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Application of extraction chromatographic techniques for separation and purification of emerging radiometals $^{44/47}\text{Sc}$ and $^{64/67}\text{Cu}$

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ABSTRACT

Considerably increasing interest in using the theranostic isotopes/ isotope pairs of radiometals like $^{44/47}\text{Sc}$ and $^{64/67}\text{Cu}$ for diagnosis and/or therapeutic applications in the nuclear medicine procedures necessitates its reliable production and supply. Separation and purification of no-carrier-added (NCA) isotopes from macro quantities of the irradiated target matrix along with other impurities is a cardinal procedure amongst several other steps involved in its production. Multitudinous methods including but not limited to liquid-liquid (solvent) extraction, extraction chromatography (EXC), ion exchange, electrodeposition and sublimation are routinely applied either solitarily or in combination for the separation and purification of radioisotopes depending on their production routes, radioisotope of interest and impurities involved. However, application of EXC though has shown promises towards the numerous separation techniques have not received much attention as far as its application prospects in the field of nuclear medicine are concerned. Advances in the recent past for application of the EXC resins in separation and purification of the several medically important radioisotopes at ultra-high purity have shown promising behavior with respect to their operation simplicity, acidic and radiolytic stability, separation efficiencies and speedy procedures with the enhanced and excellent extraction abilities. In this mini review we will be talking about the recent developments in the application and the use of EXC techniques for the separation and purification of $^{44/47}\text{Sc}$ and $^{64/67}\text{Cu}$ for medical applications. Furthermore, we will also discuss the scientific and practical aspects of EXC in the view of separation of the NCA trace amount of radionuclides. ***J Radiopharm Mol Probes 2(2):84-95, 2016***

Key Word: Scandium - 44, 47($^{44/47}\text{Sc}$), Copper - 64, 67($^{64/67}\text{Cu}$), Theranostic isotope / isotope pair, Extraction chromatography (EXC), Radiochemical separation/ purification.

Introduction

Transmutation of the stable elemental target matrix (natural/ enriched) using either research reactor or particle accelerator into the idiosyncratic radioisotopes with suitable nuclear, physical as well as chemical properties for diagnostic and/or therapeutic applications have been experiencing the exponential growth and transition since its inception

(1-4). The recent developments and sophistications in the available technologies, modes of radioisotope productions, better understandings of the biochemical and bimolecular behavior of the newly designed radiopharmaceuticals with the involved mechanisms have overall taken the fastest growing branch of nuclear medicine to preminent level in clinical research (5). Use of radioisotopes for PET/CT imaging (6-7) and targeted therapy (8) are powerful tools

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Table 1. Nuclear characteristics and properties of the theranostic isotopes (single isotope) and their radioisotopic pairs (same element) (8, 10).

	Isotope	Half Life	Used for	Imaging Emission* γ/β^+ energy in keV(abundance)	Therapy Emission β^- mean energy in keV
Theranostic Isotope/ Isotope Pair of Sc	^{44}Sc	4.00 h	Imaging	$\beta^+ = 632$	-
	^{47}Sc	3.35 d	Theranostic	$\gamma = 159$ (100%)	162
Theranostic Isotope/ Isotope Pair of Cu	^{64}Cu	12.7 h	Imaging	$\beta^+ = 278$	-
	^{67}Cu	2.58 d	Theranostic	$\gamma = 184$ (49%)	141

*Most likely used imaging emission

in medical sciences. This headway has encouraged the researchers to think out of the box and look into several newer possibilities to employ the same radioisotopes and/or its pairs for simultaneous diagnostic as well therapeutic purposes. Radiological emissions from this radioisotopes/pairs integrated with contemporarily available medical facilities and techniques can be used to develop inherent and combined methodologies to combat the diseases like cancer.

Distinguished properties of few isotopes make them available for diagnostic as well as therapeutic purposes and are known as theranostic (THERApy+ diagNOSTIC) isotopes (8-10). Depending upon the features and possessing passable γ -emission/ β^+ -emission for imaging with Auger electrons/ conversion electrons/ α -particles/ β^- -emission for therapy they are further precisely categorized as (a) Theranostic isotopes- same element and isotope viz. ^{131}I , ^{188}Re , ^{47}Sc , ^{67}Cu , etc.; which uses coexistence of γ -emission and β^- -emission from the same isotope for imaging and therapy respectively (b) Theranostic isotope pairs- same element different isotope viz. $^{86/90}\text{Y}$, $^{123/131}\text{I}$, $^{44/47}\text{Sc}$, $^{64/67}\text{Cu}$, etc.; which uses γ -emission/ β^+ -emission and β^- -emission from the different isotope of same element for imaging and therapy respectively (8, 10). These theranostic isotopes and / or pairs have several individualistic advantages which make them unique amongst the other isotopes possessing either therapeutic or diagnostic applications (11-12). The most promising use

of this theranostic isotopes/isotope pairs lies in the fact that one can use these isotopes to acquire the reliable information like disease staging, drug delivery, bio-distribution and dosimetry concurrently. This will provide the concerned firsthand information apropos the pharmacokinetics and pharmacodynamics of the radiopharmaceutical and further ensure the effective imaging and/or therapy of the tissue/organ under consideration (8-12). Development of the new isotopes having the theranostic properties and established procedure using these isotopes in clinical applications will pose a breakthrough in the area of nuclear medicine and will play a crucial role in molecular imaging and targeted radiotherapeutics.

Two such promising theranostic isotopes ^{47}Sc (13), ^{67}Cu (14) and their pairs ^{44}Sc (15)- ^{47}Sc , ^{64}Cu (16-18) - ^{67}Cu have been in limelight since recent past and considerate efforts are being made in all the directions to substantiate their high purity production and application in the medical procedures. The decay properties of these isotopes commendatory for imaging as well as therapy are tabulated in table 1. In addition to its nuclear and physical properties the chemistry of Scandium (19-20) and Copper (21-24) is encouraging as far as its complexation with the well-studied radiopharmaceuticals is concerned.

Despite of all the above mentioned advantageous nuclear characteristics and chemical properties, the mainstream utilization of these radiometals based pharmaceuticals is not usual because of three major pitfalls (i) high cost of the

Table 2. Established extraction chromatographic techniques for separation of diagnostic/ therapeutic radioisotopes.

Extractant	Radioisotope Separation	Reference
Dithiazone	$^{115}\text{Cd} / ^{115}\text{In}$	28
Bis (2-ethylhexyl) phosphoric acid (HDEHP)	$^{228}\text{Ra} / ^{228}\text{Ac}$	29
	$^{90}\text{Sr} / ^{90}\text{Y}$	30
	$^{166}\text{Dy} / ^{166}\text{Ho}$	31
	$^{225}\text{Ac} / ^{225}\text{Ra}$	32
	$^{172}\text{Hf} / ^{172}\text{Lu}$	33
Di-tert-butylcyclohexano-18-crown-6(DTBCH18C6)	$^{90}\text{Sr} / ^{90}\text{Y}$	34

enriched target materials (ii) production difficulties (iii) lack of adequate and reliable supply which indeed further slows down the research and development activities (4, 14). One of the major step and concern involved in the production of these radiometals is the employment of selective separation and purification procedures which guarantee the high specific activity with exorbitant radionuclidic and radiochemical purity of these isotopes that suits the radiolabeling of the specific pharmaceutical. Moreover, the macro quantities of highly enriched expensive target material used to produce the significant amount of needed isotope pushes us to simultaneously develop a procedure which assures the separation of the target material too. Diverse separation techniques mentioned earlier in this review have been regularly employed for achieving highest possible purity. Nevertheless, development of efficient and selective procedure to ease the production with the enhancement of the purity is a ceaseless process for the researchers.

EXC is a method usually described as the system that combines merits of the solvent extraction with the multistage separation characteristics of chromatographic techniques and has been successfully implemented in miscellaneous separation procedures (25). This method is flexible and efficacious as compared to the other separation techniques and has been turned out to be the promising as far as its specific selectivity towards the metal ion is concerned. Recent substantial advances and development in the structural modifications of the available extractants and manipulation of the attached skeletal groups to the

organic extractants enhances the metal ion selectivity and makes the technique task specific (25-26). The EXC resins developed using different extractants and inert supports for the separation and preconcentration of assorted radionuclides especially the actinides and fission products in the backend of the nuclear fuel cycle have found the promising role in the field of nuclear medicine owing their chemical similarities and are mentioned in table 2 (25, 27).

A large volume of published literature is available for the development of essential separation processes relevant to the radiochemical purification of Scandium (35-37) and Copper (14, 17). However, ours is being very first attempt to summarize available EXC methods for $^{44/47}\text{Sc}$ and $^{64/67}\text{Cu}$ radioisotopes purification in the form of this mini-review. The main objective of this review is to explore the available well-established EXC methods and make the researchers aware of the possible application of such methods in the routine practice. Comparing the suitability of EXC for the separation of transmuted product and recovery of the target material from the irradiated target with the available and well-studied systems would be an evitable exercise and would further help in designing the innovative systems. We expect that this mini-review will form the basis for understanding the fundamental practices involved in EXC and its application in separation of $^{44/47}\text{Sc}$ and $^{64/67}\text{Cu}$. This will help in establishing the novel scientific developments and modus operandi further nurturing its promising and

potential applications in the nuclear medicine departments for separation and purification of emerging therapeutic as well diagnostic radionuclides at legitimate purities.

Elements of Extraction Chromatography(EXC)

EXC, as described earlier, is a fusion of solvent extraction and ion exchange chromatography which can be employed in the specific and selective separation of a metal ion. Moreover, use of smaller inventory of exorbitant extractants, small amount of VOCs (volatile organic compounds), lower volume of secondary waste, no third phase formation and no issue of the phase disengagement are few other superiorities which make it unique when compared with widely used solvent extraction technique (38-39).

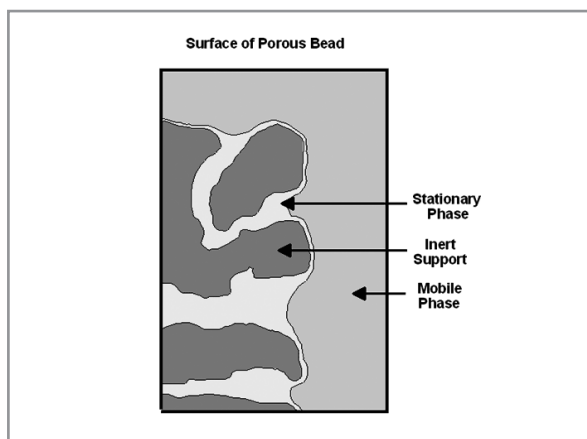


Figure 1. Extraction chromatography resin bead (40, 41)

The extraction chromatographic material is synthesized by anchoring the organic extractant on the porous inert support like polymeric resin or an inorganic matrix as depicted in figure 1 and they are conventionally known as solvent impregnated / extraction chromatographic resins (40, 41). The organic extractant proposed should pose several satisfying criteria like high solubility in organic solvents, negligible aqueous phase solubility, suitable kinetics and thermodynamics towards the metal ion, precise complexation abilities with a metal ion, radiolytic and acidic stability, should be non-volatile/ toxic/

inflammable etc. (25, 42). The selected organic solvent is then agitated with the mixture of volatile solvent and the inert stationary phase which is having the acceptable physical and chemical stability. After which the volatile solvent is evaporated using rotary vapor and dried which ensures the strong physical binding of the extractant on the inert material. In some cases, the extractant is chemically attached to the substrate during the synthesis process (25, 43). This substrate should be chemically inactive as far as its interaction with extractant and the metal ion is concerned, any such interference would break down the system with the direct effect on the selectivity and retention of metal ion on the resin material (44).

The performance and the capacity of the EXC resin depends on the amount of loaded extractant, metal ion selectivity, retention abilities, resolution, physical and chemical stability, particle size of inert support, column dimensions, flow rate of the mobile phase (aqueous phase with metal ion), reusability and reproducibility (25, 42-43). One of the important factors which are closely associated with the column efficiency is the Height Equivalent to Theoretical Plate (HETP) (45) and is recognised by Van Deemter equation:

$$\text{HETP} = A + (B/\mu) + C \cdot \mu$$

Where,

A = Eddy-diffusion parameter, related to channeling through a non-ideal packing [m]

B = Diffusion coefficient of the eluting particles in the longitudinal direction [$\text{m}^2 \text{s}^{-1}$]

C = Resistance to mass transfer coefficient of the analyte between mobile and stationary phase [s] μ = Linear velocity [m s^{-1}]

HETP can also be expressed as (45):

$$\text{HETP} = L / N$$

$$N = 16 (\text{retention time/peak width})^2$$

Where,

L = Length of column (m)

N = Number of plates

One should be well informed that though increasing the w/w loading of the extractant on the support material may increase the metal ion sorption capacity/ weight of EXC resin this does not make much sense as this technique is selective for a specific metal species over others.

Steps involved in EXC studies

Once this EXC resin is ready to use it is further used in batch studies and later the column studies are performed to ensure its applicability and stability towards the determined procedure and system (25). In the batch uptake studies, the known weight of EXC is thoroughly mixed with the determined volumes of the solution containing metal ion preferably at the known temperature in the shaking incubator for the prescribed time interval which is a direct function of kinetics involved in the system. The ratio of resin weight and concentration of metal ion needs to be varied depending on the experimental conditions to get the measurable and reproducible difference in initial and final concentration after equilibration. Following the equilibration, the resin is usually separated from the acidic solution using either centrifuge or the suitable filter and known volume of the aliquot is assayed. The analytical techniques involved in assaying the samples may vary depending on the nature of the elements to be quantified, if radio-emission is involved normally radiation detectors like NaI (TI) / HPGe / LSC are employed while ICP-OES/ MS are used in the case of stable elements. Later the distribution coefficient (K_d) is determined using the following equation (41):

$$K_d = [(C_0 - C_f) \cdot V] / [C_f \cdot W] \text{ cm}^3/\text{gm}$$

C_0 and C_f represent the elemental concentration in the aqueous phase before and after equilibration respectively, W is the weight of resin in grams and V is the total volume of the aqueous phase used during equilibration

in mL. The determined K_d values in combination with the column parameters form the basis for the column operation and are used to develop a precise and suitable flow chart for separating the metal ion of interest.

Column operation is a series of steps and is more or less common in all the cases used for radiochemical separations. The steps involved in the operation of the pre-packed column can be detailed as follows (25):

i) Conditioning: It is a process where the column is wetted using the suitable volume of aqueous solution in which the dissolved metal ion is loaded.

ii) Sample loading: The dissolved sample is loaded on the column in the suitable acidic media.

iii) Washing: This step is particularly meant for washing and getting rid of all the likely impurities one expects to be produced during the irradiation of the target material. The washing solution medium may be different than that used for conditioning and loading of the sample.

iv) Elution: The final step is eluting the metal ion of interest in the prescribed medium which can be further employed in the radiopharmaceutical.

Column operation can be carried out under the ambient condition while some may need vacuum operations depending on its nature and size. The time required for the above mentioned procedure may vary and strongly depend on the column parameters and efficiency. After the completion of the above steps, the column is washed thoroughly and regenerated for the future separation.

Discussion

1. Extraction Chromatographic Techniques for $^{44/47}\text{Sc}$ Separation and Purification:

The two Scandium isotopes namely Sc-44 and Sc-47 with the characteristic radio-emissions and half-life mentioned in table 1 are the emerging theranostic isotope/ isotope pairs in the field of nuclear medicine (8, 10). Sc-44 is a promising long-lived PET isotope and considered

as a good alternative to conventional isotope F-18 due to the fact that it can be produced onsite using the $^{44}\text{Ti}/^{44}\text{Sc}$ generator (19). On other hand Sc-47 is contemplated as potential auxiliary radiotherapeutic isotope parallel to ^{177}Lu and ^{90}Y (20). Numerous strategies have been studied towards the separation and purification of Sc-isotopes from the variety of matrices out of which the one employing EXC resin materials is discussed here.

1.1 DGA resin

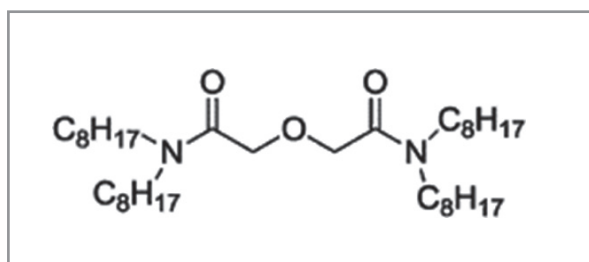


Figure 2. N, N, N', N' Tetraoctyl diglycolamide (DGA)

N, N, N', N'-tetraoctyldiglycolamide abbreviated as TODGA/ DGA (46) (Fig. 2) finds a wide range of use in extracting and partitioning the trivalent lanthanides and actinides from high level nuclear waste in nuclear fuel cycle by solvent extraction technique and as a stationary phase in EXC. The chemical aspects and applications of DGA have been comprehensively reviewed by Ansari et al. (47). A detailed distribution co-efficient study of a large number of elements in HNO_3 , $\text{HNO}_3 + \text{HF}$ and HCl has been carried out in the past (48). Horwitz et al. have developed the DGA based EXC resin and have shown its promising application as an efficient extractant for the uptake of different trivalent lanthanides and actinides including Y (III) in HNO_3 and HCl medium (49). Metal-ligand complexation is derived by reverse micelle formation in the presence of acid hydrate which involves three DGA molecules encapsulating trivalent metal ion (50) as shown in figure 3 with the following extraction mechanism:

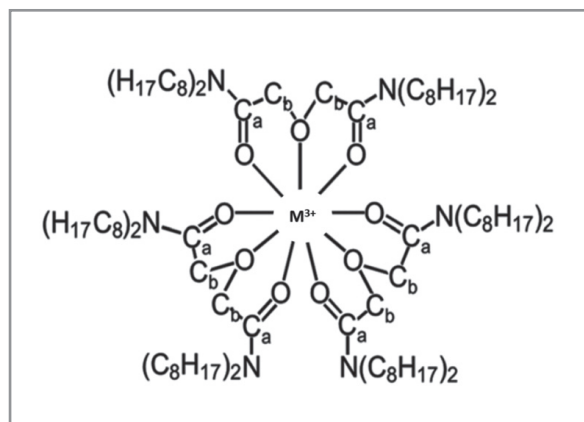
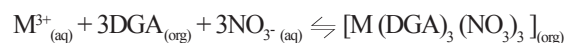


Figure 3. DGA – M^{3+} complex (50)

Furthermore, a group of scientists from India have elaborately studied ^{90}Sr – ^{90}Y separation using DGA in solvent extraction, extraction chromatography and liquid membrane studies, and they have recommended separating ^{90}Y from ^{90}Sr using DGA EXC resin (51-54). Owing to the chemical similarities between Sc and Y, researchers have been successful in optimizing the separation of different Sc isotopes using chromatographic DGA resins.

Application of DGA resin in the separation of Sc isotopes from irradiated Ca and Ti target for radiopharmaceutical applications were first presented by Dirks et al. (55) in 2010 and have been subsequently used by different groups. They suggested the potential application of DGA resin with interesting results as far as the separation and decontamination factors towards the Ca and Ti targets and other possible impurities at comparatively low acidity. The higher decontamination factors against Ca (25×10^3) and Ti (10^5) with short time required due to the fast uptake kinetics further enhance the possibility towards its application at the nuclear medicine site. Considering the particle size of the DGA resin and hydrophobic nature, DGA cartridges should be operated using the vacuum box accessories. The overall prescribed sequential separation procedure is shown in figure 4. The preconditioned column using the specified acidic medium was loaded with the dissolved target matrix

and then the successive washing was carried out using 2.5 M nitric acid in the case of Ti target while 0.1 M HNO₃ was used for Ca target. The target material was recovered during the column washing procedures and later the elution of Sc was carried out using 0.1 M HCl in both the cases. Alliot et al. (56) separated the produced ⁴⁴Sc using enriched ⁴⁴CaCO₃ target applying the same protocol prior to which they recalibrated the system using the simulated target material of natural calcium.

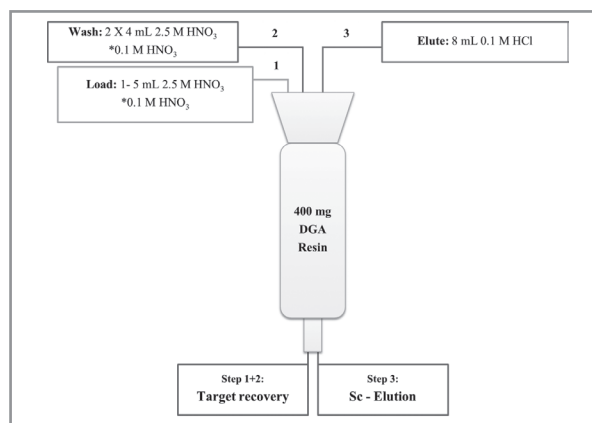


Figure 4. Steps involved in Sc separation from the irradiated Ti and * Ca target material using DGA resin cartridge (55)

Schibli et al. (15) produced ⁴⁴Sc using ⁴⁴Ca (p, n) ⁴⁴Sc nuclear reaction in a cyclotron after which they performed the separation of ⁴⁴Sc. In their protocol, they introduced secondary step where they loaded separated ⁴⁴Sc by DGA column on DOWEX-50 column and the final elution of ⁴⁴Sc from DOWEX-50 column was carried out using ammonium acetate and was used for radiolabeling after pH adjustment using dilute HCl. Using this method Meulen et al. developed a connected module to achieve the complete separation process (57). In all the processes mentioned above unmitigated efforts were made to recycle the target material and was recovered from the washings obtained from DGA cartridge prior to the elution of scandium.

1.2 UTEVA resin

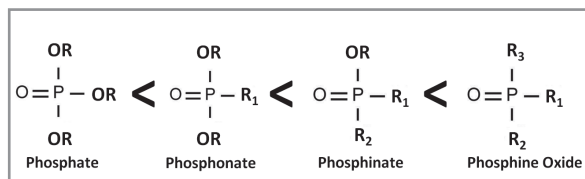


Figure 5. Organophosphorus extractants and their basicity trend (58)

Use of tributyl phosphate (TBP) in the recovery and purification of actinides is a regular business involved at the nuclear fuel reprocessing site since last six decades (59). Extraction of Sc using TBP has been reported long back (60-61). A review based on the solvent extraction and involved techniques for Sc purification by Wang et al. (62) supplements the complete overview of the available extractants including organo-phosphorus extractants. However, there are few demerits of using TBP with solvent extraction like (i) considerable solubility in aqueous phase, (ii) third phase formation with the higher amount of metal ion loading and (iii) presence of radiolytic degradation products (63). The higher homologues of TBP have exhibited extraordinary properties towards its extraction abilities, resistance to third phase formation and aqueous solubility (63). The key element responsible for the extraction properties is the basicity of the phosphoryl oxygen and the attached substitutes to the phosphorus atoms. The extraction abilities of organophosphorus can be altered and enhanced by substituting R-O-P group directly by R-P and changing “R” in the group. The trend of the basicity varies as shown in figure 5 (58).

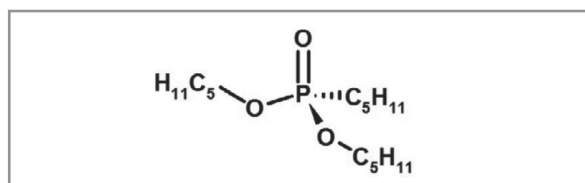
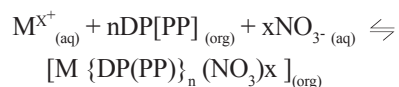


Figure 6. Dipentyl pentylphosphonate- DP(PP) (64)

Uranium and TEtra-Valent Actinide (UTEVA) resin as the name suggests is specially designed EXC resin for separation of U and tetra-valent actinides by Horwitz et al. (49). The extractant employed in this EXC resin is

Dipentyl pentyl phosphonate (DP[PP])- figure 6 (64), a higher homolog of TBP and is commercially available from Eichrom industries, USA and Triskem, France. This EXC resin has demonstrated high uptake and selectivity towards uranium and other actinide elements and the process has been well optimized (49). The uptake mechanism of metal ions using this resin is similar to that of TBP where the organophilic neutral metal ion-extractant complex is formed and this solvated species is extracted by the organic phase (62) which is DP[PP] in this case:



A novel Sc partitioning approach was proposed by Valdovinos et al. at the University of Wisconsin-Madison, in the recent past using UTEVA resin material (36). Efforts were made in the present work to develop an automated module for ^{44}Sc purification. The irradiated target was dissolved in 5-15 mL of concentrated hydrochloric acid. Prior to the actual experimentation, the authors carefully studied the distribution coefficients (K_d) of Sc (III) and Ca (II) at different HCL concentrations and standardized the complete separation protocol which was carried out using the sequential steps like, sample loading (5mL, 10 M HCl), column washing (5mL, 10 M HCl) and ^{44}Sc eluting (400 μL DI water). The complete processing was

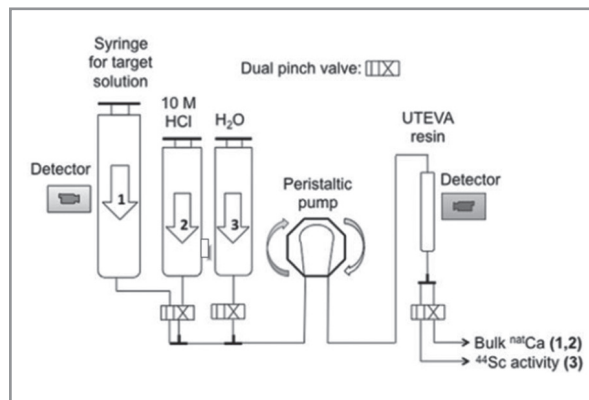


Figure 7. Automated ^{44}Sc separation module using UTEVA column (36)

carried out by loading the dissolved target material in the automated module as exhibited in the flowchart below. Similar separation was carried out by Jastrzebski et al. (65) and they were further successful in recovering the target material for its future reuse.

2. Extraction Chromatographic Technique for $^{64/67}\text{Cu}$ Separation and Purification:

Cu-64 has been projected as a notable PET imaging isotope with its nuclear and chemical capabilities (table 1) (17). While its sister isotope Cu-67 is considered as a theranostic isotope with the well suited radiological properties (table 1) (14). We will elaborate on the available EXC technique for Cu-partitioning here.

Preparation of suitable extractants and employing the same as a stationary phase for Cu-separation has been carried out by several groups (66-70). Nevertheless, we will be restricting ourselves to the one which has been developed solely for the $^{64/67}\text{Cu}$ separation purpose from Zn and Ni targets in this review. Dirks et al. have studied, characterized and optimized separation of the transmuted $^{64/67}\text{Cu}$ from the irradiated Zn / Ni target matrix and other impurities using the Cu-selective resin (69). In their studies they have tried different acidic media, using which they were successful in developing fast, selective and reliable method having higher decontamination factors as compared with the target element and the other probable interfering elements.

While developing the complete process the distribution coefficients of different elements was determined with Cu-selective resin in HCl, HNO_3 and H_2SO_4 medium with varying pH 5-1. The process involved the pre-conditioning of 50 mg Cu-selective EXC resin with 300 μL of respective acids for half an hour after which ~ 10 ppm of the initial cation concentration under consideration was added and mixed thoroughly using the shaker. Later the mix was centrifuged and 1 mL of the separated aliquot was assayed using ICP-MS for the metal ion concentrations which

were used to derive the K_d values.

Column studies included the steps as depicted in figure 8 and they used 2 mL of Cu-selective resin column in triplicates to ensure the least error if any. The volumes used for column conditioning, washing and Cu elution were optimized using various plausible interfering metal ions. Out of the three acidic mediums used for the K_d evaluations, pH 3 HNO_3 seems to be the promising acidic medium with the least interference of other metal ions and have higher decontamination and separation factor values. The performed tests indicated that the Cu-selective resin can be efficiently employed for the purification of produced Cu-isotope for medical application. Nevertheless, further studies using the irradiated samples and overall system development are still needed.

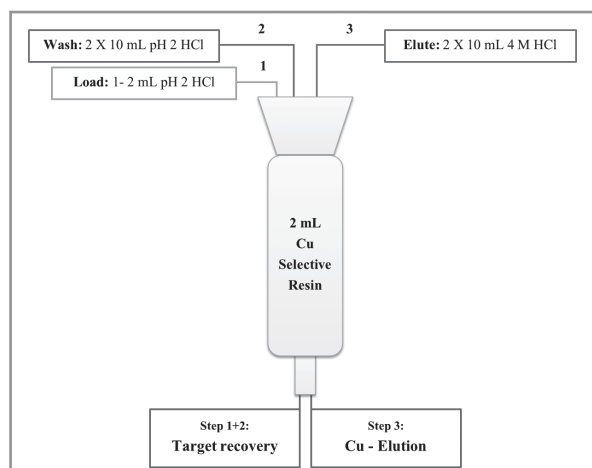


Figure 8. Optimized layout of Cu separation using Cu-resin (69)

Conclusion

There are a number of available separation and purification techniques for emerging radiometals like $^{44/47}\text{Sc}$ and $^{64/67}\text{Cu}$ with the potential capabilities in the future applications which is expected to grow steadily. The promising EXC techniques suited for their separation have been summarized and discussed in this review. The use of diverse extractants as the stationary phase, capable of selectively trapping the wide variety of metal ion of interest from the complex

system has increased the usefulness of EXC methodologies in nuclear medicine. The EXC technique provide a very simple means for trace elemental separation with an ease and have high capabilities and promising behavior for its application in process development. Also, the simplicity involved in the column operation makes it a convenient approach for setting up an automated module.

The DGA, UTEVA and CU-selective resins summarized in this review have been an appropriate choice in the way to separate $^{44/47}\text{Sc}$ and $^{64/67}\text{Cu}$ and recycle the target element. The techniques discussed are efficient with respect to the high radiochemical purity and yield from the irradiated target. Moreover, the selectivity of the resin material towards the radiometal of interest, high decontamination and separation factors, simplicity involved in the column operation and the stability of the EXC resin towards the radiation and high acid loading effect will substantially increase the use of this technique in the routine applications.

EXC techniques discussed though have proved to be efficient are at early stage of their investigations as far as their application in the production of the $^{44/47}\text{Sc}$ and $^{64/67}\text{Cu}$ radiometals are concerned. Exhaustive optimization exercise needs to be employed depending on the varying target material and needs to supplement and validate the available research results. Furthermore, the techniques mentioned in this review are not all-inclusive and additional modifications in the present extractants, resin material or the EXC techniques as a whole can be envisaged and added to the list based on their applications and other relevant considerations.

Acknowledgments

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