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Development of functionalized resins for the purification of innovative radiopharmaceuticals

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NINTH INTERNATIONAL CONFERENCE ON RADIATION IN VARIOUS FIELDS OF RESEARCH

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Development of functionalized resins for the purification of innovative radiopharmaceuticals

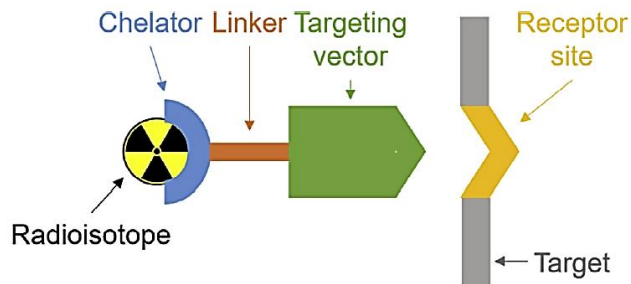
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- External-beam radiation therapy :
particle beam from an external source
Drawbacks : irradiation of healthy tissues,
treatment of localised disease only
- Targeted radionuclide therapy (TRT) :
coupling of the radionuclide with a
vector to target cancer cells



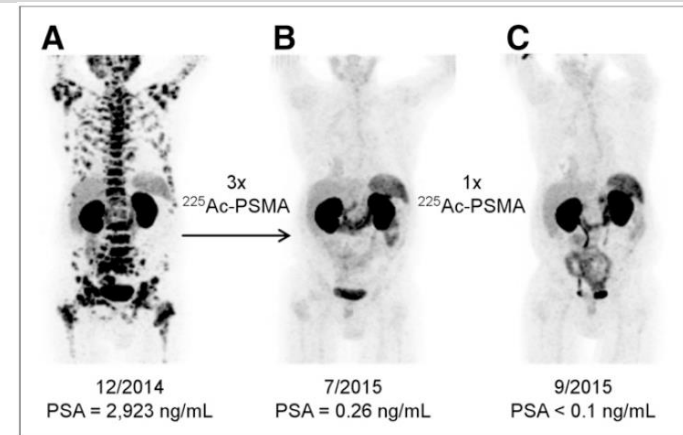
Schematic representation of a radiopharmaceutical

(Van de Voorde M. et al, *Coord. Chem. Rev.* 2019, 382, 103-125)

Radioactive decay types and their
corresponding applications in nuclear medicine

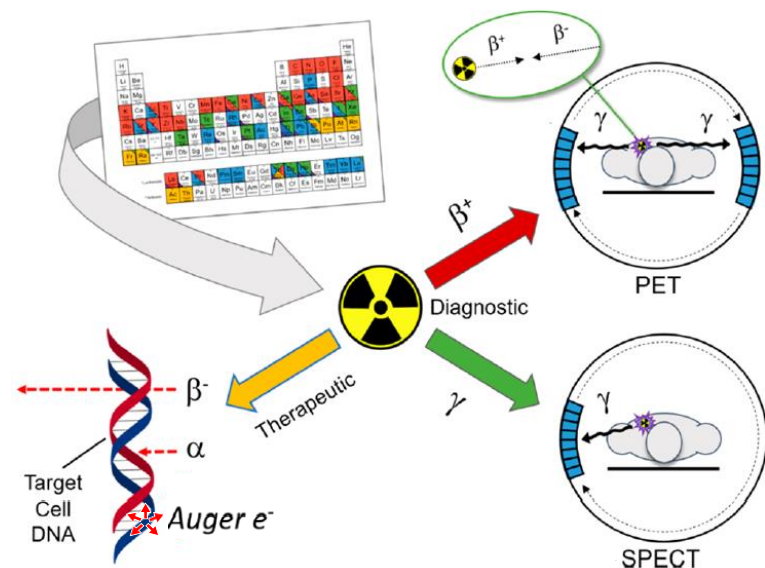
(Kostelnik T. I. et al, *Chem. Rev.* 2019, 119, 902-956)

Therapy + diagnostic = theranostic

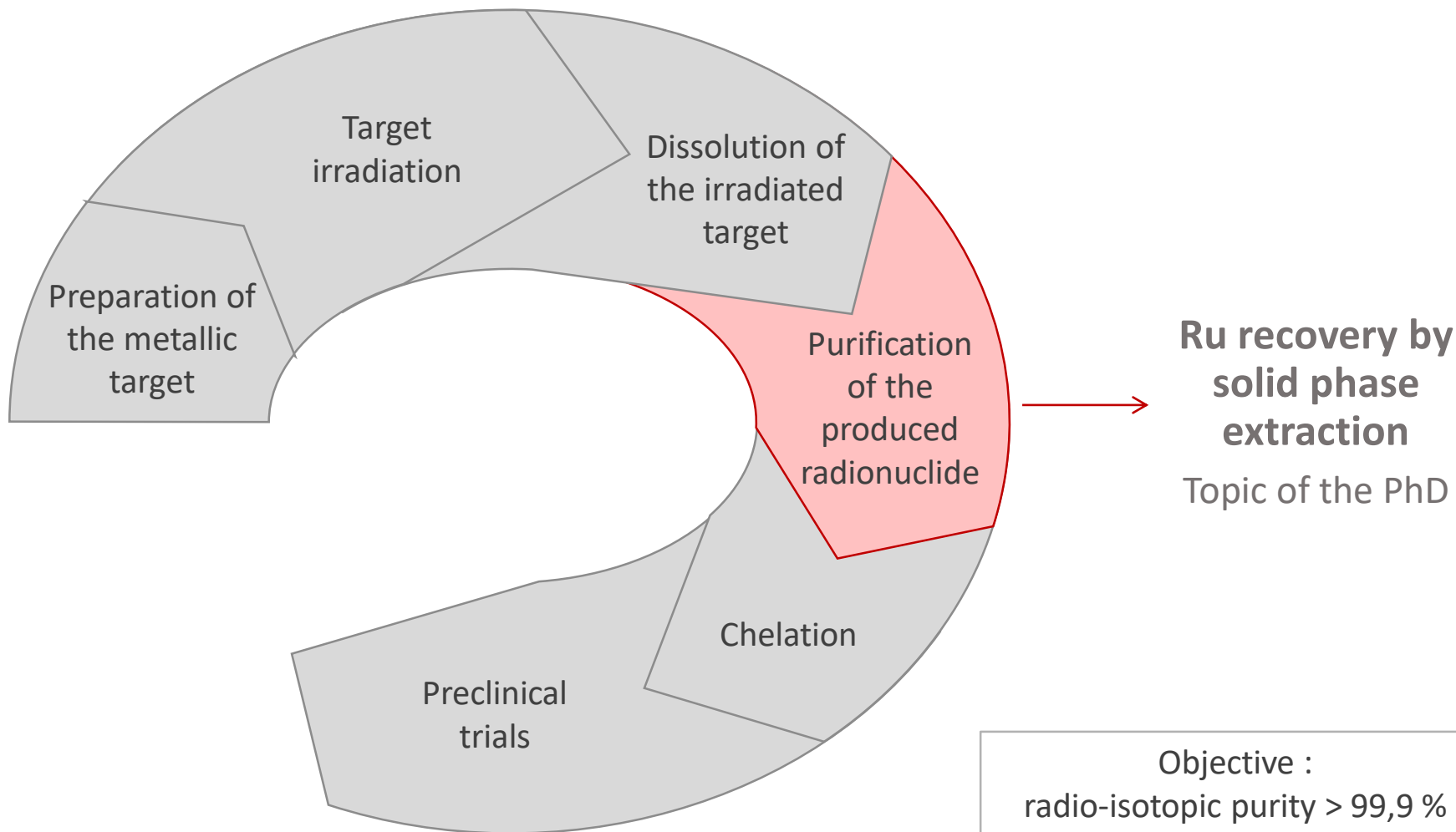


Prostate cancer treatment by TRT

(Kratochwil C. et al, *J. Nucl. Med.* 2016, 57, 1941-1944)



Selection of a ruthenium isotope for the development of a new radiopharmaceutical



Target irradiation



Target dissolution



Composition of the dissolution solution :

- Major impurity
- $[\text{RuNO}(\text{NO}_3)_x]^{3-x}$
- Mo, Rh...

Preliminary purification

Washing

Majority of the impurities

Elution

Extraction on Ru selective resin

Other impurities retention

Elution

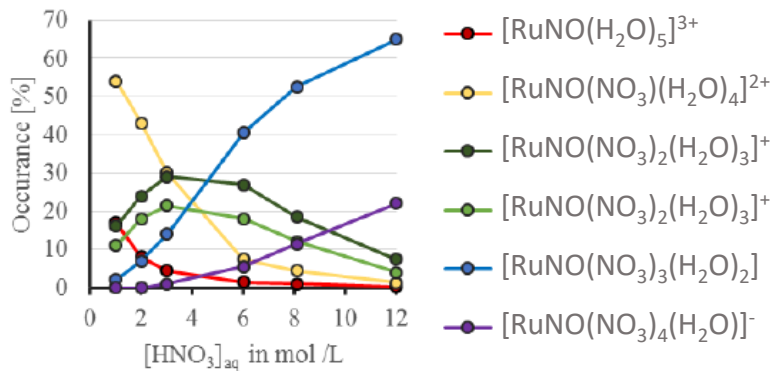
Purpose of the presentation

Purified Ru

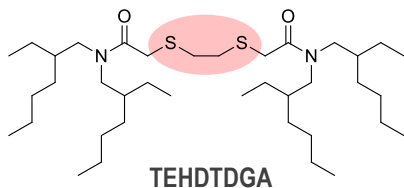
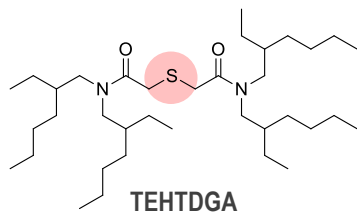
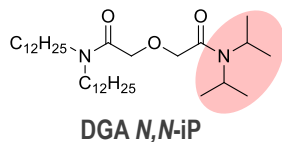
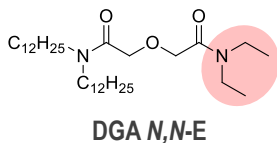
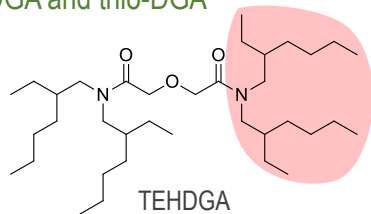
Chelation



Preclinical trials

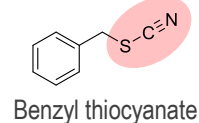
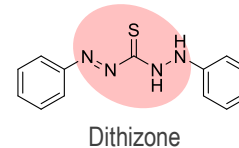
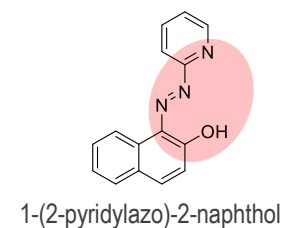
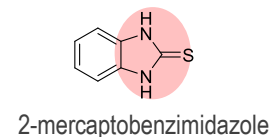
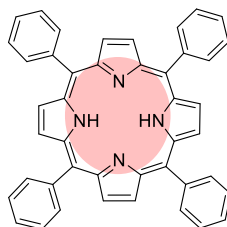
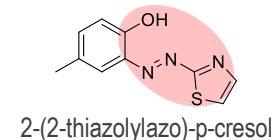
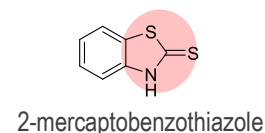
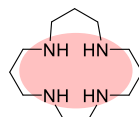
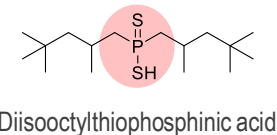
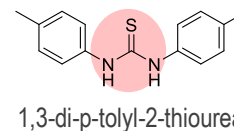
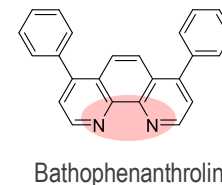
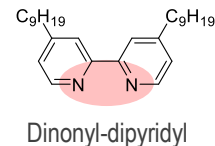
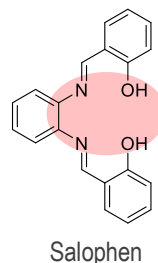
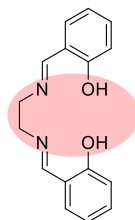
Very complicated Ru speciation, variable according to $[\text{HNO}_3]$ and time(Scargill D. et al, *J. Inorg. Nucl. Chem.* 1965, 27, 161-171)

DGA and thio-DGA



In bold : synthesised molecules

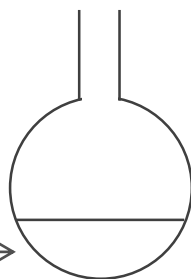
Other commercial molecules



(Swain P. et al, *J. Radioanal. Nucl. Chem.* 2013, 298, 781-796)

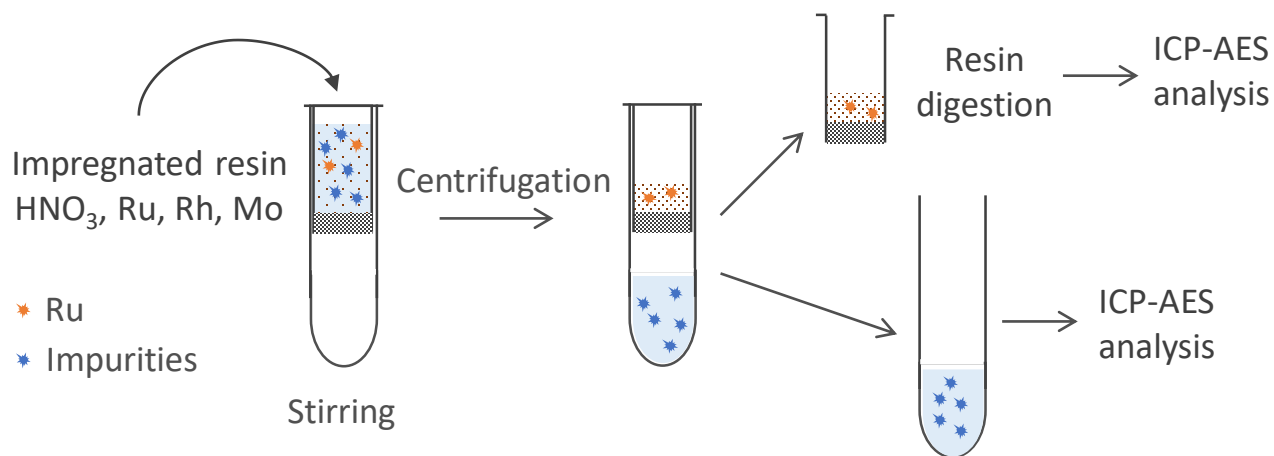
Resin functionalisation by impregnation

Polymeric support (Amberlite XAD4)
Organic molecule (1 mmol/g)
Solvent (ethanol, dichloromethane...)



1. Stirring few hours
2. Evaporation of the solvent
3. Drying of the impregnated resin

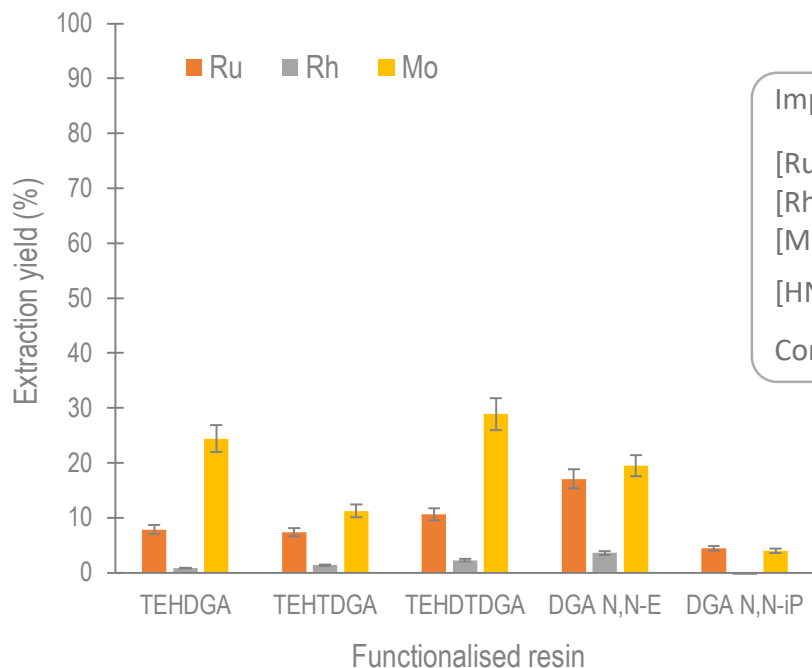
Batch extractions



Experimental conditions :

- $m_{\text{résin}} = 50 \text{ mg}$
- $[\text{HNO}_3] = 2 \text{ mol/L}$
- $[\text{Ru}] = [\text{Rh}] = [\text{Mo}] = 0,1 \text{ g/L}$
- $V = 700 \text{ }\mu\text{L}$

Batch extraction results of Ru, Rh and Mo on DGA derivatives impregnated on XAD4



Impregnation 1 mmol/g

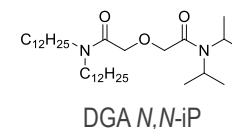
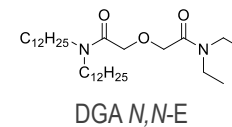
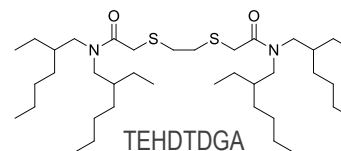
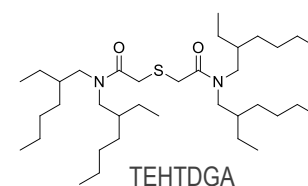
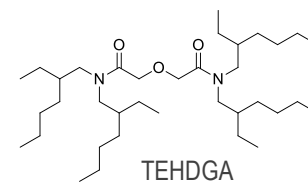
[Ru] = 0,01 g/L (0,1 mmol/L)

[Rh] = 0,01 g/L (0,1 mmol/L)

[Mo] = 0,01 g/L (0,1 mmol/L)

[HNO₃] = 2 mol/L

Contact 1 h, 25°C

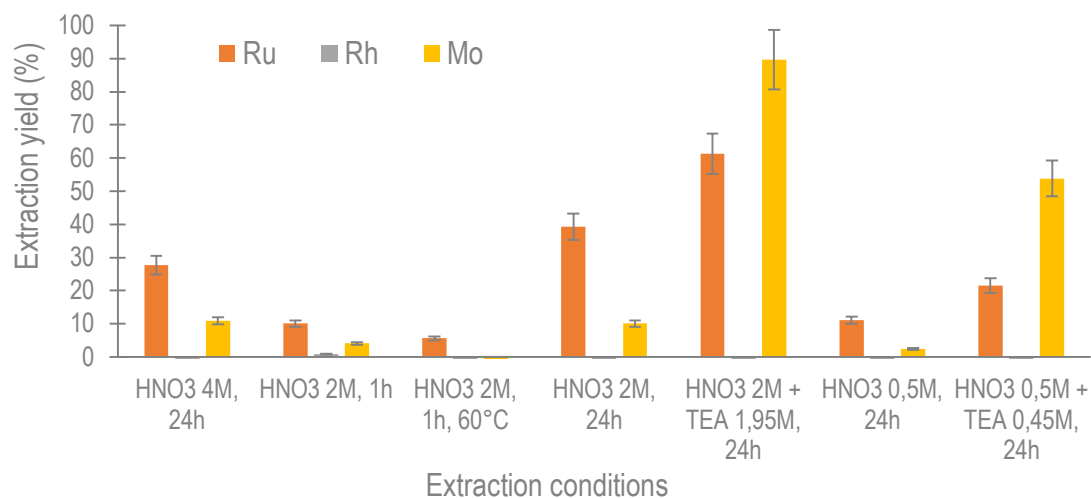


Overall, weak extraction of Ru, Rh and Mo. No selective extraction of Ru

Slight improvement of Ru extraction with sulphur atom (DGA < TDGA < DTDGA)

Asymmetric DGA : better extraction of Ru with N,N-E

Batch extraction results of Ru, Rh and Mo on salophen impregnated on XAD4

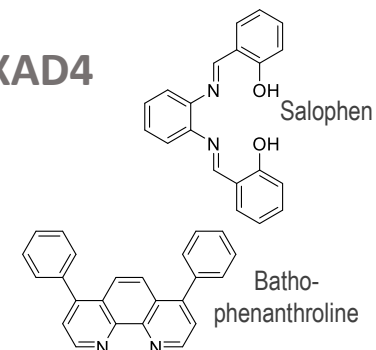


Impregnation 1 mmol/g

[Ru] = 0,01 g/L (0,1 mmol/L)

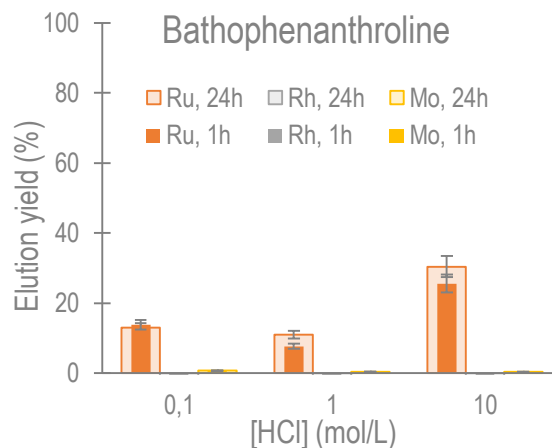
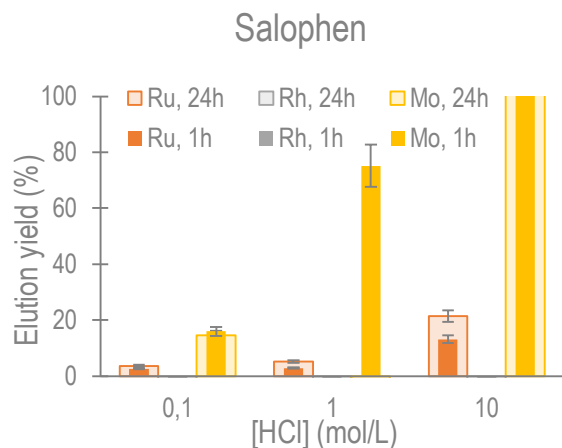
[Rh] = 0,01 g/L (0,1 mmol/L)

[Mo] = 0,01 g/L (0,1 mmol/L)



Best Ru extraction on salophen in HNO₃ 2M / TEA 1,95 M,

but best Ru selectivity in HNO₃ 2M (24h, 25°C)

Batch elution results (after extraction in HNO₃ 2 M, 24h)

Salophen :

- Low elution of Ru in chloride media
- Strong elution of Mo for [HCl] > 1 M
→ No selective elution of Ru in chloride media

Bathophenanthroline :

Not large Ru elution but selective in chloride media

After removal of the main impurities, Ru extraction was performed on a polymeric support impregnated with various motifs :

- Diglycolamide (DGA) molecules and thio-substituted analogues
 - Poor extraction of Ru
 - No selectivity regarding one of the remaining impurities (Mo)
- Commercial Ru selective molecules
 - Good Ru extraction and selectivity for **salophen** but no selective elution in HCl media
 - Satisfactory but unselective Ru extraction by **bathophenanthroline**, however selective Ru recovery with a concentrated HCl elution

Prospects :

- Application of the extraction and elution process to continuous experiments on a column
- Process optimisation by column dimensioning and flow control
- Continuous experiments on the overall process



From research to industry

Thank you for your attention