* use is the separation of bound from unbound radionuclide, since the latter may have harmful effects on patient's health. The most common technique for purification of radiopharmaceuticals is cation-exchange chromatography. Recently, we have shown that membrane-assisted LPE in miniaturized extraction systems can be used as an alternative process for the separation of unbound radionuclide from the labeled radiopharmaceutical after the labeling step^{23,24}.

The operating conditions in both systems used for extraction of Lu(III) were similar: the donor phase was the buffer which was used for further processing, the extraction was facilitated using di(2-ethylhexyl)phosphoric acid (DEHPA) as a carrier dissolved in the organic solvent, acceptor (2 mol dm^{-3} HCl) in both microextraction systems was stagnant, with a volume of 10 to 15 μl . The high removal of Lu(III) (up to 99%) from the aqueous phase is highly desirable for purifying compounds labeled with lutetium and it was achieved using both membrane-assisted LPE systems. However, the recovery of the extracted Lu(III) from the organic into the acceptor phase was low in both systems due to high mass transfer resistance either in the membrane or acceptor phase.

According to the literature data^{29,30} and our previous results²⁴, the removal of Lu(III) from the donor solution as well as the transport of Lu(III) across SLM containing DEHPA as a carrier strongly depends on pH of the donor solution. Although the Lu-DEHPA complex permeating through the liquid membrane was formed in the donor at the optimum pH of 2.5–3.5, the low value of extraction efficiency (20%) suggested that the complex was accumulated within the membrane. On the other hand, the distribution coefficient of Lu(III) between the acceptor and organic phase was 0.2, as determined by static liquid-liquid extraction at 1:1 phase volume ratio²³, indicating that almost all of the Lu(III) was re-extracted from the organic phase. The length of hollow fibre had little effect on the removal of Lu(III) from the donor phase, but the extraction efficiency was higher for the longer membrane. Based on the

above findings, it was assumed that a small acceptor volume could be the reason for a low re-extraction of Lu(III). This assumption was supported by the overall mass transfer resistances determined in stagnant HF-LPME³¹. The acceptor volume in the batch extraction system is limited by the length of the hollow fibre (the maximum length is about 30 cm) that can be immersed in a small volume of the donor phase (5-10 cm³), because the acceptor phase is held in the lumen of the fibre. The acceptor volume can be decoupled from the fibre length using SLM extraction system with continuous recirculation of the acceptor phase.

The purpose of this study was to compare two miniaturized membrane systems for solvent extraction of Lu(III), a novel recirculating HF-LPE system with U-shaped contactor and previously used batch HF-LPME system²⁴. The novel HF-LPE system was operated under continuous closed-loop recirculation of both the donor and acceptor phase with the aim of improving the efficiency of re-extraction of Lu(III) from the organic phase, which was the main bottleneck in the static system²⁴. The influence of the donor flow rate on the mass transfer of Lu(III) in the applied system was also studied.

2. EXPERIMENTAL SECTION

2.1. Chemicals and materials.

LuCl₃, DEHPA, di-n-hexyl ether (DHE), ZnCl₂ and ethylenediaminetetraacetic acid (EDTA) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Potassium perchlorate, sodium acetate and hydrochloric acid were purchased from Lach Ner (Brno, Czech Republic). All the chemicals were of 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, was supplied from Membrana GmbH (Wuppertal, Germany).

The standard stock solution of LuCl₃ containing 100 mg dm⁻³ or 0.6 mmol dm⁻³ Lu(III) was prepared by dissolving 16.1 mg of LuCl₃ in 0.1 dm³ water. The stock solution was stable for months at room temperature. Working donor solutions were prepared shortly before each experiment by appropriate

dilution of the stock solution with sodium acetate buffer solution. The organic phase was prepared by dissolving DEHPA in DHE and the acceptor (stripping) phase was prepared by diluting HCl with water.

2.2. HF-LPME in a stagnant system.

A stagnant (non-recirculating) HF-LPME system consisted of a donor phase reservoir and a single hollow fibre membrane of variable length that was dipped into the donor phase (Fig. 1 (i)). The membrane wall was impregnated with 5% (v/v) DEHPA, while the lumen of the fibre was filled with 2 mol dm⁻³ HCl. The acceptor volume was controlled within the range of 0.01–0.06 cm³ by changing the fibre length. The Lu(III) ions were extracted from 20 cm³ of the donor solution containing 2 mg dm⁻³ Lu(III) in 0.2 mol dm⁻³ sodium acetate buffer at pH 3.5. During the extraction process, the HF-LPME system was shaken on a shaker at 100 rpm to improve the rate of mass transfer in the donor phase. The samples of the donor and acceptor phase were collected after 120 min of extraction to determine Lu(III) concentration. More detailed description of the experimental procedure can be found in our previous papers^{24,31}.

Figure 1. Schematic of the experimental set-up used for the SLM extraction of Lu(III): (i) static, HF-LPME system, (ii) dynamic, HF-LPE system: C – contactor, R1 – feed reservoir, R2 – stripping reservoir, P1, P2 – peristaltic pumps for the donor and acceptor phase, respectively, M – magnetic stirrer.

2.3. Experimental set-up of a recirculating HF-LPE system.

The membrane-assisted LPE of Lu(III) was performed in a membrane contactor designed and constructed in our laboratory, which consisted of a single polypropylene hollow fibre membrane. The fibre was inserted within a U-shaped glass tube equipped with separate inlet and outlet tube connections for both aqueous phases. The membrane had a wall thickness of 50 μm , an inner diameter of 280 μm , a mean pore size of 0.1 μm , and a porosity of 60%³². The effective membrane length in the contactor was 10 cm, and the effective outer ($A_o = \pi d_o L_{ef} \varepsilon$) and inner ($A_i = \pi d_i L_{ef} \varepsilon$) surface area of the membrane was 0.7 and 0.5 cm^2 , respectively. The organic phase immobilized in the pores of the membrane was 0.16 mol dm^{-3} (5%) DEHPA in DHE. The volume of the organic phase was approximately 3 μl , calculated from the equation: $V_o = \pi(d_o^2 - d_i^2)L_{ef}\varepsilon/4$.

A schematic of the experimental set-up is shown in Fig. 1 (ii). SLM extraction system consisted of a hollow-fibre module (C), two reservoirs for the aqueous donor and acceptor solutions (R1 and R2, respectively), two peristaltic pumps (Perkin-Elmer, Waltham, Mass., USA), P1 and P2, tubes (PharMed[®], Cole-Parmer Instrument Company, Vernon Hills, Ill., USA) and magnetic stirrer (M). The donor solution (11 $\mu\text{mol dm}^{-3}$ Lu(III) in the 0.2 mol dm^{-3} sodium acetate buffer, pH 3.5) with a total volume of 20 cm^3 was fed along the shell side of the fibre and recirculated in a closed loop between the module and reservoir R1 using peristaltic pump P1. pH of the donor phase was maintained at a constant level due to the presence of a sodium acetate buffer in the donor phase and a relatively high donor to acceptor volume ratio. The flow rate of the donor phase was 0.4-5.3 $\text{cm}^3 \text{min}^{-1}$ and the total holdup volume of the tubing used for the recirculation of the donor phase was 1 cm^3 . The donor phase was vigorously mixed in reservoir R1 by a magnetic stirring bar to obtain nearly ideal mixing conditions. The acceptor solution (2 mol dm^{-3} HCl) with a total volume of 3 cm^3 was pumped through the lumen of the hollow fibre using peristaltic pump P2 and recirculated between the module and reservoir R2. The flow rate of the acceptor phase was 0.4 $\text{cm}^3 \text{min}^{-1}$ and the total holdup volume of the tubing used for the

acceptor phase recirculation was 0.6 cm^3 . The donor and acceptor aqueous phases were circulated co-currently through the module.

All experiments were carried out at room temperature. Samples were periodically collected from the donor and acceptor reservoir to determine Lu(III) concentration. The withdrawn volume of each phase was sufficiently small to keep the total volume constant.

2.4. Procedure for the measurement of Lu(III) concentration.

The concentrations of Lu(III) in the donor and acceptor phase were determined using previously developed indirect voltammetric method via Zn-EDTA complex³³. A 797 VA Computrace analyzer (Metrohm, Herisau, Switzerland) was used for all voltammetric measurements, controlled by 797 VA Computrace software ver. 1.2. A Metrohm 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 supporting electrolyte consisted of 0.86 mol dm^{-3} KClO_4 , 0.05 mol dm^{-3} sodium acetate buffer (pH 5.4) and $0.4 \text{ } \mu\text{mol dm}^{-3}$ Zn-EDTA. The calibration curve method was used for determining the Lu(III) concentration in the samples.

3. THEORETICAL CALCULATIONS

3.1. Basic parameters of the SLM extraction process.

The efficiency of Lu(III) transfer through the liquid membrane was evaluated using several performance parameters. The extraction efficiency (E) was calculated as the amount of Lu(III) found in the acceptor phase divided by the initial amount of Lu(III) in the donor phase:

$$E = \frac{n_A}{n_D^{in}} = \frac{c_A V_A}{c_D^{in} V_D} \quad (1)$$

where n_D^{in} is the initial number of moles of Lu(III) in the donor phase, n_A is the number of moles of Lu(III) collected in the acceptor phase reservoir at time t , c_D^{in} is the initial molar concentration of Lu(III)

in the donor phase, c_A is the molar concentration of Lu(III) in the acceptor phase reservoir at time t , and V_D and V_A are the donor and acceptor volumes, respectively. The extraction efficiency depends on the flow rate of both aqueous phases, the rate of diffusion in the feed solution and through the membrane, the efficiency of the stripping into the acceptor phase, the volume ratio between the donor and the acceptor phase, and some other easily adjustable factors, such as pH and presence of some ligands, but not primarily the distribution coefficient³⁴. The removal efficiency (E_R) represents the fraction of Lu(III) removed from the donor phase with respect to the initial amount of Lu(III) in the donor phase:

$$E_R = \frac{n_D^{in} - n_D}{n_D^{in}} = \frac{c_D^{in} - c_D}{c_D^{in}} \quad (2)$$

where n_D and c_D are the number of moles and the molar concentration of Lu(III) in the donor phase reservoir at time t , respectively. The removal efficiency primarily depends on the distribution coefficient of the analyte between the aqueous donor and organic phase, but also on the donor flow rate in a continuous flow membrane extraction system. For the SLM extraction system under recirculation mode of operation, the removal efficiency per single donor pass (E'_R) can be written as¹⁴:

$$E'_R = 1 - \exp\left(-\frac{K_D A_o}{Q_D}\right) \quad (3)$$

where Q_D is the donor flow rate, K_D is the overall mass transfer coefficient based on the aqueous phase and A_o is the effective outer contact area of the membrane. The memory effect is a fraction of Lu(III) captured in the organic phase with respect to the amount of Lu(III) initially present in the donor phase and can be calculated as a difference between the removal and extraction efficiency ($M = E_R - E$).

In order to quantify the rate of transfer through the membrane in a continuous steady-state system operated under recirculation of the aqueous phases, the mean flux of Lu(III) across the membrane can be calculated using the equation¹⁴:

$$J_m = -\frac{Q_D E'_R}{A_o} c_D^{in} \exp\left(-\frac{Q_D E'_R}{V_D} t\right) \quad (4)$$

3.2. Overall mass transfer coefficient in a recirculating HF-LPE system.

According to the resistance-in-series approach, the mass transfer of an analyte through supported liquid membrane comprises three steps: diffusion of the analyte from the aqueous feed phase to the membrane interface, diffusion of the analyte through organic phase entrapped within the membrane pores, and diffusion of the analyte from the stripping membrane interface to the bulk of the stripping (acceptor) phase. If the extraction is accompanied by chemical reactions, e.g. formation and decomposition of an analyte-carrier complex at feed and stripping phase, respectively, the reaction kinetics parameters have to be included in the transport equation³⁵. If the chemical reaction is fast, the overall rate of the process is independent on the reaction kinetics and only depends on the mass transfer rates. In that case, the overall mass transfer resistance, in terms of the driving force in the donor phase (K_D), can be described as a sum of the three resistances (the resistance of the donor phase, the resistance of the organic phase, and the resistance of the acceptor phase):

$$\frac{1}{K_D} = \frac{1}{k_D} + \frac{d_o}{k_M d_{LM} m_D} + \frac{d_o m_A}{k_A d_i m_D} \quad (5)$$

where k_D , k_M , and k_A are the individual mass transfer coefficients of the donor phase, the organic phase entrapped in the membrane pores and the acceptor phase, respectively, d_i and d_o are the inner and outer diameter of the hollow fiber, respectively, d_{LM} is the log mean diameter of the fiber, m_D is the distribution coefficient between the organic phase and the aqueous donor phase, and m_A is the distribution coefficient between the organic phase and the acceptor phase. The above equation is valid for the donor phase flowing through the shell side and the acceptor phase flowing through the lumen of the fibre³⁶. This configuration offers a larger surface area for the extraction step than the lumen-feed configuration.

The individual mass transfer coefficients of the donor and acceptor phase can be estimated using mass transfer correlations involving Sherwood, Schmidt and Reynolds numbers³⁷⁻³⁹. The membrane mass transfer coefficient can be predicted from the membrane morphology:

$$k_M = D\varepsilon/(\delta\tau) \quad (6)$$

where ε , δ and τ are the porosity, thickness and tortuosity of the hollow fiber wall, respectively, and D is the diffusivity of analyte-carrier complex in the organic phase entrapped within the pores. D can be estimated from the Wilke-Chang correlation or the Scheibel equation⁴⁰.

The overall mass transfer coefficient in a continuous steady-state SLM extraction system with closed-loop recirculation of both aqueous phases was determined experimentally using the equation:^{14,41}

$$K_D = -\frac{Q_D}{A_o} \ln \left[1 - \frac{V_D}{Q_D} \frac{d \ln(C_D^{in} / C_D)}{dt} \right] \quad (7)$$

The individual mass transfer coefficients can be estimated using the aforementioned equations or graphically by the Wilson-plot method^{42,43}.

4. RESULTS AND DISCUSSION

Extraction of Lu(III) in a three-phase system with DEHPA as a carrier combines two separation processes in a single device: extraction of Lu(III) from the aqueous donor phase to the organic phase containing carrier molecules and re-extraction of Lu(III) from the organic phase to the aqueous acceptor phase. The overall mass transfer process involves three diffusional steps and complexation/decomplexation reactions at donor-membrane and membrane-acceptor interfaces. Lu(III) ions are transferred through the membrane using DEHPA as a carrier by facilitated coupled counter-transport, i.e. the transfer of Lu(III) ions from the donor to the acceptor side of the membrane is coupled with the transport of protons in the opposite direction. Thus, the driving force for the mass transfer of Lu(III) is a pH gradient across the membrane directed toward the donor phase.

The optimum experimental conditions for the efficient removal of Lu(III) from the donor phase have been established in our previous study using stagnant (non-recirculating) HF-LPME system²⁴. We have achieved the maximum removal efficiency of Lu(III) higher than 99 % after 2 h of operation at the donor-to-acceptor phase volume ratio of 180, pH 3.5 in the donor phase, and using 5% (v/v) DEHPA/DHE and 2 mol dm⁻³ HCl as the organic and acceptor phase, respectively. Although a high degree of Lu(III) re-extraction was expected, because of the low distribution coefficient of Lu(III)

between the organic and acceptor phase and a good predicted permeability of Lu-DEHPA complex in the organic phase, the extraction efficiency was less than 20%. In addition, typically more than 80% of the Lu(III) extracted from the donor phase was captured inside the organic phase. In order to investigate this behavior into more detail, first we will use a stagnant HF-LPME system containing a hollow fibre of different lengths, i.e., different acceptor volumes.

4.1. The extraction efficiency of Lu(III) in a stagnant (non-recirculating) HF-LPME system.

Table 1. The efficiency parameters, E_R , E , and M , as a function of the acceptor volume for the extraction of Lu(III) in a stagnant HF-LPME system. The acceptor volume was controlled by changing the HF length.

V_A , μl	V_D/V_A	E_R , %	E , %	M , %
11	1818	87.8	3.5	84.3
23	870	96.1	5.1	91.0
35	571	97.4	6.9	90.5
56	357	97.1	8.8	88.3

The experimental conditions in stagnant (non-recirculating) HF-LPME of Lu(III) have been selected to correspond to the above mentioned optimal conditions for removing unbound radionuclide $^{177}\text{Lu(III)}$ from a $^{177}\text{Lu(III)}$ labeled compound. The influence of the acceptor volume within the range of 0.01 – 0.06 cm^3 on the Lu(III) extraction was investigated. The values of E_R , E , and M as a function of the acceptor volume are listed in Table 1. As can be seen from this table, an increase in the acceptor volume by a factor of 5, led to an increase in the extraction efficiency by a factor of 2.5, but the maximum extraction efficiency was just 8.8%, achieved at the acceptor volume of 56 μl . On the other hand, there was no significant effect of the acceptor volume on the Lu(III) removal efficiency from the donor phase, except for the shortest membrane. There are two main problems with this stagnant HF-LPME system: (i) a limited amount of the acceptor phase can be accommodated within the lumen of the fibre; (ii) in the absence of flow of the acceptor phase through the lumen, the rate of transfer of Lu(III) from the organic/acceptor phase interface to the bulk of the acceptor phase is slow and the process is limited by the availability of the interfacial area. It can be expected that any further increase in the fibre length (i.e., the acceptor volume) would lead to further increase in the extraction efficiency, but the maximum fibre length is limited by the fact that the fibre must be fully dipped into the donor phase, which has a volume

of just 20 cm³. For example, at $V_A = 56 \mu\text{l}$, the effective fibre length was 91 cm. In order to improve the rate of transfer of Lu(III) through the lumen and to decouple the fibre length and the acceptor volume, we have used recirculating HF-LPME system in the further work.

4.2. The time-dependent variations of process performances in a recirculating HF-LPE system.

In these experiments, we have used the extraction rig with a U-shaped module shown in Fig. 1 (ii). The extraction conditions used were the same as those applied in the stagnant system: the donor phase was kept at pH 3.5, the organic phase was 5% (v/v) DEHPA in DHE and the acceptor phase was 2 mol dm⁻³ HCl²⁴. The donor phase was chosen to flow on the shell side because this configuration offered a larger mass transfer area for the removal of Lu(III) from the donor phase than the lumen-feed configuration. The donor and the acceptor phase were recirculated in a closed loop between the respective reservoirs and the module in order to improve the rate of mass transfer in both aqueous phases.

Figure 2 shows the variations of the concentration of Lu(III) ions in the donor and acceptor phase with time at five different donor flow rates. The acceptor flow rate was kept constant at 0.4 cm³ min⁻¹. As can be seen, the concentration of Lu(III) in the donor phase reservoir decreased sharply during the first 60 min of operation and gradually reached a plateau afterwards, whereas the concentration of Lu(III) in the acceptor phase reservoir increased nearly in the same manner. As shown in Fig. 2, the steady state was established after about 90 min of extraction, which means that after that time the mass fluxes of Lu(III) from the donor to acceptor phase and *vice versa* were equilibrated. The concentration of Lu(III) in the donor and acceptor phase at steady state was dependent on the flow rate of the donor phase. The lowest concentration of Lu(III) in the donor phase and the highest concentration of Lu(III) in the acceptor phase were achieved at the highest donor flow rate of 5.3 cm³ min⁻¹. At steady state, $c_A > c_D$ for all investigated flow rates of the donor phase, indicating that in the present SLM extraction system uphill facilitated transport of Lu(III) ions from the donor solution to the acceptor phase was successfully achieved.

Figure 2. Time dependence of Lu(III) concentration in the donor and acceptor phase reservoir at different donor flow rates. Donor phase: 20 cm³, 11 μmol dm⁻³ Lu(III), pH 3.5; Acceptor phase: 3 cm³, 2 mol dm⁻³ HCl; Organic phase: 0.16 mol dm⁻³ DEHPA in DHE; Donor flow rates: (■) 0.4 cm³ min⁻¹; (□) 1.2 cm³ min⁻¹; (▲) 2.1 cm³ min⁻¹; (Δ) 3.6 cm³ min⁻¹; (●) 5.3 cm³ min⁻¹; The acceptor flow rate: 0.4 cm³ min⁻¹.

The influence of the extraction time on the process efficiency at the highest donor flow rate used in this study of 5.3 cm³ min⁻¹ and the acceptor flow rate of 0.4 cm³ min⁻¹ is shown in Fig. 3. As can be seen, both the removal and extraction efficiency of Lu(III) increased with time before reaching a constant value of 88 and 84 %, respectively, after about 80 min of operation. The memory effect, M , of 25% was observed in the first sample taken after 5 min, but after that it was negligible. For example, after 60 min less than 5% of Lu(III) extracted from the feed solution remained in the organic phase. This result indicates that Lu(III) was not accumulated in the membrane phase and that the stripping reaction was sufficiently fast.

Figure 3. Time dependence of the efficiency parameters E (●), E_R (■) and M (○) in the SLM extraction system with the recirculation of aqueous phases. Donor phase: 20 cm^3 , $11 \mu\text{mol dm}^{-3}$ Lu(III), pH 3.5; Acceptor phase: 3 cm^3 , 2 mol dm^{-3} HCl; Organic phase: 0.16 mol dm^{-3} DEHPA in DHE; The donor flow rate: $5.3 \text{ cm}^3 \text{ min}^{-1}$; The acceptor flow rate: $0.4 \text{ cm}^3 \text{ min}^{-1}$.

By comparing the results obtained using two miniaturized membrane extraction systems, static HF-LPME and dynamic HF-LPE, it can be concluded that the process performances were significantly improved by increasing the acceptor volume and providing circulation of the acceptor phase through the lumen. In the HF-LPME system with a stagnant acceptor phase and very small acceptor volumes (at microliter level), a large majority of Lu(III) extracted from the feed solution was accumulated in the organic phase. In the HF-LPE system with U-shaped module, owing to the faster diffusion within recirculating acceptor phase and the lower donor-to-acceptor phase ratio, V_D/V_A of 6.7 (as compared to 357–1818 in the stagnant system), almost all Lu(III) extracted from the feed solution was re-extracted from the membrane to the acceptor phase. Thus, in the investigated HF-LPE system with recirculating aqueous phases, a great majority of Lu(III) was removed from the aqueous feed solution, but Lu(III) was also efficiently recovered from the organic solvent and concentrated in the aqueous strip solution.

4.3. Effect of the donor flow rate.

The mass transfer in continuous-flow contactors is strongly influenced by the flow rate of the phases involved in the process. In the present continuous-flow HF-LPE system, the flow rate of the donor phase flowing through the shell side of the contactor was varied from 0.4 to $5.3 \text{ cm}^3 \text{ min}^{-1}$ whilst the flow rate

of the acceptor phase in the fibre was kept constant at $0.4 \text{ cm}^3 \text{ min}^{-1}$. As shown in Fig. 2, the Lu(III) concentration in the donor phase reservoir drops rapidly with an increase in the donor flow rate and thus, the process becomes more efficient. The equilibrium concentrations of Lu(III) in the donor and acceptor phase reservoirs at variable flow rate of the donor phase are presented in Table 2. The obtained results indicate that the equilibrium concentration of Lu(III), i.e. the minimum concentration of Lu(III) that can be reached in the donor phase decreased with increasing the donor phase flow rate. It should be noted that this is a typical behaviour for the donor-controlled membrane-based extraction^{14,44}. As expected, the equilibrium Lu(III) concentration in the acceptor phase increased with increasing the donor flow rate, which can be explained by the fact that in a steady state, there is no accumulation of Lu(III) in the membrane phase and thus, any decrease in the Lu(III) concentration in the donor phase must be accompanied by a corresponding increase in the Lu(III) concentration in the acceptor phase.

Table 2. The equilibrium concentrations of Lu(III) in the donor and acceptor phase reservoirs and the efficiency parameters as a function of the donor flow rate. $V_D/V_A = 6.7$, $c_D^{in} = 2.5 \text{ mg dm}^{-3}$, $c_A^{in} = 0$.

Q_D $\text{cm}^3 \text{ min}^{-1}$	c_D^* mg dm^{-3}	c_A^* mg dm^{-3}	E_R %	E %	M %
0.4	1.6	7.0	37.7	37.2	0.5
1.2	1.0	9.6	57.3	53.4	3.9
2.1	0.9	11.4	67.6	65.8	1.8
3.6	0.4	14.6	83.3	80.0	3.3
5.3	0.3	14.9	88.2	84.1	4.1

The steady-state values of the extraction parameters (E , E_R and M) are plotted against the donor flow rate in Fig. 4. It can be seen that both the removal and extraction efficiency at steady state increased with increasing the donor phase flow rate, whereas the memory effect was independent on the donor flow rate. At any flow rate, the amount of Lu(III) remaining in the organic phase was less than 5% of the total amount of Lu(III) extracted. The removal and extraction efficiency of Lu(III) were improved from 37 % to 88 and 84 %, respectively, when the donor flow rate increased from 0.4 to $5.3 \text{ cm}^3 \text{ min}^{-1}$. With increasing the donor flow rate from 0.4 to $3.7 \text{ cm}^3 \text{ min}^{-1}$ the removal and extraction efficiencies of Lu(III) increased almost twice, but the effect was less pronounced with further increase in the donor

flow rate. Similar behaviour was reported earlier for the extraction of aroma compounds in hollow fibre membrane contactors^{36,45}.

Figure 4. The effect of the donor phase flow rate on the efficiency parameters E (●), E_R (■) and M (○) in the SLM extraction system with the recirculation of aqueous phases. Donor phase: 20 cm³, 11 μmol dm⁻³ Lu(III), pH 3.5; Acceptor phase: 3 cm³, 2 mol dm⁻³ HCl; Organic phase: 0.16 mol dm⁻³: The acceptor flow rate: 0.4 cm³ min⁻¹.

With regard to an efficient and fast recovery of Lu(III) from the organic phase, the continuous-flow HF-LPE system used in this work showed excellent performance with less than 5% accumulation of Lu(III) in the liquid membrane. On the other hand, for the purpose of elimination of free Lu(III) from radiolabeled substance in the fabrication of ¹⁷⁷Lu-radiopharmaceutical, the maximum removal efficiency of 88% achieved in the current module is insufficient for commercial applications. The higher removal efficiency (above 95%) could be achieved using a hollow fibre contactor with the higher effective membrane area, for example using a bundle of hollow fibre membranes rather than a single hollow fibre.

4.4. Determination of the overall mass transfer coefficient of Lu(III).

The overall mass transfer coefficient based on the donor phase concentration, K_D , for the investigated recirculating SLM extraction system was calculated from the experimental data using Eq. (7). Plotting $\ln(c_D^{in}/c_D)$ against time should give a straight line and the overall mass transfer coefficient can be

calculated from the slope of that line. A graph of $\ln(c_D^{in}/c_D)$ against time at five different flow rates of the donor phase is shown in Fig. 5. As suggested by Eq. (7), good linear relationships between $\ln(c_D^{in}/c_D)$ and t were obtained, with $R^2 > 0.99$ in all cases, except for the highest donor flow rate of $5.3 \text{ cm}^3 \text{ min}^{-1}$. The slopes of these lines and the overall mass transfer coefficients determined from the slopes are listed in Table 3. As can be seen from Table 3, K_D increased from 2.3 to $8.8 \times 10^{-5} \text{ m s}^{-1}$ with increasing the donor phase flow rate from 0.4 to $5.3 \text{ cm}^3 \text{ min}^{-1}$, which is generally observed behaviour for extraction systems with $m_D \gg 1$ ¹⁴.

Figure 5. The plot for the determination of the overall mass transfer coefficient. Donor phase: 20 cm^3 , $11 \mu\text{mol dm}^{-3} \text{ Lu(III)}$, pH 3.5; Acceptor phase: 3 cm^3 , $2 \text{ mol dm}^{-3} \text{ HCl}$; Organic phase: $0.16 \text{ mol dm}^{-3} \text{ DEHPA}$ in DHE; Acceptor flow rate: $0.4 \text{ cm}^3 \text{ min}^{-1}$; Donor flow rates: ($\blacktriangle$) $0.4 \text{ cm}^3 \text{ min}^{-1}$; ($\square$) $1.2 \text{ cm}^3 \text{ min}^{-1}$; ($\blacksquare$) $2.1 \text{ cm}^3 \text{ min}^{-1}$; ($\circ$) $3.6 \text{ cm}^3 \text{ min}^{-1}$; ($\bullet$) $5.3 \text{ cm}^3 \text{ min}^{-1}$.

Table 3. The slope of the line in Fig. 5, the overall mass transfer coefficient, K_D , and the removal efficiency per single donor pass, E'_R , as a function of the donor phase flow rate for the extraction of Lu(III) in recirculating HF-LPE system. $V_D/V_A = 6.7$.

Q_D $\text{cm}^3 \text{ min}^{-1}$	$d\ln(C_D^{in}/C_D)/dt$ min^{-1}	$K_D \times 10^5$ m s^{-1}	R^2	E'_R %
0.4	0.0047	2.3	0.991	20.5
1.2	0.0095	4.3	0.991	14.0
2.1	0.0117	5.3	0.991	10.1
3.6	0.0168	7.6	0.991	8.5
5.3	0.0199	8.8	0.963	6.7

Fig. 6 (i) is a plot of K_D versus the donor phase flow rate, Q_D , on a log-log scale. A linear dependence was obtained, indicating that the overall mass transfer resistance ($1/K_D$) is controlled by the donor phase resistance, so that the overall mass transfer coefficient is approximately equal to the mass transfer coefficient in the donor phase, $K_D \approx k_D$. From Fig. 6 (i), $Sh \propto Re^{0.63}$ in the range of $3 < Re < 34$, where 0.63 is the slope of K_D vs. Q_D line. The exponent on Re of 0.63 is similar to 0.60, found by Prasad and Sirkar for shell side flow parallel to the fibers at $0 < Re < 500$ ⁴⁶. It should be noted that for the applied membrane contactor configuration (donor phase flowed through shell side of the module and acceptor phase through the lumen of fiber), it was found that the influence of tube side flow rate on mass transfer coefficient is less significant than that of shell side flow rate³⁶. Because of this fact, acceptor phase flow rate was kept constant.

Figure 6. (i) The effect of the donor flow rate on the overall mass transfer coefficient of Lu(III) based on the donor phase. The acceptor phase flow rate was kept constant at $0.4 \text{ cm}^3 \text{ min}^{-1}$. (ii) The Wilson plot of $1/K_D$ vs. $1/Q_D^b$, where b is a slope of the linear fit from Fig. 6 (i).

The overall mass transfer resistance ($1/K_D$) in the applied HF-LPE system is given by Eq. (5). Assuming that the reaction of formation of the Lu-DEHPA complex is fast, as well as the stripping reaction at the membrane-acceptor interface, the reaction kinetics at both interfaces can be neglected. Therefore, the mass transfer of Lu(III) through supported liquid membrane takes place in three successive diffusion steps: diffusion of Lu(III) through the boundary layer of the aqueous feed phase to the membrane interface, diffusion of Lu-DEHPA complex through the organic phase entrapped within the membrane pores, and diffusion of Lu(III) through the boundary layer of the stripping phase.

The sum of the membrane and the acceptor mass transfer resistances can be determined graphically from the Wilson plot. This method assumes that the overall mass transfer resistance is controlled by the flow rate of the mass transfer-limiting phase which is the donor phase in this case. The Wilson plot of $1/K_D$ as a function of $1/Q_D^b$ is shown in Fig. 6 (ii). The value of the exponent, b of 0.63 was determined by a least-square fit of K_D versus Q_D (Fig. 6 (i) and Table 3). The intercept on the $1/K_D$ axis is equal to $0.36 \times 10^4 \text{ m}^{-1} \text{ s}$ and represents a sum of the membrane and acceptor phase resistances (the second and third term in Eq. (5)). The donor phase resistance is the major mass transfer resistance in the system and its contribution in the overall mass transfer resistance ranges from 75% at the highest donor phase flow rate to 92% at the lowest Q_D value. The membrane mass transfer coefficient, k_M , predicted from Eq. (6) is $1 \times 10^{-6} \text{ m s}^{-1}$, based on $\varepsilon = 0.6$, $\delta = 50 \text{ }\mu\text{m}$, $\tau = 1.7$ (estimated from the Wakao-Smith relation⁴⁷), and $D = 1.4 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ (estimated from the Scheibel equation⁴⁰). The diffusivity of Lu(III)-DEHPA complex estimated from the Scheibel equation is similar to the D value of $1.33 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ for Zn(II)-DEHPA complex, estimated by Fernandez et al.⁴⁸. Putting $k_M = 1 \times 10^{-6} \text{ m s}^{-1}$ into the second right-hand term of Eq. (5) gives the value which is approximately the same as the value of the intercept in the Wilson plot, which means that the mass transfer resistance of the acceptor phase is negligible. It may be concluded that the overall rate of the process in the recirculating HF-LPE system is controlled by the donor phase boundary diffusion. The mass transfer of Lu(III) across the boundary layer of the donor

phase strongly depends on the donor phase flow rate and consequently, when the donor flow rate is higher the applied system has better performances.

4.5. The influence of the donor flow rate on the Lu(III) mass flux.

The mean Lu(III) flux through the interfacial area in the HF-LPE system with the recirculation of phases depends on the donor phase flow rate, the volume of the donor phase reservoir, the removal efficiency per single donor pass, the time elapsed since the process started and the interfacial area, and can be calculated from Eq. (4). The removal efficiencies per single donor pass, E'_R , at different donor flow rates are given in Table 3. The time variations of the mean flux of Lu(III) at different donor phase flow rates are shown in Fig. 7. Obviously, there is a linear relation between J_m and t on the semilog scale, as predicted by Eq. (4). The flux shows a descending trend with time, because the Lu(III) concentration gradient across the liquid membrane decreases with time and the driving force for the mass transfer is gradually reduced. The flux of Lu(III) decreases until the steady-state is achieved, when the net flux becomes zero. The rate of flux decline is higher at the higher donor phase flow rates which is also in accordance with Eq. (4).

Figure 7. The variation of the mean Lu(III) flux through the interfacial area with the time of extraction at different donor flow rates: (▲) $0.4 \text{ cm}^3 \text{ min}^{-1}$; (□) $1.2 \text{ cm}^3 \text{ min}^{-1}$; (■) $2.1 \text{ cm}^3 \text{ min}^{-1}$; (○) $3.6 \text{ cm}^3 \text{ min}^{-1}$; (●) $5.3 \text{ cm}^3 \text{ min}^{-1}$.

5. CONCLUSIONS

We have developed a new, simple and efficient supported liquid membrane technique for solvent extraction of Lu(III) from the aqueous feed solution and simultaneous re-extraction in the acidic stripping solution based on closed-loop recirculation of aqueous phases through a U-shaped hollow fibre contactor. The removal and extraction efficiencies of Lu(III) increased with increasing the donor flow rate, while the memory effect was independent on the donor flow rate. The accumulation of Lu-DEHPA complex within the organic phase immobilized in the membrane pores was less than 5%, meaning that the HF-LPE system, with the acceptor recirculation, enables almost complete re-extraction of Lu(III) into the acceptor.

The overall mass transfer coefficient of Lu(III) was proportional to the donor flow rate raised to the power of 0.63 and was in the range of 2.3 to $8.8 \times 10^{-5} \text{ m s}^{-1}$. Using the Wilson plot, it was found that the diffusion through the boundary layer of the donor phase was a rate-controlling step in the process.

Based on the obtained results, it can be concluded that a miniaturized U-shaped hollow fibre contactor operated in recirculation mode can be used efficiently for the re-extraction of Lu(III) from the organic phase, for the purpose of its recovery. The removal of Lu(III) achieved in the current module was insufficient for commercial applications and the higher removal efficiencies (above 95%) could be achieved using either a hollow fibre contactor with a larger membrane area or two-stage process.

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List of symbols

A_o	effective outer surface area of membrane, m^2
A_i	effective inner surface area of membrane, m^2
b	gradient of the line in Fig. 6 (i)
c_A	molar concentration of Lu(III) in the acceptor phase at any time t , mol m^{-3}
c_A^*	equilibrium concentration of Lu(III) in the acceptor phase, mol m^{-3}
c_D	concentration of Lu(III) in the donor phase reservoir at any time t , mol m^{-3}
c_D^*	equilibrium concentration of Lu(III) in the donor phase, mol m^{-3}
c_D^{in}	initial Lu(III) concentration in the donor phase reservoir, mol m^{-3}
d_i	inner diameter of a hollow fiber, m
d_o	outer diameter of a hollow fiber, m
d_{LM}	log mean diameter of a hollow fiber, m
E	extraction efficiency, -
E_R	removal efficiency, -
E_R'	removal efficiency per single donor phase pass, -
J_m	mean flux of Lu(III), $\text{mol m}^{-2} \text{s}^{-1}$
K_D	overall mass transfer coefficient based on the donor phase, m s^{-1}
k_D	mass transfer coefficient for the donor phase, m s^{-1}

k_M	mass transfer coefficient for the organic phase in the membrane pores, m s^{-1}
k_A	mass transfer coefficient for the acceptor phase, m s^{-1}
L_{ef}	effective length of a hollow fibre, m
M	fraction of Lu(III) captured in the organic phase with respect to the initial amount of Lu(III) in the donor phase, -
m_A	distribution coefficient between the organic phase and the acceptor phase, -
m_D	distribution coefficient between the organic phase and the donor phase, -
L_{ef}	effective length of a fibre, m
n_A	number of moles of Lu(III) present in the acceptor phase at any time t , mol
n_D	number of moles of Lu(III) present in the donor phase at any time t , mol
n_D^{in}	initial number of moles of Lu(III) in the donor phase, mol
Q_D	flow rate of the donor phase, $\text{m}^3 \text{s}^{-1}$
Q_A	flow rate of the acceptor phase, $\text{m}^3 \text{s}^{-1}$
R^2	coefficient of determination, -
Re	Reynolds number, -
Sh	Sherwood number, -
T	time, s
V_A	volume of the acceptor phase, m^3
V_D	volume of the donor phase, m^3

V_O volume of the organic phase, m³

Greek symbols

δ membrane thickness, m

ε membrane porosity, -

τ tortuosity of membrane pores, -

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