Iron Removal from Radionuclides Utilized in Nuclear Medicine

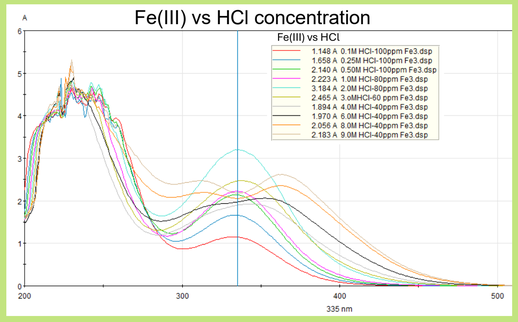
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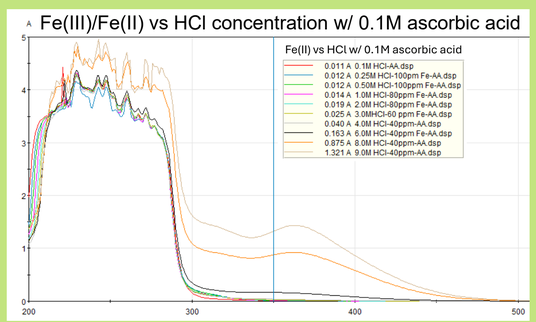
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Abstract Iron is a common matrix impurity encountered in the purification of radionuclides for nuclear medicine applications and must be removed effectively to produce high specific activity radionuclides which can be efficiently bound to targeting molecules via chelation for targeted nuclear medicine applications. Chromatographic separation systems for many radionuclides utilized in nuclear medicine have been studied with particular attention paid to methods for the separation of iron from the radionuclide of interest. Techniques employed include reduction of Fe(III) to Fe(II), stationary phases to selectively retain or reject Fe(III), and mobile phases that promote iron extraction or removal.

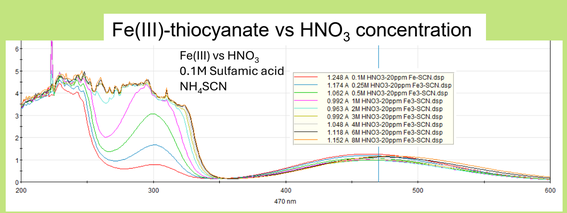
UV-VIS spectra of Fe(III) and Fe(II)

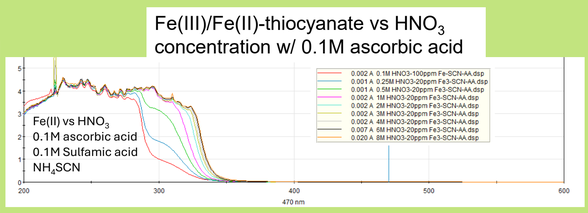
In HCl, the spectra of Fe(III) exhibit bands corresponding to Cl → Fe(III) charge transfer transitions. The bands below 300 nm are obscured by absorptions from ascorbic acid, however, the bands from 340 to 365, from $FeCl_3$ and $[FeCl_4]^-$ species are clear. The 340 – 365 nm bands disappear upon addition of ascorbic acid, indicating near complete reduction to Fe(II) except for 8-9M HCl.





Additional bands from HNO_3 further obscure the region up to 350 nm, however addition of NH_4SCN forms $Fe(SCN)^{2+}$ complexes which absorb strongly at 460 nm. Upon addition of ascorbic acid, the 460 nm absorptions disappear, indicating near complete reduction to Fe(II).

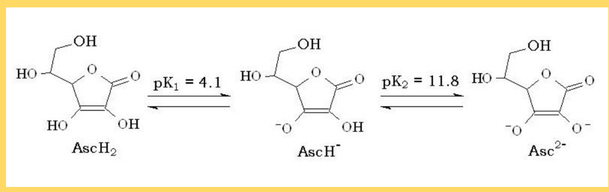


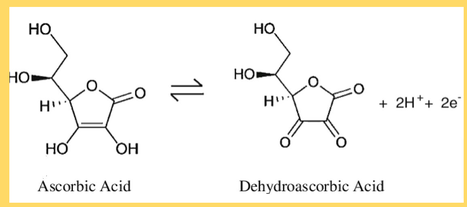


Iron Reduction with Ascorbic Acid

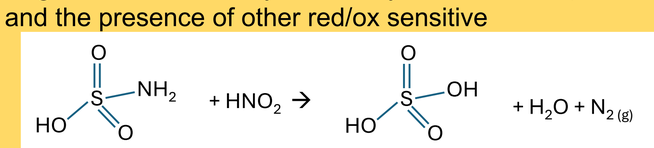
Reducing agents such as ascorbic acid, titanium trichloride, and hydroxylamine may improve iron removal from trivalent and tetravalent metal ions by improving resin selectivities. However, reducing agents can adversely impact separations for metal ions with multiple potential aqueous oxidation states, such as Cu(II) and Cu(I).

$Fe^{3+} + e^- \leftrightarrow Fe^{2+}$ $E^o = 0.771$ V



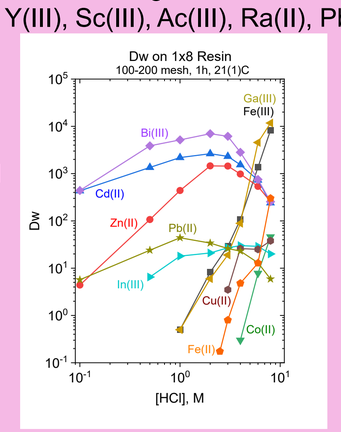


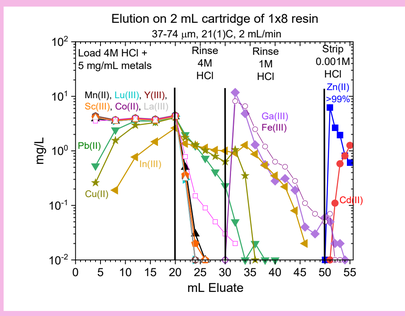
Ascorbic acid has two acidic protons with pKa values of 4.1 and 11.8. Additionally, the reduction of Fe(III) to Fe(II) by ascorbic acid produces two acidic protons and oxidizes ascorbic acid to dehydroascorbic acid. The efficiency and rate of the iron reduction is expecting to be influenced by the acidity of the solution, complexation of iron in the aqueous or resin phase, and the presence of other red/ox sensitive species. From nitric acid, the addition of sulfamic acid can improve iron reduction by scavenging nitrite/nitrous acid impurities which can oxidized Fe(II) back to Fe(III).[2]



Anion Exchange Resin

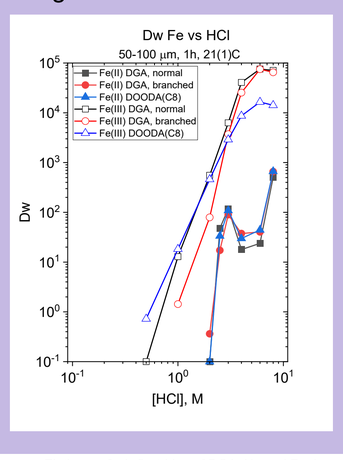
Anion exchange resin can be used to selectively remove Fe(III) from a large number of divalent transition metal ions and trivalent rare earths, actinides, and Y(III) and Sc(III) due to the formation of the $[FeCl_4]^-$ anion. Loading1x8 anion exchange resin from 4M HCl, retains Fe(III), Ga(III), Cu(II), Zn(II), Cd(II) and Bi(III), while Lu(III), Tb(III), Y(III), Sc(III), Ac(III), Ra(II), Pb(II), Co(II), Mn(II), and Cu(II) pass through the column. Rinsing with 1M HCl removes Ga(III) and Fe(III) and allows recovery of iron-free Zn(II) with dilute HCl. Recovery of Zn(II) with 0.001M HCl will co-elute Cd(II); however, increasing the HCl concentration to 0.05M HCl keeps Cd(II) on the resin, while Zn(II) is recovered.

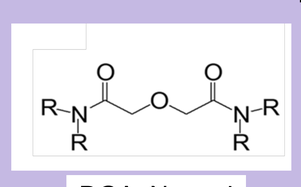




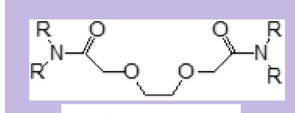
Neutral Solvating Resins

From HNO_3, EXC resins based on the neutral solvating extractants DGA and DOODA reject Fe(III) and Fe(II). This selectivity can be utilized to purify Sc(III), Y(III), Ac(III), Ln(III), Ca(II), Pb(II), Sr(II) and Mn(II) and other metal ions from iron impurities. From HCl concentrations >2M, Fe(III) and Fe(II) exhibit significant retention on the DGA and DOODA resins providing little purification from iron.

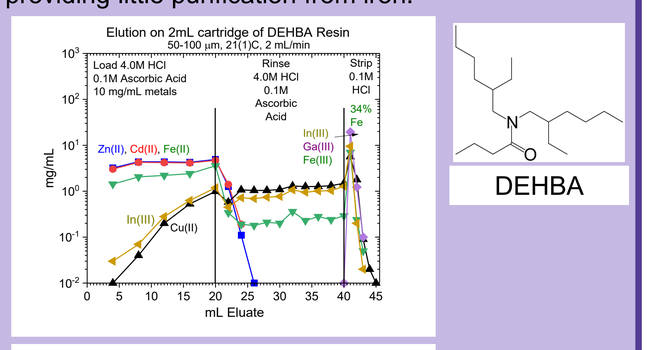




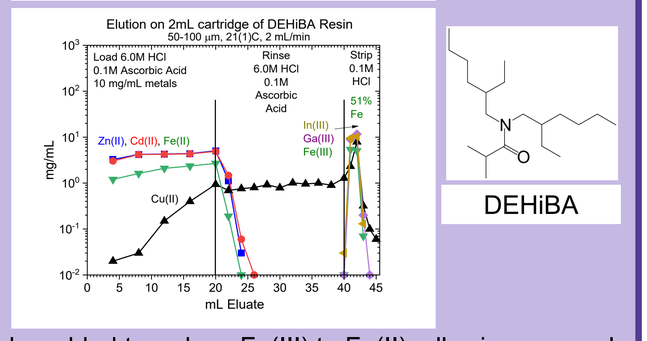
DGA, Normal
R = 1-octyl



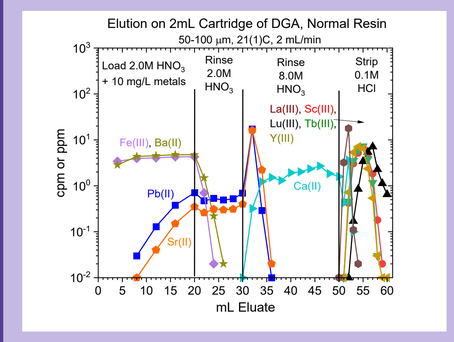
DOODA(C8)
R = 1-octyl



DEHBA



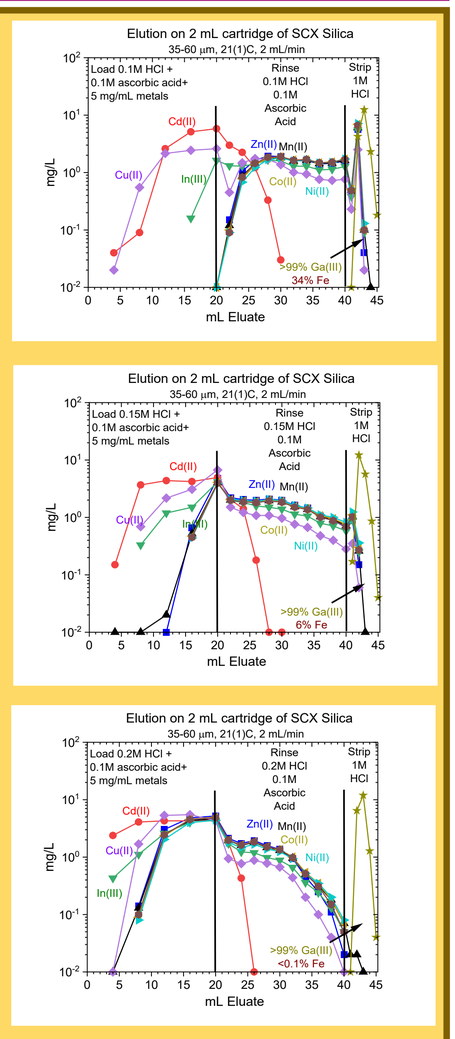
DEHiBA

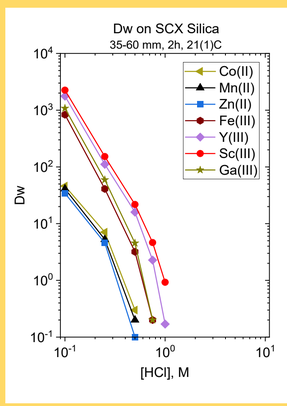


Ascorbic acid can be added to reduce Fe(III) to Fe(II), allowing removal of Fe from Ga(III) and In(III) using the monoamide resins based on the DEHBA and DEHiBA extractants. However, the Fe removal becomes less efficient as the HCl concentration increases, most likely due to incomplete reduction of Fe(III) at higher acidities.

Cation Exchange

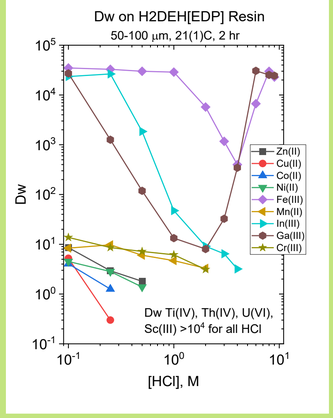
Reducing Fe(III) to Fe(II) with ascorbic acid improves the selectivity of several key radionuclides over iron on strong cation exchange (SCX) silica. The reduction of iron and the retention of other metal ions is most efficient from dilute HCl or from acetate buffers at pH 4.5 to 6.5. The acidity of the feed needs to be adjusted to decrease Fe(II) retention, while still retaining the metal ion(s) of interest. For example, Fe(III) and Ga(III) have nearly the same retention on the SCX silica. However, Fe(II) behaves more like Zn(II) or Ni(II) and can be removed from Ga(III) using 0.10 to 0.20 M HCl. The Fe(II) removal and the removal of other divalent transition metals improves as the acidity increases. Increasing the acidity higher than 0.20M HCl risks loss of gallium during the load and rinse steps.

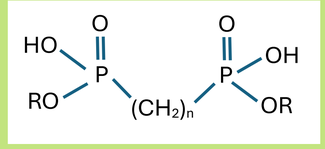




Acidic Organophosphorus EXC Resins

EXC resins based on acidic organophosphorus extractants (HDEHP or diphosphonates) retain Fe(III) strongly from all HCl and HNO_3 concentrations and can even be used to separate Fe(III) from Ga(IIII). Ga(III) passes through the diphosphonate EXC resin in 3M HCl, while Fe(III) is retained strongly. Ga(III) can then be retained on a second EXC resin containing a monoamide extractant (DEHBA). Recovery of Ga(III) from the DEHBA resin in dilute HCl is impacted by the small amount of extractant which leaches from the organophosphorus resin and is trapped on the DEHBA. A small cartridge of organic scavenger improves Ga(III) recovery from the DEHBA, with 1-octanol loaded prefilter being the most effective.



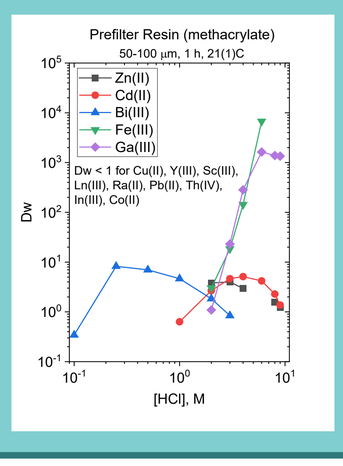


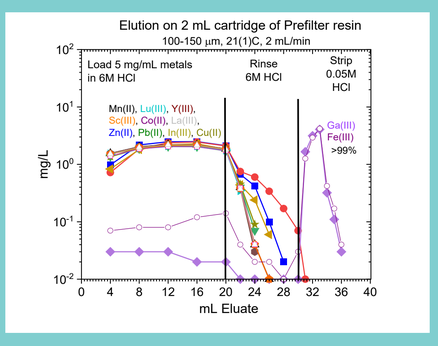
H2DEH[EDP]
n = 2

^{68}Ga Separation (EDP/DEHBA)		
Scavenger	**% ^{68}Ga Yield**	**% ^{68}Ga on DEHBA post-strip**
None	85	15
Prefilter	65	29
SDVB	87	12
tC18	73	18
1-Octanol	98	<0.1

Prefilter Resin

Polymethylmethacrylate prefilter resin, more commonly used to scavenge organic material or to serve as the inert support for extraction chromatography resins, retains Fe(III) and Ga(III) from > 4.0M HCl, while rejecting most other metal ions. Loading a feed of almost any other metal ion in 6M HCl through prefilter resin will remove Fe(III) and Ga(III) while allowing the other metal ions to pass through unretained.





References

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2) Brunstad, A. “Oxidation of Pu(III) by sodium nitrite,” Report number HW-51655, Hanford Atomic Products Operation, Richland, Washington, July 17, 1957.
3) Elmagirbi, A.; Sulistyarti, H.; and Atikah, “Study of Ascorbic Acid as Iron(III) Reducing Agent for Spectrophotometric Iron Speciation,” J. Pure App. Chem. Res., 1(1), 11-17 (2012).
4) Liu, W.; Etschmann, B.; Brugger, J.; Spiccia, L.; Foran, G.; and McInnes, B. “UV-Vis spectrophotometric and XAFS studies of ferric chloride complexes in hyper-saline LiCl solutions at 25-90C,” Chemical Geology, 231, 326-349 (2006).

Conclusions and Future Work

Methods for the efficient removal of iron impurities from a wide range of metal ions have been explored, including many of the most promising radionuclides for nuclear medicine applications. Through the use of selective chromatographic resins and valence adjustments between Fe(III) and Fe(II), it is possible to produce high purity radionuclides with very low levels of iron contamination. Additional work is being performed to reduce extractant bleed from EXC resins, reduce the impact of extractant bleed through the use of effective scavengers, and demonstrate methods for the removal of other common impurities.