The Concentration and Recovery of Nuclear Medicine Radionuclides in Buffer Solutions

Madeleine A. Eddy[1] and Daniel R. McAlister[1]

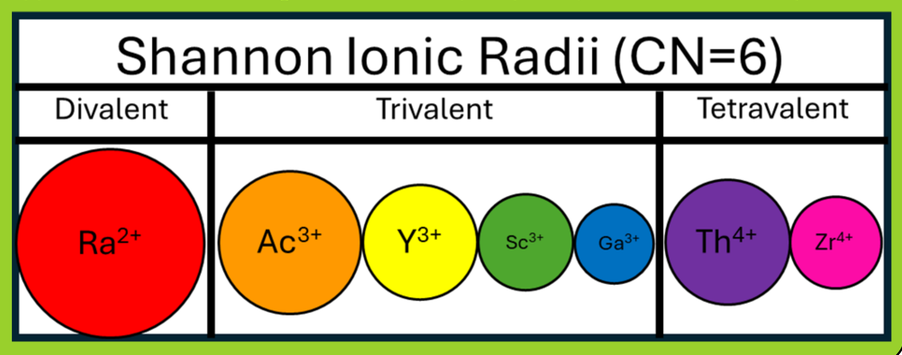
[1]Eichrom Technologies, LLC, 1955 University Lane, Lisle, IL 60532 USA

eichrom TECHNOLOGIES — A GCI COMPANY
1955 University Lane • Lisle, IL 60532 USA
www.eichrom.com

WTTC 19

Abstract

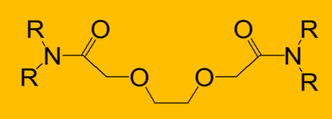
The recovery of high-specific-activity nuclear medicine isotopes in dilute acid or buffer is ideal for streamlined drug labeling reactions. Upstream separation and processing chemistry may not provide the isotopes in a compatible solution. The addition of a single cartridge of resin to achieve this isotope concentration and matrix conversion is a simple process change that can lead to effective recovery of many radionuclides in small volumes of buffer solution. This work evaluated the elution of several high-specific-activity radiotracers on strong cation exchange resin (SCX) and extraction chromatography resins containing *N,N,N′,N′*-tetraoctyl-diglycolamide (TODGA), *N,N,N′,N′*-tetraethylhexyl-diglycolamide (TEHDGA), *N,N,N′,N′*-tetraoctyl-3,6-dioxaoctane (DOODA), or DGA + diamyl amylphosphonate (DAAP). Isotopes were loaded onto the resin in 10 mL of HCl adjusted to a concentration that correlated to maximum loading efficiency. The tracer was then stripped off the column using 5 mL of 1 M NH_4OAc pH = 6, which is a commonly reported labeling solution for several developing nuclear medicine drugs. Herein, the elution and recovery of ^{44}Sc, ^{68}Ga, ^{95}Zr (^{89}Zr), ^{90}Y, ^{223}Ra, ^{225}Ac, and ^{227}Th in acetate buffer from strong cation exchange (SCX), DGA, DGA+DAAP, and DOODA resins are presented.



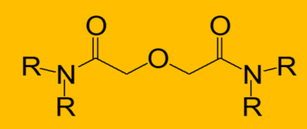
Background

- Existing separations are already done on DGA or SCX for many isotopes (Ga, Ac, Y…)
- Recovery of nuclear medicine isotopes in dilute acetate buffer is ideal for future labeling
- Charge and ionic radii have significant influence on loading and elution
- High specific activity isotopes are more strongly impacted by acidic impurities or cation exchange sites.
- DAAP can act as a masking agent to complex cation exchange sites, improving isotope recovery

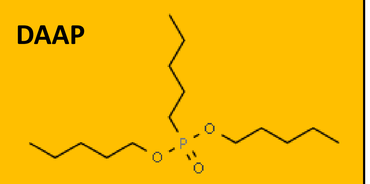
DOODA



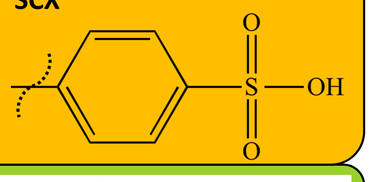
DGA



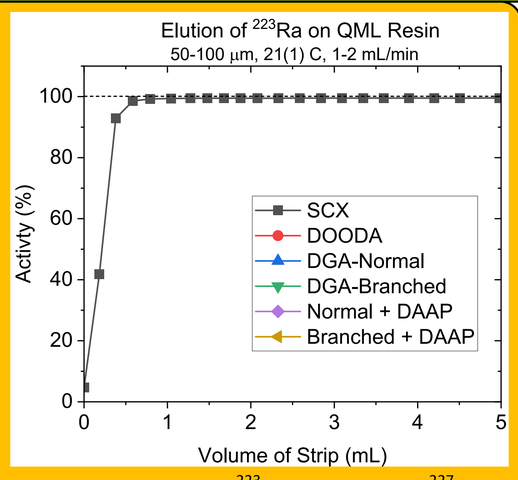
DAAP



SCX



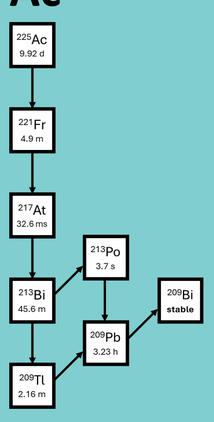
^{223}Ra

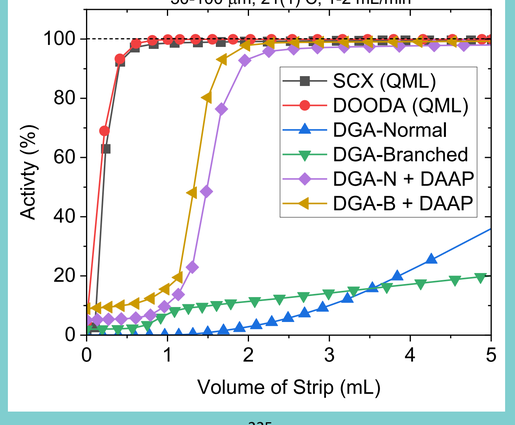


Radium is the largest +2 cation on the periodic table. ^{223}Ra is part of the ^{227}Th decay series, providing 4 alpha emissions for targeted alpha therapy (TAT). ^{223}Ra is currently used as $^{223}RaCl_2$ in treatments, known as Xofigo®, but investigations into Ra chelators for new drug-labeling inspires investigation into the elution of ^{223}Ra in buffer solutions.

Selective extraction of Ra is difficult due to its low z/r. ^{223}Ra is not extracted by DGA or DOODA, but is extracted by SCX in dilute HCl, with easy and complete recovery in 1 M NH_4OAc pH = 6.

^{225}Ac

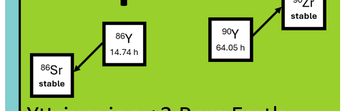




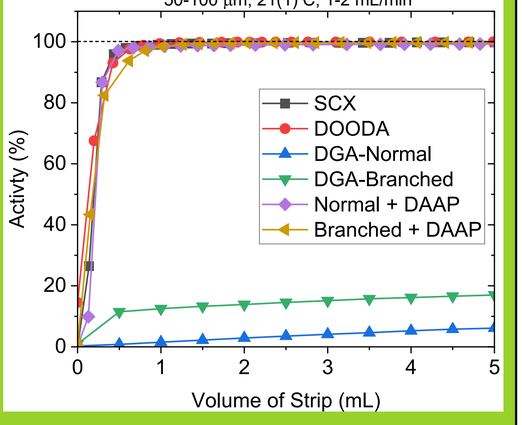
Actinium is the largest +3 cation on the periodic table. ^{225}Ac provides 4 alpha emissions, and is an industry standard for targeted alpha therapy.

^{225}Ac experiences significant breakthrough on the DGA resins, and a 2ML bed volume is required for sufficient loading. Recovery on DGA is hampered by ion exchange interactions. Adding DAAP improves recovery, but the decrease in DGA content leads to breakthrough during loading. Loading on DOODA and SCX is much more complete for QML cartridges, and the ^{225}Ac is readily stripped from either resin in 1 M NH_4OAc pH = 6.

$^{86/90}Y$

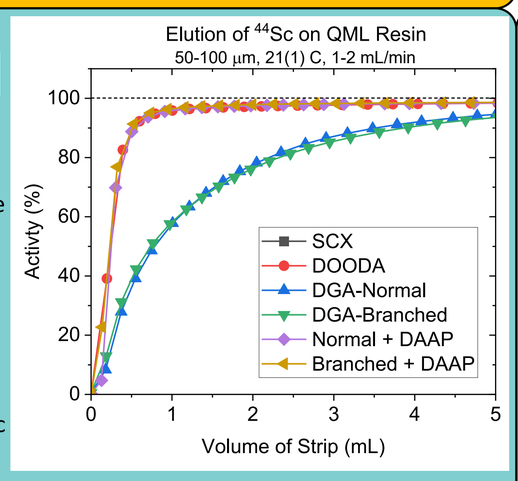


Yttrium is a +3 Rare Earth Element with a relatively low z/r. ^{90}Y is a well known beta emitter that can be used in cancer therapies and is readily produced via $^{90}Sr/^{90}Y$ generators. A diagnostic PET emitter ^{86}Y provides the imaging counterpart to ^{90}Y.



Y was insufficiently loaded on DOODA (14.5% breakthrough), however minimal breakthrough was seen for SCX and DGA. Recovery of the isotope from SCX and DOODA was easily achieved in small volume buffer, but only a fraction of the ^{90}Y was stripped from DGA. Stable Y is easily recovered from DGA, leading to the conclusion that trace extractant impurities are tying up the high specific activity tracer, impacting elution. By adding DAAP to complex DGA impurities, recovery of ^{90}Y in a small volume of 1 M NH_4OAc pH = 6 was achieved.

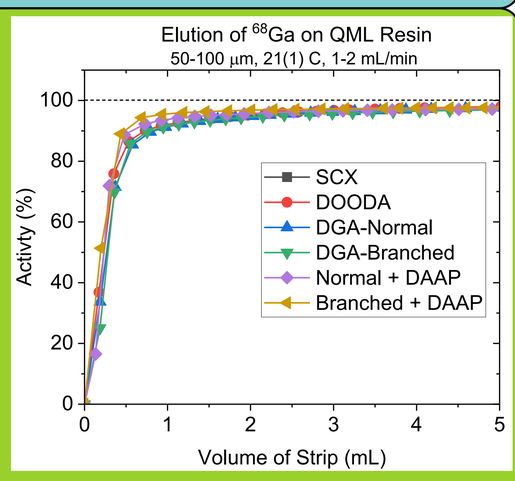
$^{44/47}Sc$



Scandium is the smallest of the +3 Rare Earth Elements and susceptible to hydrolysis. ^{44}Sc is a short-lived PET emitter readily available via $^{44}Ti/^{44}Sc$ generators. ^{47}Sc acts as the therapeutic counterpart to ^{44}Sc providing low energy beta and gamma treatments.

The small +3 Sc ion has a high affinity for extraction on SCX, DGA, and DOODA resins. Conversely, it is more challenging to recover than the other rare earth elements due to electrostatics and hydrolysis. Sc recovery from SCX was ineffective even with added NaCl. Recovery of Sc on DGA was slow and gradual, but improved significantly upon the addition of DAAP to mask DGA extractant impurities. DOODA resin successfully demonstrated complete loading and recovery of high-specific-activity Sc in a small volume of 1 M NH_4OAc pH = 6.

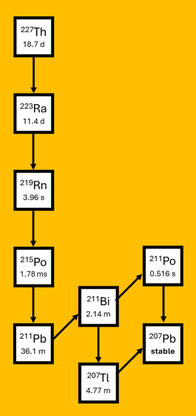
^{68}Ga

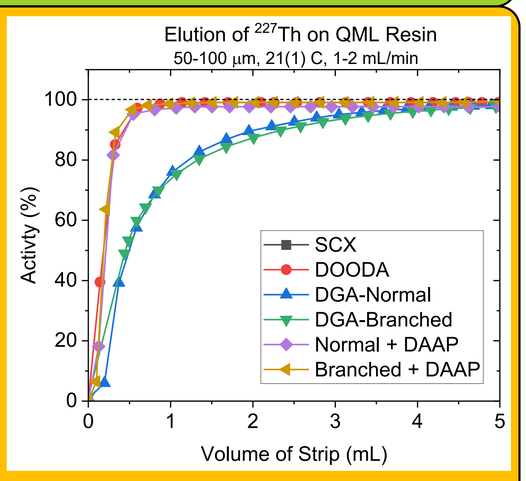


Gallium is one of the smallest +3 cations, resulting in a high z/r and ready hydrolysis. ^{68}Ga was one of the first PET emitters used in imaging, and is readily available in a regenerative supply thanks to $^{68}Ge/^{68}Ga$ generators.

The high ionic potential of ^{68}Ga allows for complete and efficient loading on SCX, DOODA, and DGA resin. Elution of Ga from SCX is ineffective in NH_4OAc solutions, even with NaCl present to increase ionic strength. The large DOODA extractant forms a relatively weak complex with the small Ga ion, allowing for complete elution in less than 2 mL. ^{68}Ga was successfully stripped off of DGA resins regardless of extractant impurities. The ^{68}Ga elution profile was improved with the addition of DAAP to DGA, however this is likely due more so to the 50% decrease in DGA extractant.

^{227}Th





Thorium is a +4 cation, and common parent isotope in nuclear medicine. ^{227}Th is being investigated as a direct TAT isotope which decays to ^{223}Ra, adding a fifth alpha emission and more chelator options for drug labeling.

The high z of ^{227}Th allows for complete loading on DGA, DOODA, and SCX, however, this makes stripping the ion from SCX nearly impossible. Complete stripping from DOODA was achieved, but stripping from DGA resulted in a slow bleed-off of the isotope. Adding DAAP to mask DGA impurities from resulted in much cleaner recovery in 1 M NH_4OAc pH = 6.

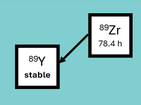
Conclusions

- **SCX** elution controlled by ionic potential, ionic strength, and hydrolysis reactions
- **DGA** elution dictated by DGA-complex strength and cation-exchange impurities
- Adding **DAAP** to **DGA** will mask ion exchange sites allowing for the elution of smaller metal ions
- **DOODA** is a large, relatively weak extractant allowing for easy stripping of metal ions

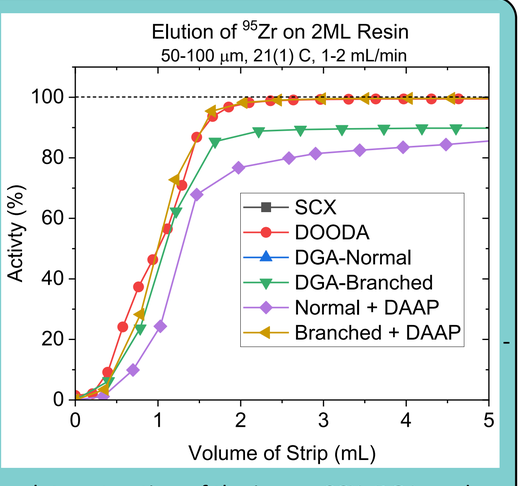
95% isotope recovery in 1 M NH_4OAc pH=6 (mL)

	SCX	DOODA	DGA (N/B)	DGA + DAAP (N/B)
^{225}Ac	0.59	0.81		
^{223}Ra	0.79			
^{227}Th		0.59	3.32 / 3.94	0.55 / 0.53
^{68}Ga		1.97	2.24 / 2.41	1.52 / 0.94
$^{86/90}Y$	0.43			0.49 / 0.81
^{89}Zr		1.86		5.00+ / 1.65
$^{44/47}Sc$		1.00		0.91 / 0.73

^{89}Zr



Zirconium is challenging to maintain as +4 in solution without a strong complexant due to its high ionic potential and ready hydrolysis. ^{89}Zr is a PET emitter with a longer half life than ^{18}F or ^{68}Ga, allowing for imaging of slower clearing vectors.



The high z/r of Zr allows for complete extraction of the ion on SCX, DGA, and DOODA. However, recovery of the small, highly charged metal ion is quite difficult. Zr could not be removed from SCX even with the addition of NaCl to increase solution ionic strength. Stripping of Zr from the DGA resins was ineffective due to interactions with extractant impurities. Adding DAAP to the DGA allowed for partial recovery of the Zr though it still remained strongly complexed with the DGA's. Zr was successfully recovered from a 2ML cartridge of DOODA resin using 1 M NH_4OAc pH=6.

References

Eddy, M. *et al.* Evaluation of an Extraction Chromatographic Resin Based on the DOODA Extractant: Characterization, Comparison to DGA, and Potential Applications. *Solvent Exr. Ion Exch.* **Accepted** (2024).

Sharma, S., Pandey, M. Radiometals in Imaging and Therapy: Highlighting Two Decades of Research. *Pharmaceuticals.* **16,** 1460 (2023).

Robertson, A. *et al.* Development of ^{225}Ac Radiopharmaceuticals: TRIUMF Perspectives and Experiences. *Current Radiopharmaceuticals.* **11,** 156 (2018).

Spang, P. *et al.* Bifunctional Gallium Chelators: Past, Present, and Future. *Seminars in Nuclear Medicine.* **46,** 373 (2016).

Saito, N. Selected Data on Ion Exchange Separations in Radioanalytical Chemistry. *Pure & Appl Chem.* **56,** 523 (1984).