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REVIEW

Radiochemical separation of ^{89}Zr: a promising radiolabel for immuno-PET

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ABSTRACT

^{89}Zr with the favorable nuclear decay kinetics and chemical properties is an appealing radiometal for its application in immuno-PET using radiolabeled monoclonal antibodies. Rising demand of ultrahigh purity and high-specific activity ^{89}Zr has propelled the radiochemist worldwide to develop an overall efficacious method for its promising separation from the target matrix ^{89}Y. The requirement of elevated radiochemical purity (≥ 99.99%) has accelerated the efforts since last two decades to achieve higher decontamination and separation factors of carrier free ^{89}Zr over ^{89}Y using several suitable separation techniques. However, each of the technique has its own pros and cons which prior to its actual medical application needs to be optimized and thoroughly scrutinized to avoid further complications during radiolabelling of the pharmaceuticals. In this short review article we will specifically consider as well focus on the historical development and the recent advances on the radiochemical separation of ^{89}Zr from ^{89}Y which will be helpful for the separation scientist involved in this area to understand the existing available means and plan the strategy to investigate and develop the novel techniques to overcome the problems involved in the present methods.

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Key Words: Zirconium-89 (^{89}Zr), Immuno-PET, Radiochemical separation/purification, Solvent extraction, Ion exchange, Hydroxamate resin

Introduction

Non-invasive molecular imaging and radiotherapy using several radioisotopes for clinical purposes have been a fascinating area of research for the scientific community (1,2). Hybrid imaging like positron emission tomography (PET) fused with Computed Tomography (CT) commonly known as PET-CT is playing a crucial role in revealing and evaluating different medical conditions especially cancers, heart disorders and brain diseases (3). In some cases, radiolabeling of antibodies for imaging purposes gives an in-depth idea of the cause and treatment (4). PET using radiolabeled monoclonal antibodies (mAbs); conventionally known Immuno-PET is often described as a technique that combines the sensitivity of PET with the highly specific antigen and mAbs interaction (5,6). Radioisotopes like ^{89}Zr ($t_{1/2}$ = 3.3 d), ^{68}Ga ($t_{1/2}$ = 67.63 m), ^{124}I ($t_{1/2}$ = 4.2 d), ^{86}Y ($t_{1/2}$ = 14.7 h) and ^{64}Cu ($t_{1/2}$ = 12.7 h) have shown promising characteristics for antibody labeling based PET imaging (7). However, not all possesses the desirable properties for Immuno-PET application due to the lack of peculiar nuclear properties, production cost, low radiochemical purity, cumbersome separation procedures, etc. Among all the above-mentioned metallo- radionuclides, ^{89}Zr shows nonpareil physical as well as chemical properties for its ideal application for immuno-PET (8-12). Thus, in this mini-review, we will focus and epitomize on the radiochemical separation of ^{89}Zr from ^{89}Y.

^{89}Zr with the half-life ($t_{1/2}$) of 78.4 hours is one of the

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Table 1. Nuclear characteristics and properties of the predominant radionuclides formed during ^{89}Y target bombardment with protons using energy window E_p = 10-20 MeV.

Nuclear reaction	Q-value[a]	Energy window[b] (Ep)	Product nuclide	Half life ($t_{1/2}$)	Principal γ-ray Energies[c] (intensity[d])
(p, n)	-3.61	6-12	^{89}Zr	78.4 h	909 (100)
(p, 2n)	-12.93	13-20	^{88}Zr	83.4 d	393 (97)
(p, pn)	-11.47	12	^{88}Y	106.6 d	898 (93.7), 1,836 (99.2)
(p, αn)	-9.80	12	^{85}Sr	64.9 d	514 (96.4)

[a]Q-value- MeV; [b]Energy Window: MeV; [c]γ-ray Energies: keV; [d]Intensity: % (21,22).

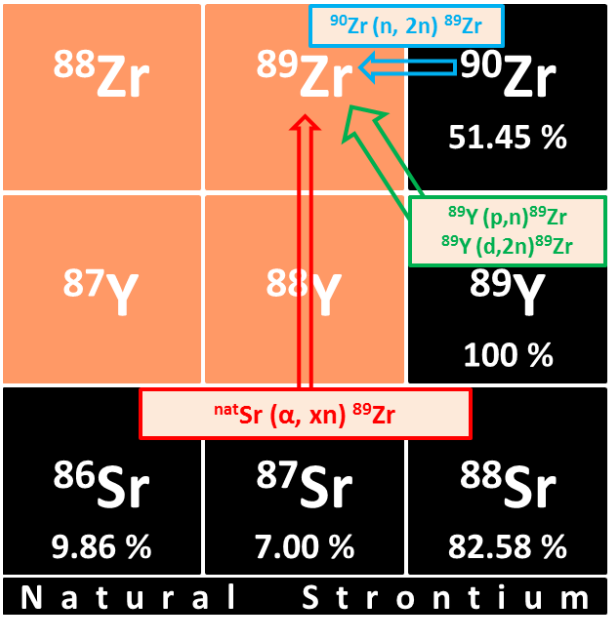

Figure 1. Different nuclear reactions for ^{89}Zr production using strontium, yttrium and zirconium as target element (18).

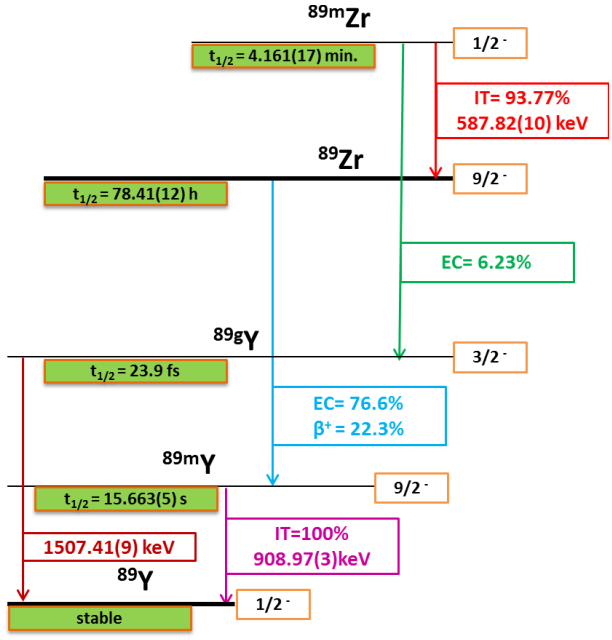

Figure 2. ^{89}Zr decay scheme with characteristic nuclear data (23).

long-lived and high-intensity positron emitting radionuclides favorable for the development of novel immuno-PET probes for *in-vivo* cancer imaging and further ease the radioimmunotherapy (RIT) planning (13). Its unique half-life of 78.4 hours, simple production procedure using ^{89}Y target in the hospital cyclotron, suitable conjugation chemistry and its complementary behavior with the biological half-life of the counter mAbs makes it a promising radio-label for immuno-PET (14,15). The studies using ^{89}Zr having highly tenable decay kinetics with purposeful mAbs and proteins have found to be encouraging for immuno-PET application. It is ideally suited for the in vivo time consuming biodistribution and tumor targeting procedures (16). Major PET radionuclides being short lived have limitations to study slow metabolic processes due to the long time required for achieving the whole body distribution for precise imaging (17). Production of ^{89}Zr (Figure 1) may be achieved by varying nuclear reactions out of which notably acclaimed by the scientific community being (a) via proton or deuteron bombardment on ^{89}Y; ^{89}Y(p, n)^{89}Zr/ ^{89}Y(d, 2n)^{89}Zr (b) via α bombardment on natural Sr; ^{nat}Sr(α, xn)^{89}Zr and (c) via neutron bombardment of ^{90}Zr; ^{90}Zr(n, 2n)^{89}Zr (18).

However, ^{89}Zr production using ^{89}Y target is a favorable due to its monoisotopic (^{89}Y ~ 100%) availability which further cuts down the complex enrichment process and hence the cost (19,20). Depending upon the irradiation energies of proton on ^{89}Y target different isotopes may be formed as listed in Table 1 (21,22).

Thus, it becomes a priority to separate the metal ion of interest from the target matrix and other impurities which may hamper the chelation chemistry with the radiopharmaceutical. The physical decay kinetics with the decay characteristics of

^{89}Zr to stable ^{89}Y is illustrated schematically in Figure 2 (23). ^{89}Zr decays to ^{89m}Y via positron emission and electron capture which further decays by emission of γ-rays to stable ^{89}Y. The low energy β^+ ($E_{\beta^+ max}$ = 395.5 keV) results in the straightforward high spatial resolution images providing value added information to the physicians which help in targeting the tumor and planning the treatment with high-end precision (13). Nevertheless, non-availability of the reliable and robust separation techniques makes the use of ^{89}Zr limited despite its encouraging in vivo preclinical research upshots. Thus, it is substantial to develop and progress the intrinsically matured separation and purification technology for medical application of ^{89}Zr which ensures the persistent support from the scientific community around the world.

Any radionuclide for its topical application in medical diagnostic or therapeutic purposes should meet stringent criteria prior to its use in the hospital based nuclear medicine departments. From which one of the vital prerequisite being the ultrahigh radiochemical purity of the radionuclide one wishes to apply in the medical procedures. Separation and purification methodologies play a pivotal role in any nuclear medicine department. Hence, the procedures should be closely monitored to assure high quality production of radionuclides before ingraining them as a radio-label into desirable radiopharmaceutical to ensure the non-interference of the impurities during its in-vivo utilization. Separation of ^{89}Zr from ^{89}Y should essentially meet the following standards for its aforesaid implication as an immuno-PET isotope: (a) higher decontamination factor (D.F.) denoted as the ratio of ^{89}Zr/ ^{89}Y or other impurities in the product as compared to that of feed which should meet the requirements laid down by the radiopharmacist; (b) fast processing methodologies to lower the loss of the ^{89}Zr; (c) concentrated product with high specific activity; (d) final product should be in the desired medium with respect to the post separation chelation chemistry of ^{89}Zr with specified ligand molecule and (e) minimal volume of secondary waste. Following these steps with the utmost care, one must expect a high purity product possessing prospective for large scale applicability for commercial production and its further implication.

While lot of work focusing on the radiochemistry of zirconium in spent nuclear fuel have been done and published in past (24,25) not much has been studied in regards with ^{89}Zr separation from ^{89}Y. Few techniques reported in the literature focus on the radiochemical separation of ^{89}Zr from ^{89}Y include solvent extraction, ion exchange and hydroxamate resins. Cumbersome lengthy procedures including poor recovery are the technical problems faced by separation chemists using some of the above mentioned techniques. Furthermore, poor recovery results in poor chelation which indeed deteriorates the in vivo PET imaging results. Thus, from the application point of view, it is desirable to explore the different novel possibilities for radiochemical separation of ^{89}Zr with high yield and purity. Though there are few excellent reviews available in hand dealing with the possible application of ^{89}Zr in immuno-PET (17,26,27) a comprehensive review on the radiochemical separation aspects is still not available. In a wake of this we will try to provide a track of the development and recent advances in the separation chemistry of ^{89}Zr in the present review. We will specifically emphasize on the well-studied separation techniques using solvent extraction, ion exchange and hydroxamate resin for the separation of ^{89}Zr for medical purpose only. This article will also focus on the future perspectives which will provide insight for the scientific community involved in this research for the development of the novel radiochemical separation techniques for ^{89}Zr.

Zirconium chemistry

It is of immense importance for the separation chemists involved in the research to understand the chemical properties of a particular metal ion under consideration in aqueous condition before he proceeds with the use of appropriate extractants for its separation. This will give a cognizance for metal ion extraction chemistry and its post extraction chelation with desired ligand for its radiopharmaceutical application.

Zirconium a group IVB transition metal is a hard Lewis acid with the atomic radius of 2.2 Å and the cationic radius of 0.84 Å (28). Normally it exists as Zr^{4+} with the tendency to bond with higher coordination number (favoring 8-cordination) like hard Lewis bases having oxygen donating moieties (29). Zirconium is fairly inactive and its oxides and hydroxides show low solubility in the water and forms assorted hydrolyzed species under different pH conditions (30,31). However, zirconium salts as compared with its hydroxides are

soluble in acidic medium (30).

Separation and purification of ^{89}Zr

In spite of appreciable and sizeable successes in the preclinical application of ^{89}Zr for immuno-PET, it has been receiving less attention due to the several issues involved (13,23). Amongst these issues, one is being inefficacious methods which produce contaminated products unacceptable and unmatched to the radiopharmaceutical standards. To address this issue, separation and purification of ^{89}Zr acceptable for its efficient use in the prescribed protocol is a hot topic amongst the radiochemists involved in medical research and in particular efforts have been made to explore and design the resilient extractants applicable in either solvent extraction or ion exchange chromatographic mode (27). Out of which complexation chemistry of solid-phase hydroxamate resin extractant has shown excellent behavior pertaining for its implication in radiochemical separation procedure yielding high radiochemical purity of ^{89}Zr in the oxalate form (23). In this section, we will discuss some of those ell-studied separation techniques.

Solvent extraction more commonly known as liquid-liquid extraction (LLE) and ion exchange chromatographic techniques have been extensively studied for separation of several metals due to their exceptional selectivity and durable chemical behavior (32). Few groups have studied the extraction abilities of few extracting agents towards its capabilities for separation and purification of ^{89}Zr from ^{89}Y applying LLE and ion exchange chromatography out of which major studies are discussed below.

Link et al. (33) have used the previously studied methods for ^{95}Zr separation and analysis (25,34) to purify ^{89}Zr and conjugate it with the antibody under consideration. The method was based on the use of LLE in coalition with anion exchange resin. LLE was carried out using 4,4,4-trifluro-1-(2-thionyl)-1-3-butanedione (TTA) as an extractant in xylene wherein the back extraction of ^{89}Zr is carried out by the mixture of 0.5 M HNO_3+0.5M HF. Further purification is achieved by passing the solution using 12 M HCl using Dowex 1X8 chloride from and final elution of ^{89}Zr was done using 1M HCl+0.01M $H_2C_2O_4$. The overall efficiency of this complete process was $\leq$ 25% which is the major drawback of this process for bulk production. Similar to the anion separation method used in the above process was studied in detail by Zweit et al.(35).

Another solvent extraction process based on di-n-butyl phosphate (DBP) in ether was studied by Dejesus et al. (36) for the separation process of ^{89}Zr from ^{89}Y following similar procedure employed by Scadden et al. (37). However, later was used for the separation of zirconium from the mixture of fission products. In this study, the irradiated yttrium matrix was dissolved using the mixture of H_2SO_4 (4 M) and concentrated HCl. Following this, the quantitative extraction of ^{89}Zr was carried out at 1 M acidity of either H_2SO_4/HCl in the above mentioned solvent and the behavior of the mentioned solvent was investigated under the different condition to optimize the said protocol. In the process of optimization it was found that addition of trace amount of oxalic acid ($H_2C_2O_4$-0.0004 M) improves the back extraction and increases the yield of the product. Subsequently, back extraction of ^{89}Zr was carried out using 4 M HF. Further purification was carried out using the anion extraction chromatography using 100-200 mesh size of Dowex 1X8 chloride form. Using this process high separation as well decontamination factor of ^{89}Zr/^{89}Y achieved (~ 97%). However, this method uses multiple steps with several highly corrosive and concentrated acids which pose the high risk of introducing metal ion impurities during the complete process. Furthermore, picogram impurities of yttrium may complicate the task ahead.

Lahiri et al. reported three different methods in the view of enhancing the yield and purity of the final product (38-40). One being the simultaneous partitioning of ^{90,91m,92m}Nb and ^{89}Zr from α-irradiated Y_2O_3 using LLE system (38) using 0.1 M trioctylamine and cyclohexane (diluent) with 0.167 M H_2SO_4 as organic and aqueous phase respectively. In the first step, they separated ^{90,91m,92m}Nb and ^{89}Zr and later extracted ^{90,91m,92m}Nb in the aqueous phase by addition of $H_2C_2O_4$ (10^{-3} M) to the aqueous phase. Formation of extractable $[ZrO_2(SO_4)_2]^{2-}$, $[ZrO(SO_4)_2]^{2-}$ and $[Nb_2(SO_4)_7]^{6-}$ anionic species pushes the metal ion to organic phase expediting the separation process. This process reports yield equivalent to ~90% and there exists a third phase formation problem at higher level of extractant concentration impeding the use at larger concentration of metal ion if required hindering the separation process. Hence, this

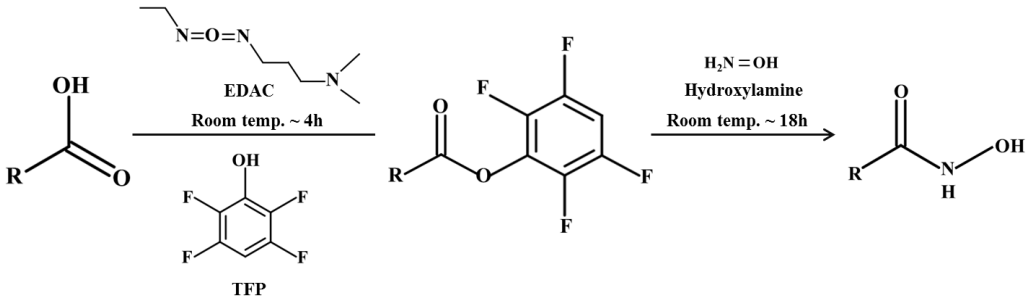

Figure 3. Reaction mechanism for hydroxamic resin synthesis (27).

method needs to be studied well and standardized before its large scale application. Other two methods reported by this group include LLE using liquid cation exchanger (39) and further modifying the process employing the solid cation exchanger (40). In this method, they reported the separation using di-(2-ethylhexyl) phosphoric acid (HDEHP) (39,40) as liquid cation exchanger and Dowex 50WX8 hydrogen form as solid cation exchanger (40). The studies assigned the poor cationic behavior of Zr ion in H_2SO_4 medium which forms non-extractable species like $Zr(SO_4)_2$ at lower extractant concentration while the higher concentration of extractant in organic phase extracts Zr forming $Zr(DEHP)_4$ (41). They further extended this method to achieve higher decontamination and separation factor which was attained by solid cation exchange resin Dowex 50WX8 hydrogen form. However, the involvement of multiple steps and use of H_2SO_4 would encounter a serious problem during post separation complexation of metal ion with the ligand for its radiopharmaceutical application.

The fitness of combined approach for separation of carrier free and high purity radio-zirconium using ion exchange sequentially followed by LLE was described by Kandil et al. (21). The solvent extraction experiment with HDEHP and cation exchange chromatography was performed in a similar way with Dutta et al. (40) but the aqueous phase in this case was HCl and the elution was carried out using 1:1 mixture of 0.5% $H_2C_2O_4$+0.1 M citric acid. Later, the anion exchange resin packed with Dowex 21 K (Cl^-) form was loaded by the product obtained from cationic exchanger at 12 M HCl. After which 3% Triphenyl phosphine oxide (TPPO) in addition to chloroform as a diluent was used as the organic extractant with 9 M of HCl. In this process, the distribution coefficient (K_d) values of zirconium were slightly more vis-à-vis yttrium which may interfere during the separation process. Also, the tailing problem involved dilutes the product with the large volume of acids (~60 mL). The method concludes that cationic resin is comparably efficient than anionic resin and solvent extraction method based on TPPO is superior to HDEHP. The overall efficiency is however low with 80-82% product yield.

Amongst all the techniques used till date for ^{89}Zr separation for medical purposes hydroxamate resin has received exceptional attention due to its propitious behavior with a well-established and encouraging results published by several authors in the past. The first ever study reporting the applicability of hydroxamate resin for radiozirconium separation was by Mejis et al. (9) based on which the widely acceptable cutting edge method have been developed by J. P. Holland's group which is certainly used and accepted by the scientific community (23). However, the synthesis of hydroxamate resin was first reported and used for $^{52}Fe/^{52m}Mn$ based generator (42) which was further conditioned and developed for its application in zirconium separation (15,23). Figure 3 shows the stepwise synthesis of hydroxamate resin (27).

In the separation process, the dissolved irradiated matrix in the mixture of 1 M HCl + H_2O_2 is loaded in < 2 M of HCl. After this, the column was sequentially washed with 2 M HCl followed by zirconium elution using 1 M $H_2C_2O_4$. This method claims the highest radiochemical purity till date with the yield of >99.99% which is ideal for radiopharmaceutical application. There have been reports on the automation of the separation modules using hydroxamate resin which have shown its applicability for routine production (43-45). Recently a France based company TRISKEM has produced a commercial resin based on the results obtained from above publications and tried to optimize the simple overall separation process as shown in Figure 4 (46).

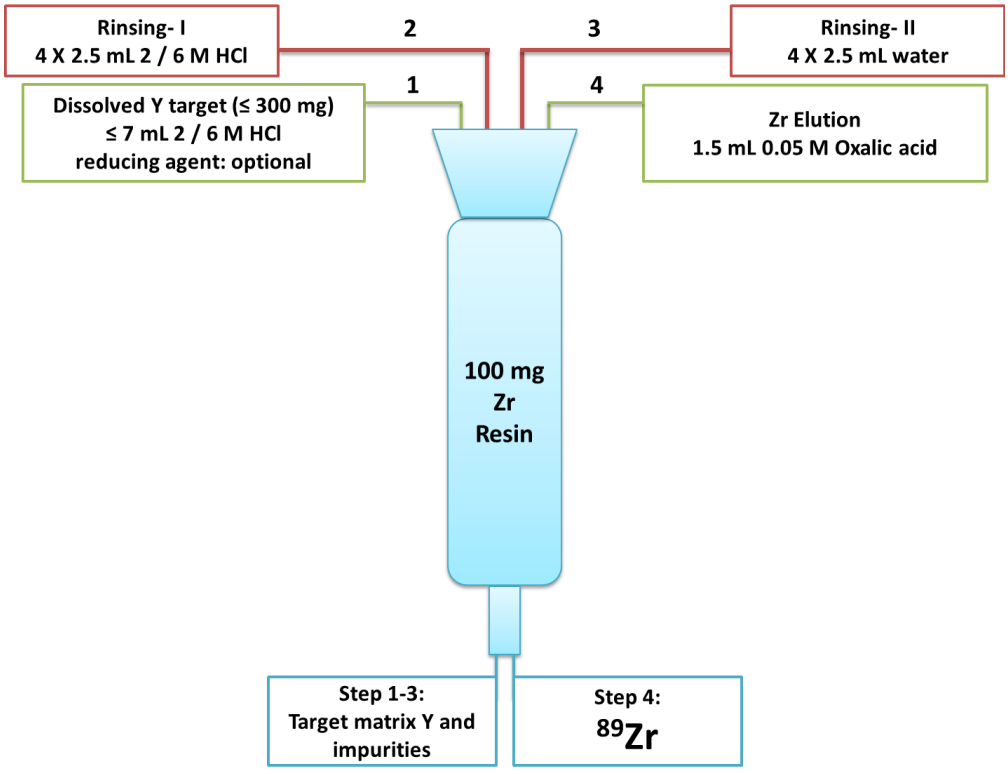

Figure 4. Proposed separation method for ^{89}Zr separation from Y target matrix using Zr-resin (46).

Although, the rising graph of the overall development and the outstanding results have shown that the hydroxamate resin can be implemented for the bulk production of radio-zirconium, use of tetraflurophenol TFP (causes severe burns), lengthy and cumbersome resin synthesis process along with low stability of the resin are some major hurdles which needs to be addressed. The major concern of this process is the use of high concentration of oxalic acid ~1 M used for the elution of final zirconium product in oxalate form. Studies have shown that the high concentration of oxalic acid may pose a serious problem once in the human system which may harm neural and muscle function ultimately affecting the kidneys (23). High concentration of $H_2C_2O_4$ in the product is impediment due to its competition with desferal (chelating agent for Zr). Thus, removal of high concentration of oxalic acid either by sublimation or evaporation is needed (9). Other method reported deals with the passage of the zirconium oxalate through strong anion exchange resin column which is a time consuming process as it needs passage of large volume of water to ensure complete removal of oxalic acid and further elution of Zr in chloride form using HCl (15).

Conclusions and Perspectives

Non-invasive immuno-PET using ^{89}Zr as a radio-label has proved a boon for rising era of hybrid nuclear medicine imaging. However, the separation of ^{89}Zr from the target matrix ^{89}Y and other impurities remains a challenge for the researchers. Notwithstanding few major concerns, recently developed hydroxamate based resin have shown extraordinary separation capabilities over other solvent extraction and ion exchange chromatography stratagem. The one modified by Holland et al. has been proved to be idiosyncratic amongst others and represented excellent separation properties required by an ideal extractant for the separation of ^{89}Zr with a remarkable yield (>99.99%). Some of the important conclusions based on our literature studies have been outlined below:

1. Though several aforementioned techniques are available for separation of ^{89}Zr from ^{89}Y and other impurities, problems like use of high concentration corrosive acids like H_2SO_4,

HCl, HF and harmful chemicals and VOC's like ether, TFPO, chloroform, $H_2C_2O_4$; several sequential steps involved in separation processes; large volume of secondary waste; high volume of product due to tailing and hence dilute concentration of ^{89}Zr and third phase formation in solvent extraction need to studied and addressed on the high priority basis. It will be of interest to permute and combine different well known extractants in a way that incorporates outstanding extraction abilities and results to further development of novel and straightforward separation methodologies.

2. Work done so far seems less focused on the extraction mechanism. It is an urgent need to deliberately study and understand the mechanism and interaction of Zr with the different extractants which seem of vital importance for the development of new materials and extractants with the exceptional separation capacities. Furthermore, the study on the stability of the extractant under severe radiation and chemical conditions are missing and need to be investigated thoroughly.
3. The implication of task specific ionic liquids, extraction chromatography, selective polymer membrane techniques and hollow fiber supported liquid membrane techniques ensuring the lower use of acids and VOC's successively reducing the secondary waste should be envisaged.

Thus, as the consequence of the challenges in the separation chemistry of ^{89}Zr, separation chemists should think of developing a dream extractant that has a property which addresses the above mentioned drawbacks and ensures the high purity radiozirconium.

Acknowledgements

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