2024 International Nuclear Atlantic Conference – INAC 2024
Escola de Guerra Naval, Rio de Janeiro, RJ, May 6 - 10, 2024

ISBN: 978-65-594-1256-3

Lu and Yb Separation: an Ion Exchange Chromatography Process Optimized by Design of Experiments

R. M. Nory[1], M. O. Damasceno[2], V. Tapetti[2], and E. G. Moreira[1]

[1] *renata.nory@ipen.br, Research Reactor Center, IPEN/CNEN*
[2] *molidam@ipen.br, Chemistry and Environmental Technology Center, IPEN/CNEN*
[2] *vitoriatapetti@gmail.com, Chemistry and Environmental Technology Center, IPEN/CNEN*
[1] *emoreira@ipen.br, Research Reactor Center, IPEN/CNEN*
Avenida Prof. Lineu Prestes, 2242, CEP 05508-000, São Paulo, SP, Brazil

1. Introduction

The increase in life expectancy in Brazil, resulting from improvements of basic sanitation conditions and advances in public health policies, has led to a process of epidemiological transition. The primary causes of death have shifted from infectious and parasitic diseases to those related to degenerative processes resulting from aging, such as heart conditions and cancer [1]. Estimates from the International Agency for Research on Cancer indicated the emergence of approximately 590,000 new cases of cancer in the country in 2020, with about 31% of cases corresponding to prostate and breast cancers [2].

The most well-known and widely accessible treatments used in the fight against cancer are chemotherapy and radiotherapy, either alone or in combination with surgery, depending on the extent and location of tumor foci. In these treatment modalities, cancer cells are targeted by chemical agents or external gamma radiation, inducing destructive cellular effects [3]. However, these agents also affect healthy cells, causing side effects, sometimes severe, such as anemia, gastrointestinal complications, infertility, skin and/or oral rashes, and burns.

In this context, drugs with a radioactive element linked to their chemical structure, called radiopharmaceuticals, have been extensively studied and applied in nuclear medicine for cancer diagnosis and therapy, showing promising results with fewer side effects [4]. ^{177}Lu (half-life of approximately 6.7 days) is a radionuclide that emits low-energy β^- radiation (E_{max} = 497 keV, 78.6%) and gamma radiation (more intense transitions: 113 keV, 6.4% and 208 keV, 11%), characteristics that make it particularly interesting for targeted therapeutic applications, with theranostic purposes: beta particles interact with tumor cells, destroying them and making therapy possible, while gamma radiation can be detected by gamma cameras (SPECT) for diagnostic purposes [5].

Despite the growing importance that this radionuclide has been presenting in modern nuclear medicine scenario worldwide, Brazil, currently, only imports ^{177}Lu and performs the radiolabeling of molecules. The import increases the costs of the final medication, impacting the reach of the use of this radiopharmaceutical, both in financial terms and in terms of meeting clinical and scientific research demands in the country. Additionally, it subjects the drug supply to external market fluctuations in availability and prices.

Hence, the development of methodologies for the production of ^{177}Lu in the IEA-R1 reactor at IPEN is of great importance. This study is specifically focused on the separation process of ^{177}Lu formed during the

irradiation of ^{176}Yb targets with neutrons in the nuclear reactor core, through the indirect production route. Aiming the optimization of the process, the statistical methodology of Design of Experiments (DOE) was applied in experimental separation trials using ion exchange chromatography.

2. Methodology

In experiments where the desired response is determined by the contribution of many variables, identifying the most relevant ones and understanding how they influence the response can be a time-consuming and laborious task. Therefore, the application of multivariate optimization systems, such as DOE, is highly useful. In the present study, DOE was applied to define the optimal experimental conditions that will lead to the highest chromatographic Lu and Yb peaks separation, as higher separation will result in higher quantities of purified lutetium and, consequently, higher fractions of recovered ytterbium for subsequent irradiations.

The separation between the elements Lu and Yb poses significant challenges, given their chemical similarities. In the literature, researchers have presented promising results using chromatographic techniques for this separation. Thus, as a first study, the separation between Lu and Yb was performed using Bio-Rad® AG 1-X4 anion exchange chromatography resin (200–400 mesh) as stationary phase and phosphoric acid (H_3PO_4) as mobile phase (eluent). For a preliminary determination of the most suitable experimental conditions to promote the separation between the elements, a 2^3 design with a central point was carried out. Three factors (variables) were analyzed (operating system temperature (T), eluent molarity (M), and eluent flow rate (f)), each with two levels (T: 3 and 83 °C / M: 0.25 and 1.0 mol L^{-1} / f: 0.6 and 3.5 mL cm^{-2} min^{-1}). The central point is represented by the average value of the maximum and minimum values for each factor. The response of interest was chosen to be the area of the intersection between Lu and Yb peaks in the resulting chromatograms. For the determination of experimental error, the central point was analyzed in quadruplicate.

The experimental process involved 12 experiments (runs), that were automatically randomized to distribute possible uncontrolled errors in the process. In all experiments, determined and identical masses of natural Lu and Yb (0.14 mg each) were used as loadings, along with radioactive tracers for both elements, to allow further analysis of the extracted liquid aliquots in a gamma spectrometer for obtaining all chromatograms. Two batches of loadings were prepared, and this was considered in the DOE statistical analysis. The extracted aliquots had a volume of 1 mL each in all runs.

The experimental setup consisted of a jacketed glass chromatographic column with an internal tube of approximately 0.4 cm in diameter. This internal tube was filled with the anion exchange resin, previously conditioned with H_3PO_4, to a bed height of 21.0 cm. On the external side of the column, water was pumped by a fixed-flow peristaltic pump. Another adjustable-flow peristaltic pump was responsible for circulating the eluent in the column. The system temperature (including resin and eluent) was controlled by a digital bath circulator (SolidSteel, SSDU10L-110 model). At the lower end of the column, 1 mL eluate fractions were collected in pre-cleaned glass vials with plastic screw caps. After each experiment, all vials were analyzed in a gamma spectrometer (Canberra, GX3018 model) for 300 s each, and the obtained data, in terms of counts per second, were corrected for radioactive decay. The analyzed energy peaks were 208 keV, for Lu, and 177 keV, for Yb. After the calculation of all areas, DOE statistics were performed in Statistica software (version 14.0.0.15).

3. Results and Discussion

In DOE analysis, third-order adjustment, for interactions between all factors, were considered, alongside with the blocking of the loadings. At this setting, the fitted model presented an adjusted R-squared (R^2 or coefficient of determination) of 0.994, which indicates that it is an excellent predictor of the observed data. A curvature analysis was also performed, in order to evaluate the adequacy of the ranges chosen for the

factors.

The Pareto chart of standardized effects is show in Fig. 1 (a). According to results, the factors that have the greatest influence on area results are system temperature and eluent flow rate, followed by the interaction between these two factors. To a lesser extent, eluent molarity and the interaction between all three factors also influenced the results. Blocking did not have a significant influence, as desired. Also, p-value for the curvature check was less than 0.05, indicating the adequacy of the chosen ranges for temperature, eluent flow rate and eluent molarity.

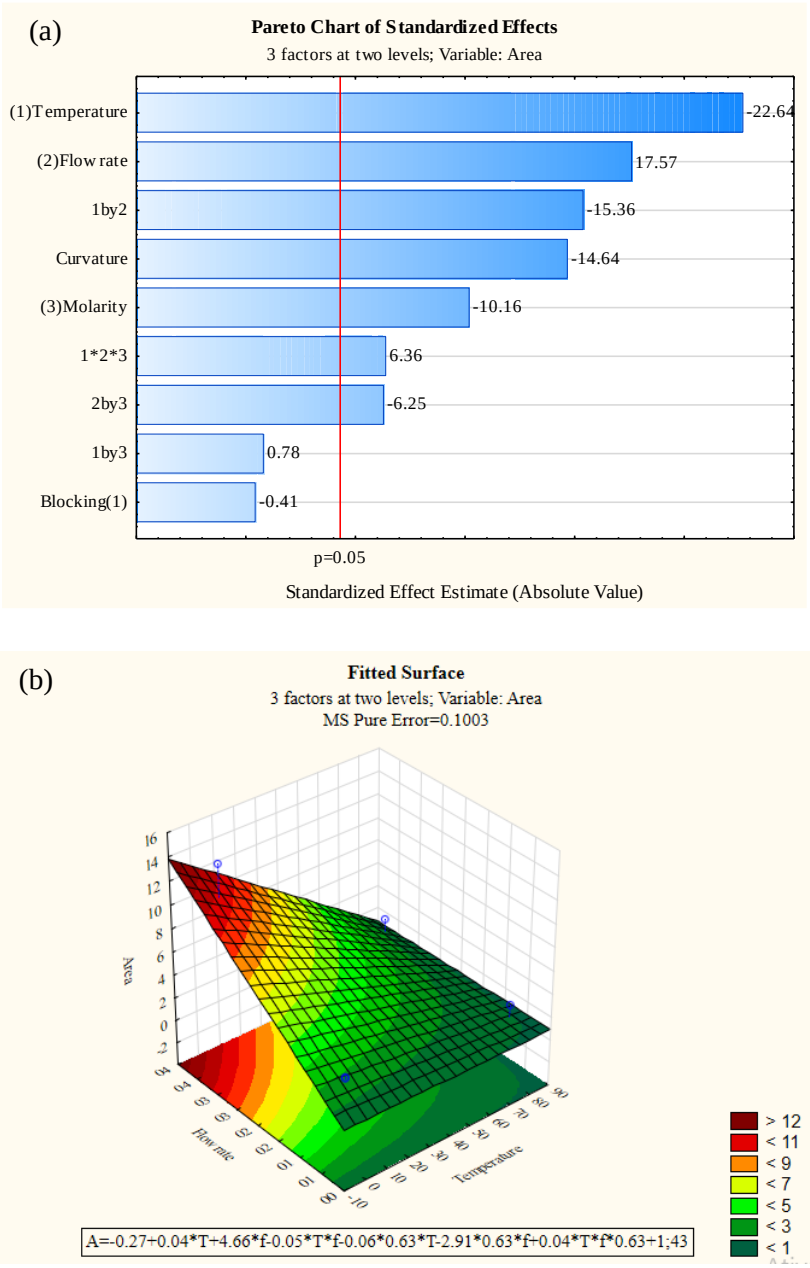

Figure 1. (a) Pareto chart of standardized effects; and (b) Fitted response surface and its correspondent equation.

Fig. 1b shows the fitted surface that describes response in terms of system temperature (T) and flow rate (f), and the equation that describes it. It can be noticed that, in general terms, the settings that are more appropriate to reduce the area of intersection between peaks involve higher temperatures and lower flow rates. Also, high eluent molarity values are shown to be related to a better separation condition. An optimal setting, in which the area is minimized, can be obtained using the fitting equation generated by Statistica software. Using Microsoft Excel solver tool, the optimal values for temperature and flow rate were found to be 83 °C and 0.6 mL cm^{-2} min^{-1}, respectively.

4. Conclusions

In this study, the Design of Experiments (DOE) statistical method was applied to determine the most suitable conditions for achieving optimal separation between elements Lu and Yb, utilizing anion exchange chromatography, in the context of the production of ^{177}Lu for medical purposes. The influence of three factors – system temperature, eluent flow rate, and eluent molarity – was analyzed, each within predefined ranges. Results indicated that the best separation for this system can be achieved when it is operated at its maximum temperature (T = 83°C) and at its lowest flow rate (f = 0.6 mL cm^{-2} min^{-1}), with molarity fixed at its maximum (M = 1.0 mol L^{-1}). In future developments, a new DOE will be applied in the separation studies utilizing a cationic ion exchange resin and an extraction exchange resin to compare results and establish the best conditions for the separation of Lu and Yb.

Acknowledgements

The authors acknowledge CAPES and IPEN for financial scholarships and funding.

References

[1] “Tábuas Completas de Mortalidade para o Brasil – 2017,” https://ftp.ibge.gov.br/Tabuas_Completas_de_Mortalidade/Tabuas_Completas_de_Mortalidade_2017/tabua_de_mortalidade_2017_analise.pdf (2018).

[2] “Population fact sheets: Brazil.,” https://gco.iarc.who.int/media/globocan/factsheets/populations/76-brazil-fact-sheet.pdf (2021).

[3] A. Dash; M. R. A. Pillai; F. F. Knapp, “Production of ^{177}Lu for Targeted Radionuclide Therapy: Available Options,” *Nuclear Medicine and Molecular Imaging*, v. 49, pp. 85–107 (2015).

[4] M. S. Hofman et al., “[177Lu]-PSMA-617 Radionuclide Treatment in Patients with Metastatic Castration-Resistant Prostate Cancer (LuPSMA trial): A Single-Centre, Single-Arm, Phase 2 Study,” *The Lancet Oncology*, v. 19, pp. 825–833 (2018).

[5] S. Banerjee; M. R. A. Pillai; F. F. Knapp, “Lutetium-177 Therapeutic Radiopharmaceuticals: Linking Chemistry, Radiochemistry, and Practical Applications,” *Chemical Reviews*, v. 115, pp. 2934–2974 (2015).