Characterization of a Cu selective resin and its application to the production of Cu-64

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On-going diploma thesis C. Dirks, Uni Marburg

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Outline

- Why Copper?
- Batch Experiments
  - Selectivity
  - Interferences with Ni or Zn
  - Kinetics
- Column Experiments
  - Simulated Ni target
  - Irradiated Ni target
  - Column size
  - Decontamination factors
  - Conversion of Cu resin eluate via AIX
- Summary
- Outlook

Copper Radionuclides

Isotope	Half Life	Radiation	Source
^{60}Cu	20 min	β^+ (93%), EC (7%)	cyclotron
^{61}Cu	3.3 hours	β^+ (62%), EC (38%)	cyclotron
^{62}Cu	9.74 min	β^+ (98%), EC (2%)	generator/cyclotron
^{64}Cu	**12.7 hours**	**β^+(18%), EC (41%), β^- (37%)**	**reactor/cyclotron**
^{66}Cu	5.2 min	β^- (100%)	reactor/cyclotron
^{67}Cu	62 hours	β^- (100%)	reactor/cyclotron

Radiopharmaceutical application[1,2]

- Suitable half-life ($t_{1/2} = 12.7$ h)
- Multiple decay mode
- Well established coordination chemistry

- **PET imaging**
- **targeted therapy (→ Cu-67)**

Comparison of production routes of Cu-64[3,4]

Nuclear process	Optimum energy range (MeV)	Thick target yield (MBq/μAh)
^{64}Ni(*p*,*n*)^{64}Cu [a]	**12 → 8**	**304**
^{64}Ni(*d*,2*n*)^{64}Cu [a]	17 → 11	430
^{68}Zn(*p*,*αn*)^{64}Cu [a]	30 → 21[b]	116
^{66}Zn(*p*,2*pn*)^{64}Cu [a]	52 → 37	316
^{64}Zn(*d*,2*p*)^{64}Cu [a]	20 → 10	27.1
^{66}Zn(*d*,*α*)^{64}Cu [a]	13 → 5	13.8
^{nat}Zn(*d*,*x*)^{64}Cu	25 → 10[c]	57.0

a: Using highly enriched target material, low enrichment will lead to impurities;
b: Below threshold of ^{67}Cu impurity *via* the ^{68}Zn(p,2p)^{67}Cu reaction;
c: Below thresholds of ^{61}Cu and ^{67}Cu impurities *via* the ^{64}Zn(d,αn)^{61}Cu and ^{68}Zn(d,2pn)^{67}Cu reactions, respectively.

General procedure for batch experiments

Weight distribution ratios D_w

- Weigh approx. 50 mg of the new Cu resin in an 2 ml Eppendorf tube
- Add 400 µl of the acid (e.g. HCl pH 2)
- Close cap and shake for 30 minutes
- Add 1ml of the standard solution (e.g. 1 mL Multi-element solution)
- Close cap and shake for another 30 minutes
- Withdraw 1 ml of the supernatant, analyze (ICP-MS)

➢ All distribution factors were determined in triplicate

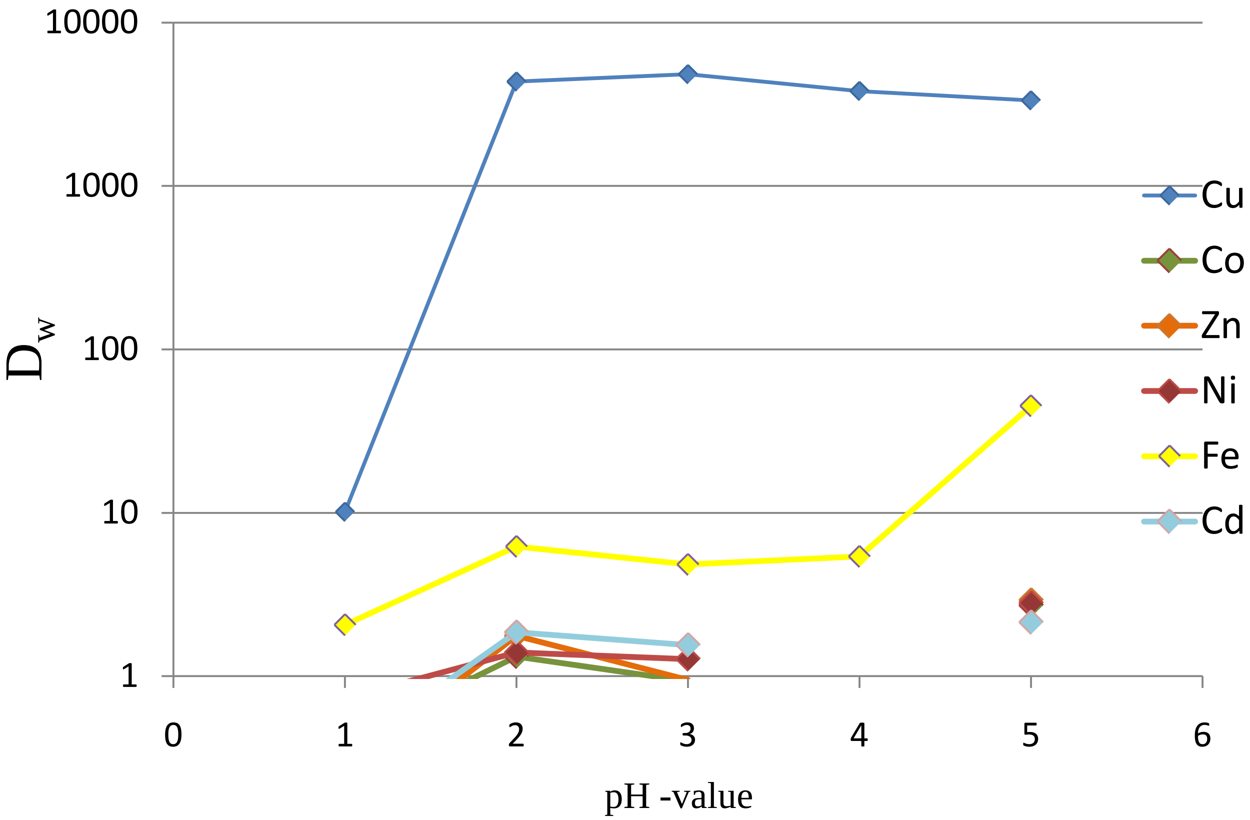
Weight distribution ratio

$$D_W = \frac{N_{A0} - N_A}{N_A} \times \frac{V}{m_R}$$

- **high D_w = Extraction**
- **low D_w = Elution**

N_{A0} = net count rate in the A_0 sample
N_A = net count rate in the sample
V = Volume of the aqueous phase (1.4 mL)
m_R = amount of the resin in g

D_w coefficients for multi 2 in HCl (each element with 10µg/ml)



Loading:

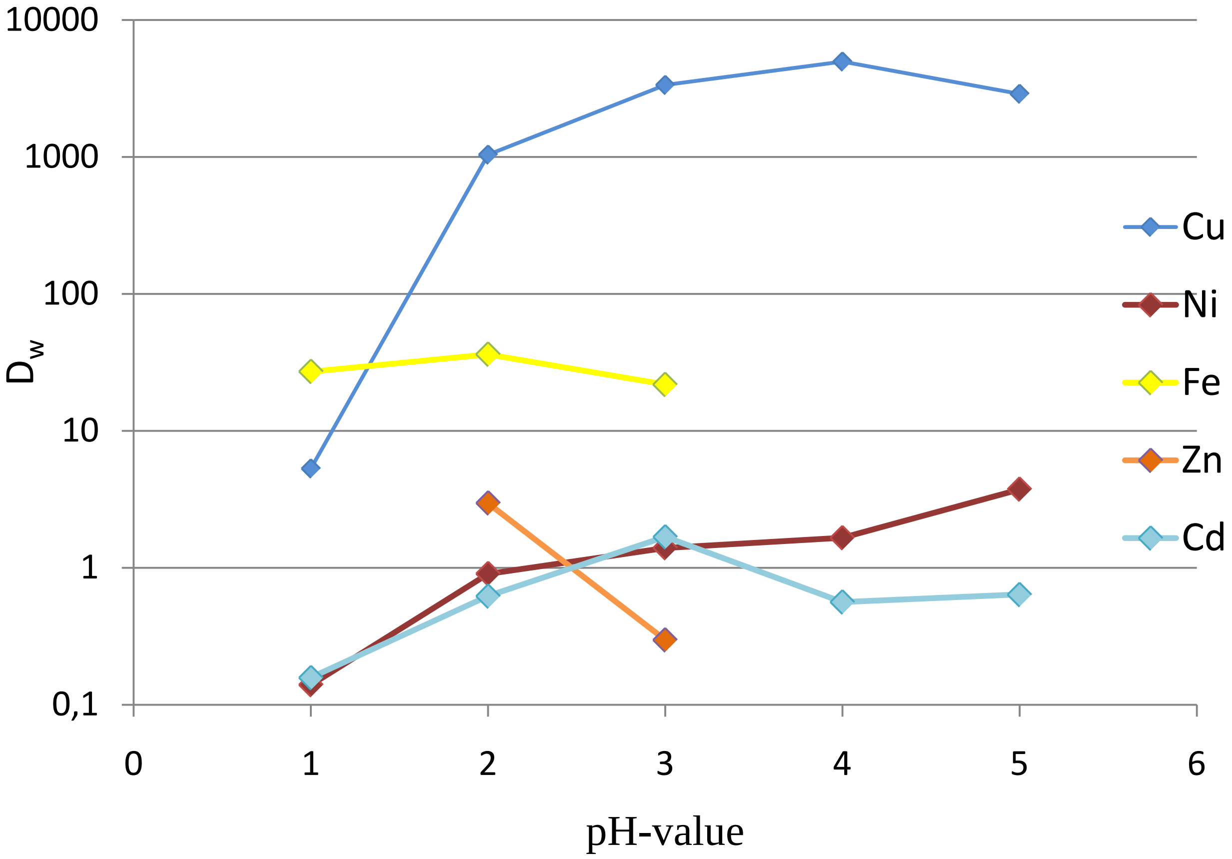
- Good selectivity for Cu
- No selectivity for other selected elements

Elution:

- Low D_w at low pH
- Tests with 4, 6 and 8 M HCl

Figure 1: D_w of Cu and selected elements on Cu resin in HCl in varying pH values

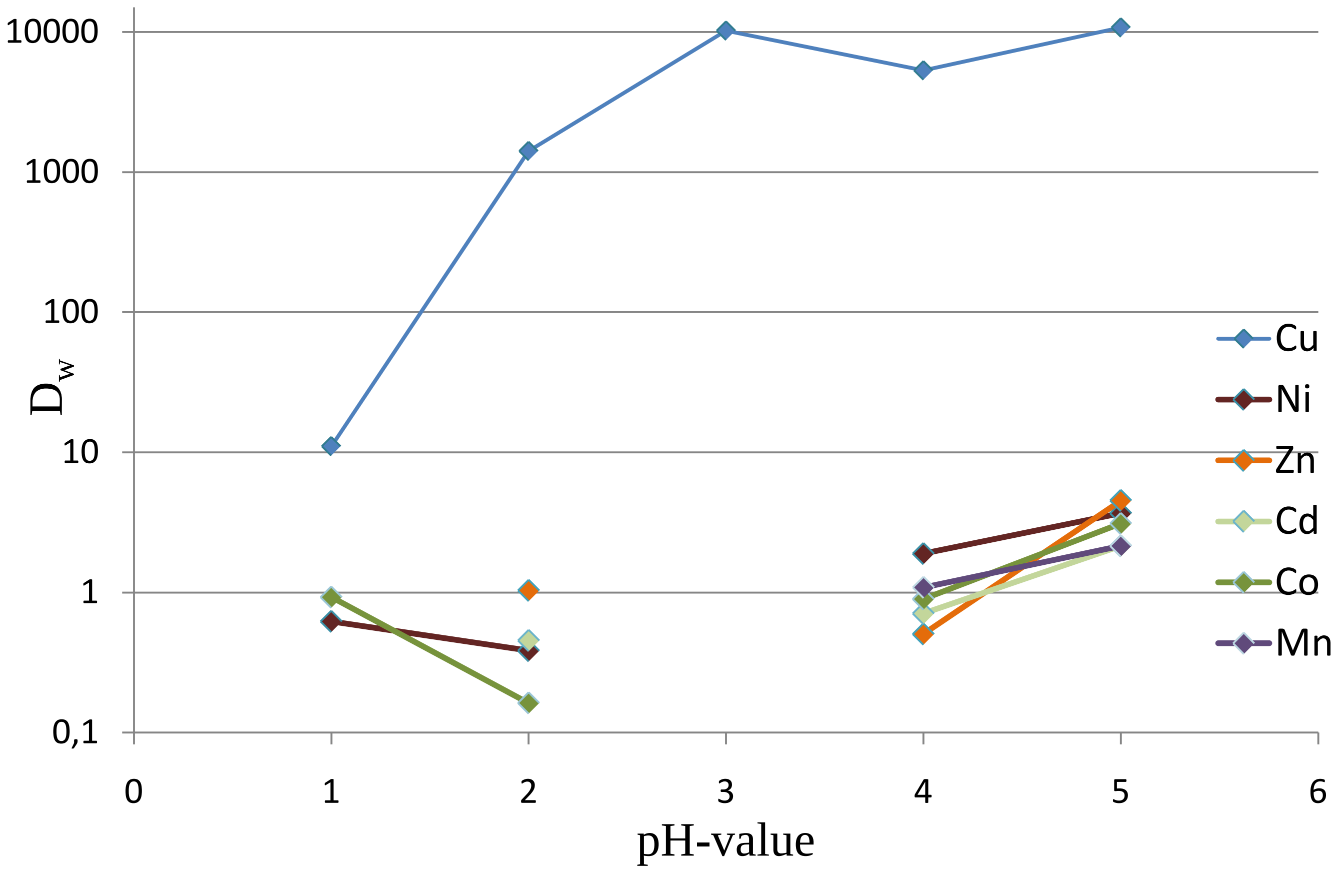
D_w coefficients for multi 3 in H_2SO_4 (each element with 10µg/ml)



- Cu: pH > 2 high D_w
- limited selectivity for iron

Figure 2: D_w of Cu and selected elements on Cu resin in H_2SO_4 in varying pH values

D_w coefficients for multi 1 in HNO_3 (each element with 10µg/ml)



- Cu: pH >2 high D_w
- overall good Cu capacity

Figure 1: D_w of Cu and selected elements on Cu resin in HNO_3 in varying pH values

Conclusions I

- Stable, high Cu D_w values at pH > 2
- High selectivity for Cu
- No selectivity for Zn or Ni
- Loading solution: HCl pH 2 (or higher)
- Elution with 6 or 8 M HCl

D_w Cu – interferences - HCl pH 2

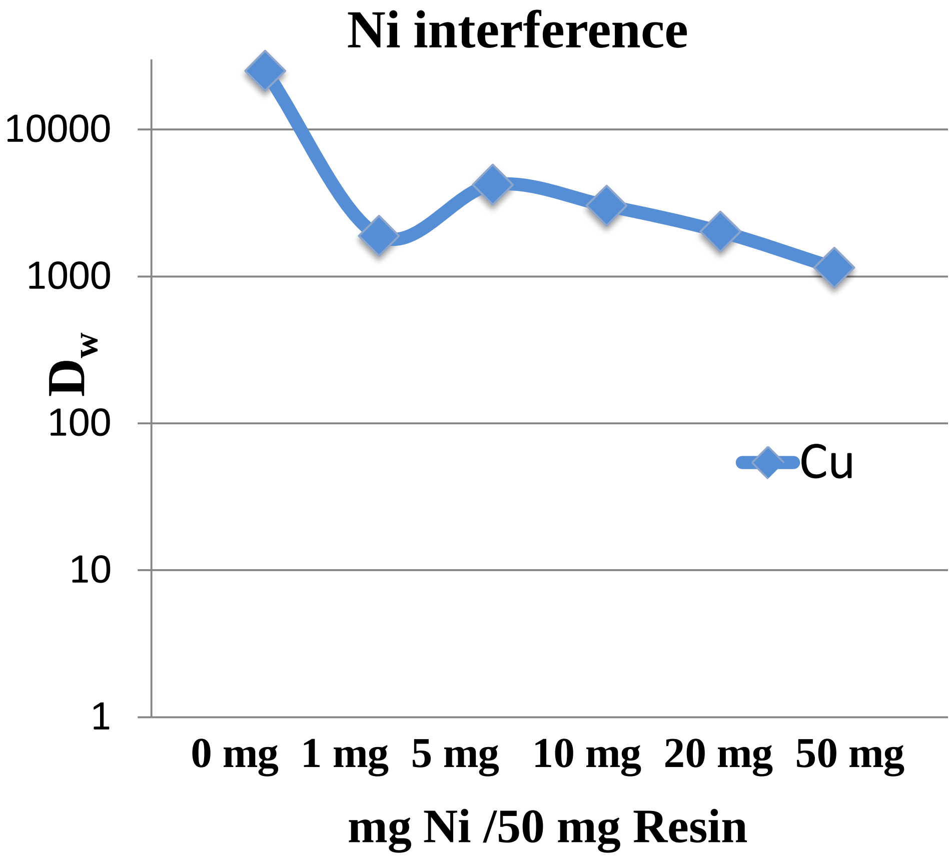


Figure 2: D_w of Cu on Cu resin in HCl, pH 2 in presence of various amounts of Ni

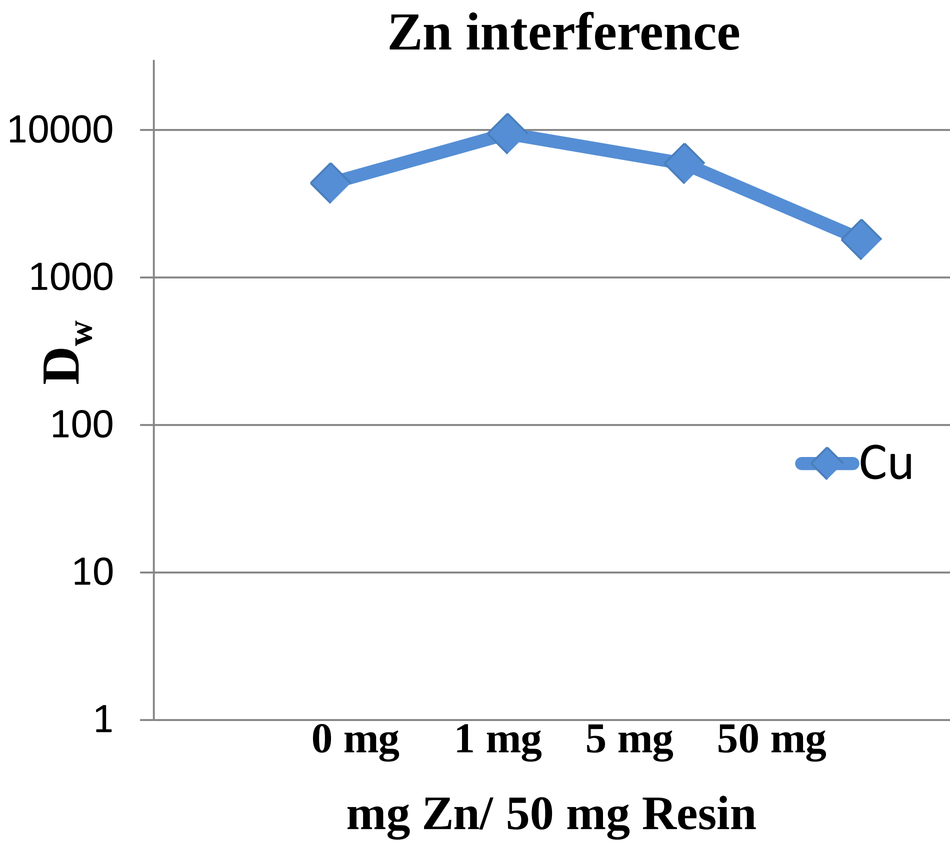


Figure 3: D_w of Cu on Cu resin in HCl, pH 2 in presence of various amounts of Zn

Interferences of Zn or Ni

- Even for high amounts of Ni or Zn D_w (Cu) > 1000 at HCl pH 2
- Up to 1 g target material pro g Resin

- **negligible interference!**

Kinetics of the Cu-resin

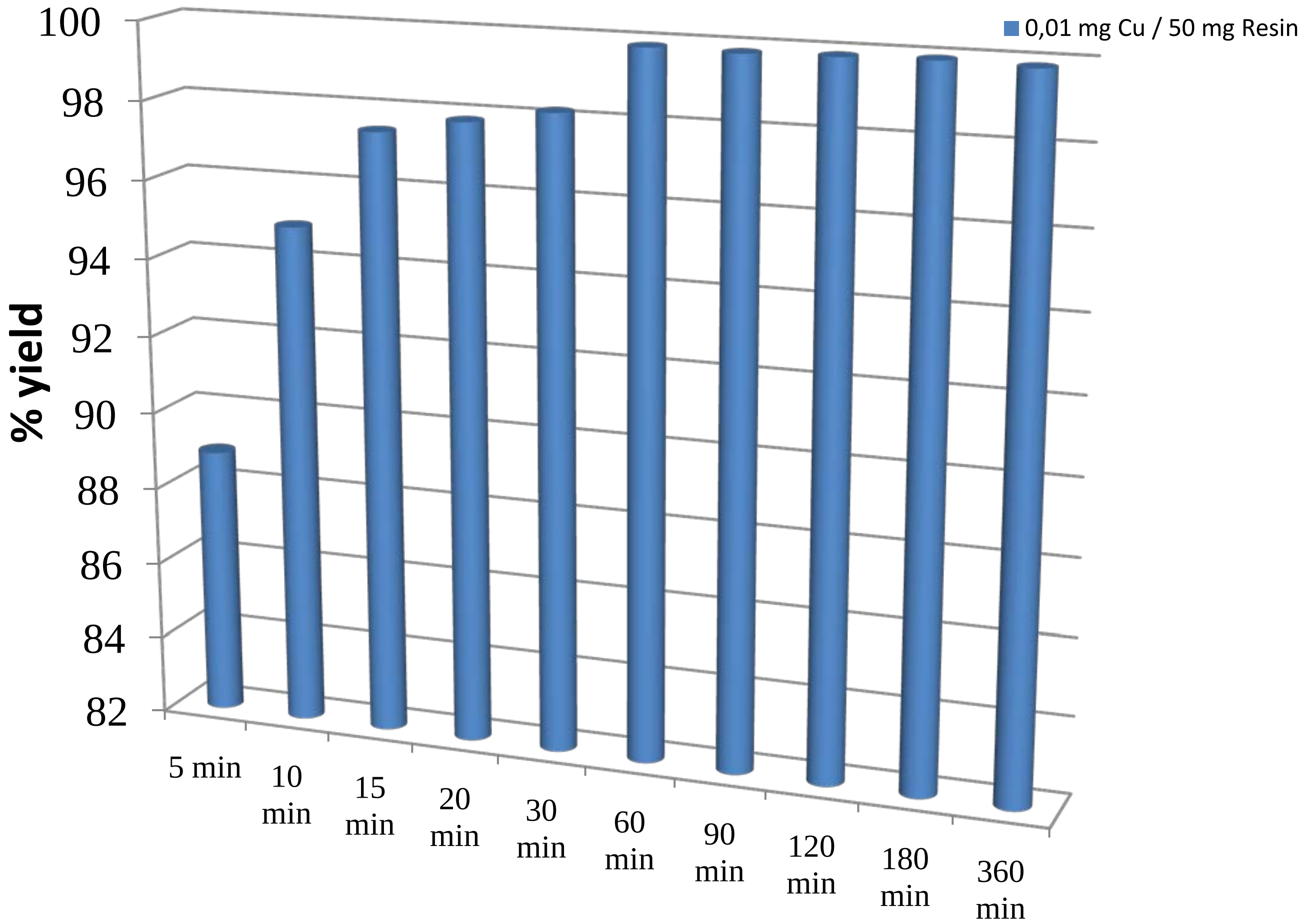
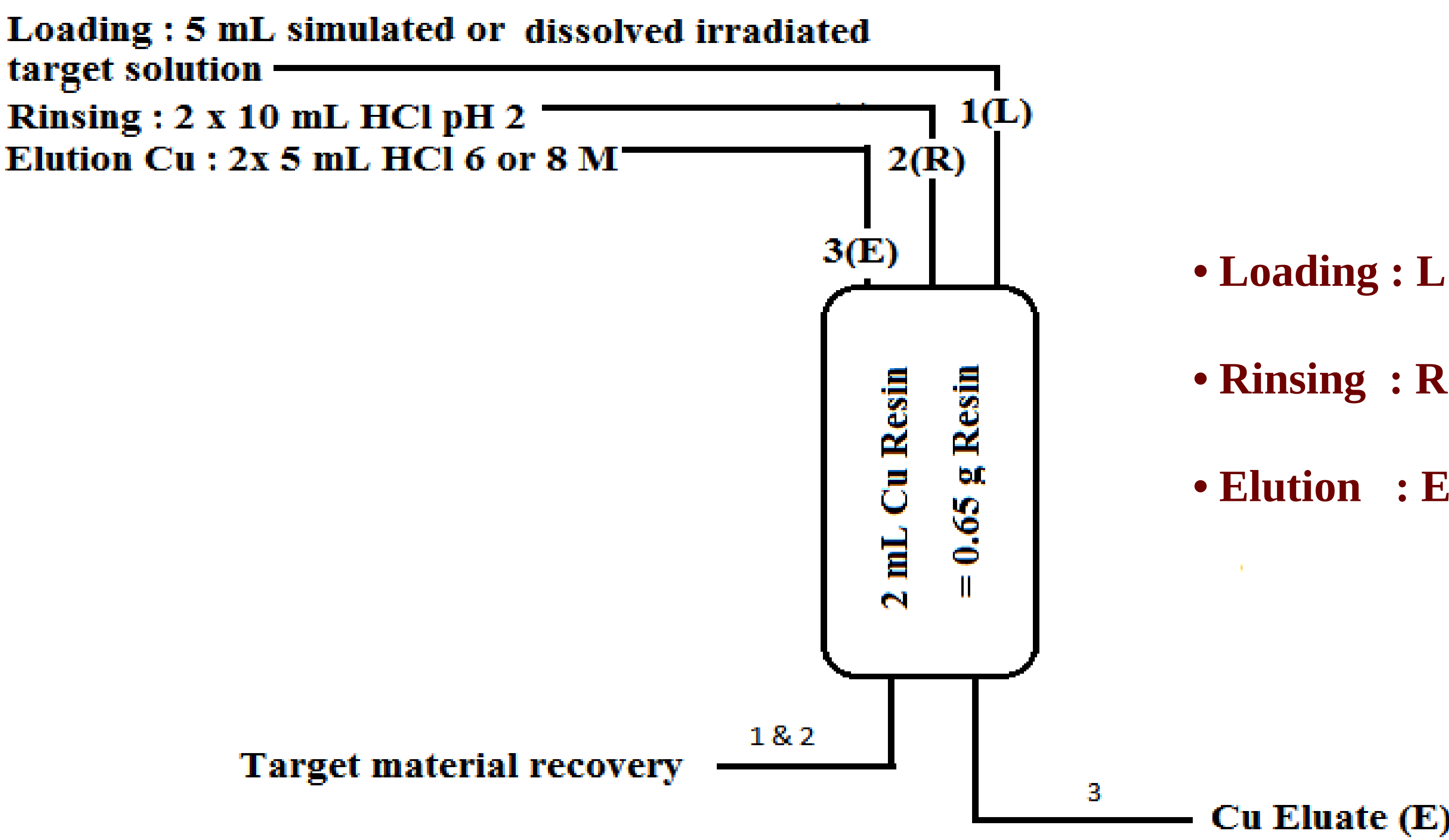


Figure 4: kinetics of Cu on Cu resin in HCl, pH 2

fast kinetic

- **5 min 89 %**
- **15 min 97 %**
- **60 min 99.8 %**

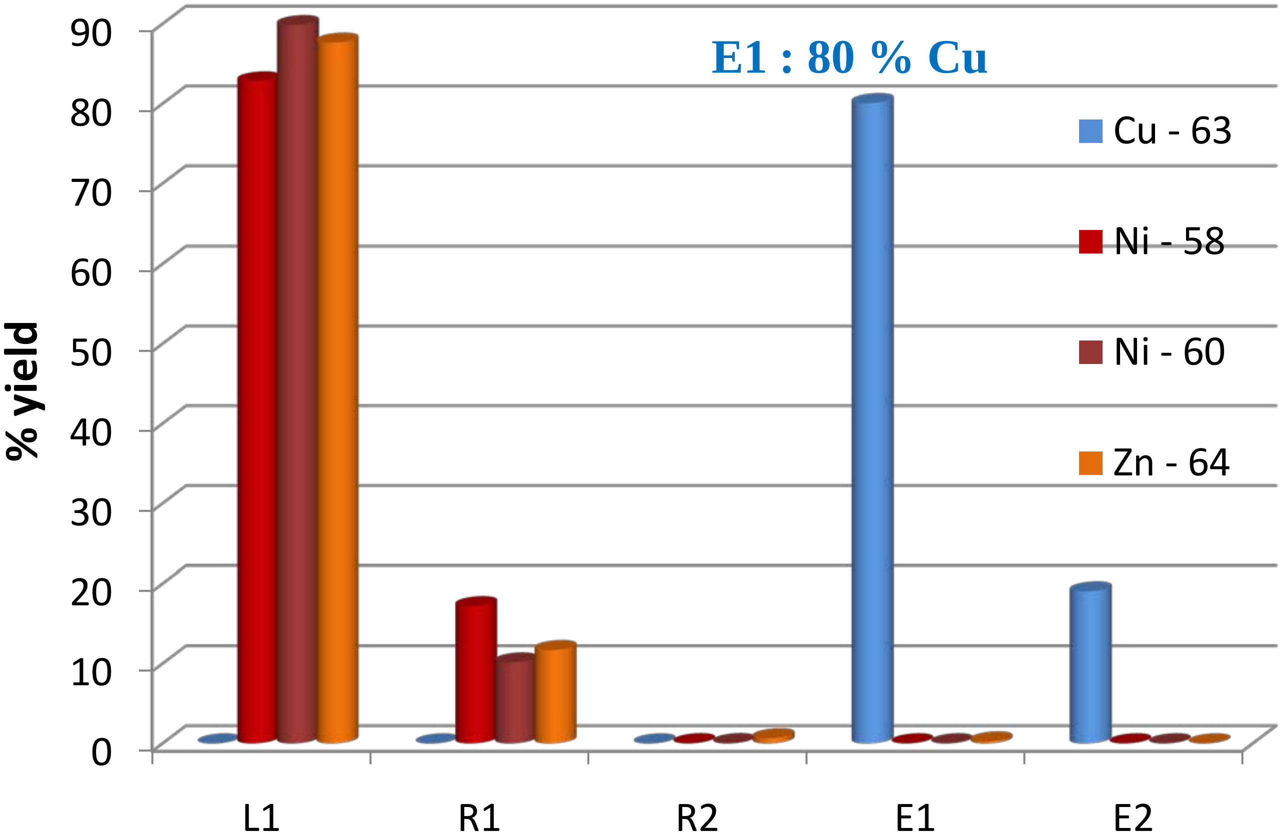
Elution method



- Loading : L1
- Rinsing : R1 & R2
- Elution : E1 & E2

Figure 5: Scheme of elution conditions of the elution study

Elution study - simulated Ni target



Loading:

L1 : 5 mL HCl pH 2

Rinsing:

R1 : 10 mL HCl pH 2

R2 : 10 mL HCl pH 2

Elution:

E1 : 5 mL HCl **6 M**

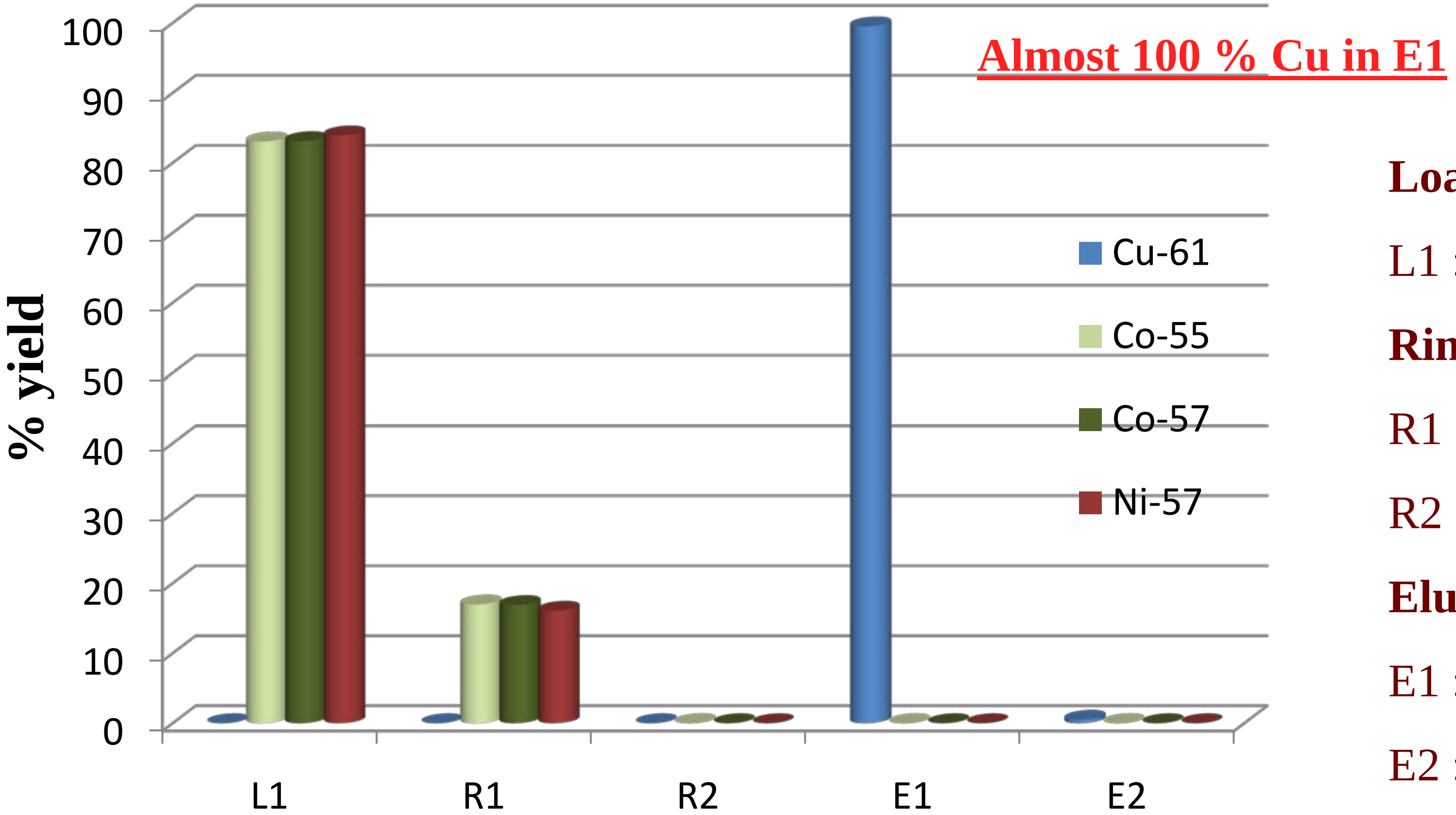
E2 : 5 mL HCl **6 M**

Figure 6: Elution profile obtained for simulated Ni target, 2 mL Cu resin column, elution conditions as described in figure 5

Elution study - irradiated Ni target

- Irradiation of a Ni foil (10 mg) :
  - (ø =13 mm, 0.025 mm thickness)
- Cyclotron BC1710 at Jülich
- E_p = 15 MeV
- 1 h; 0.5 μA
- Additionally 170 mg nonirradiated Ni-foil

Elution study – irradiated Ni target



Loading:

L1 : 5 mL HCl pH 2

Rinsing:

R1 : 10 mL HCl pH 2

R2 : 10 mL HCl pH 2

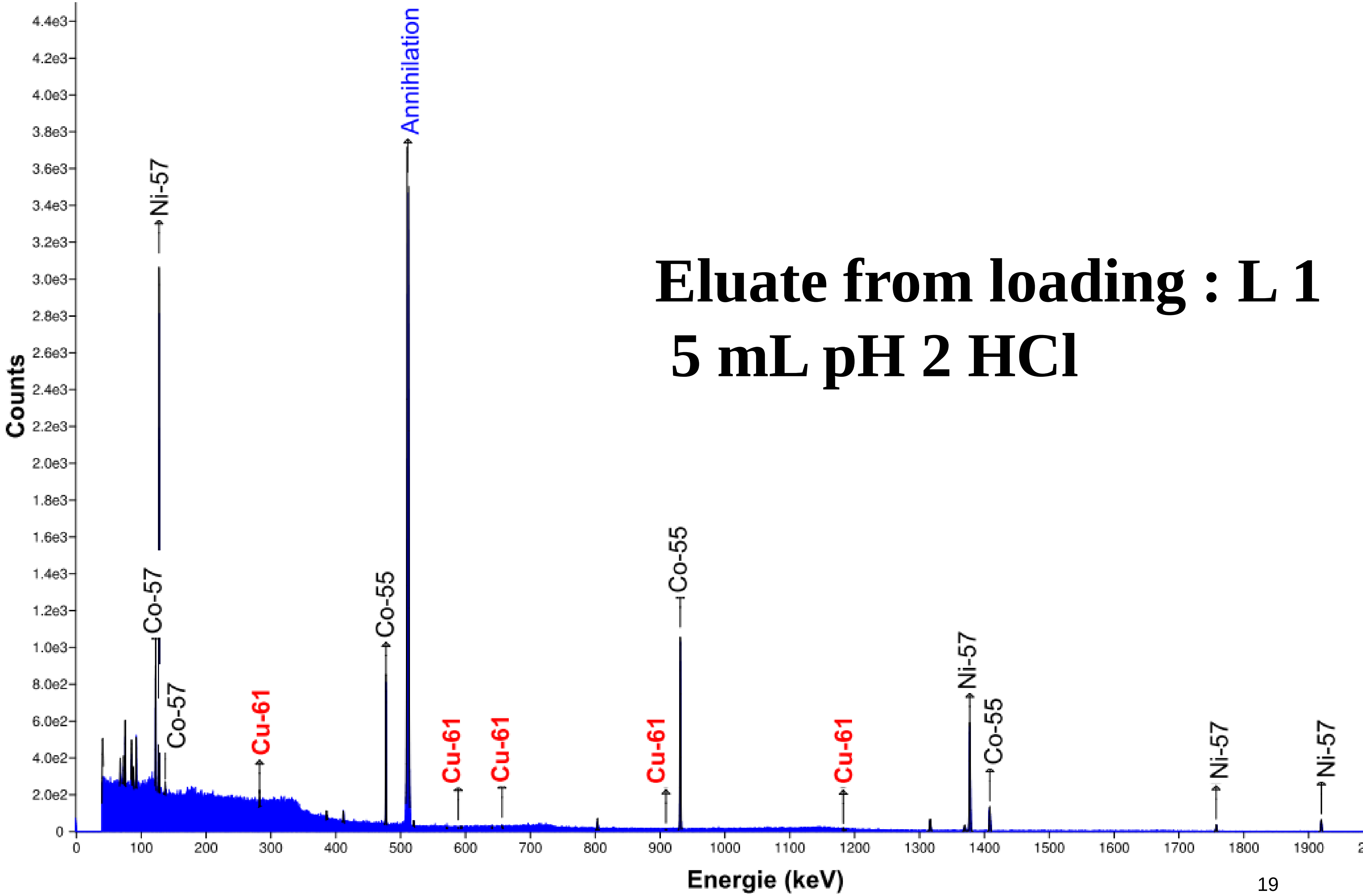
Elution:

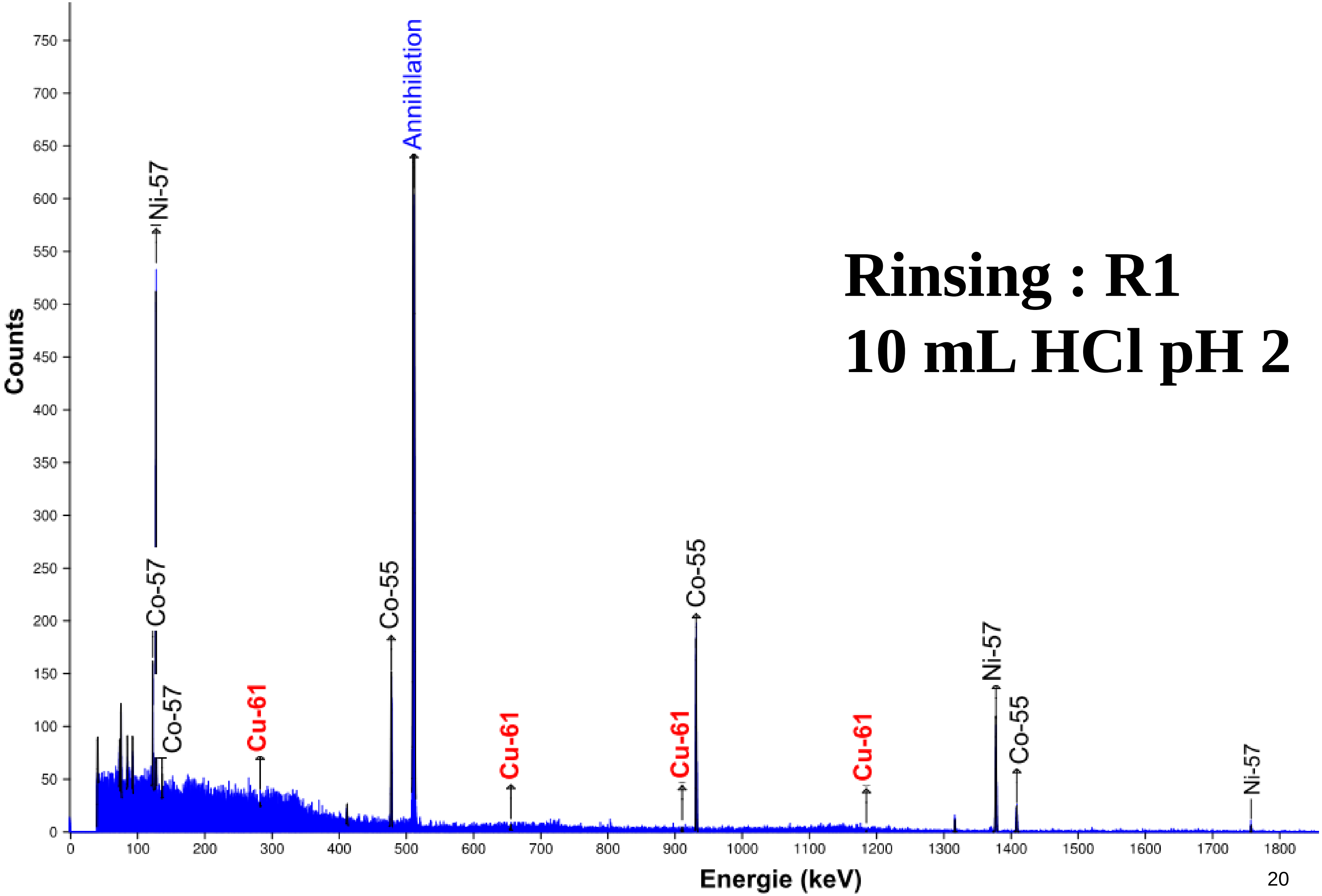
E1 : 5 mL HCl **8 M**

E2 : 5 mL HCl **8 M**

Figure 7 : Elution study: % yield of the elution study with an irradiated Ni target

Eluate from loading : L 1
5 mL pH 2 HCl

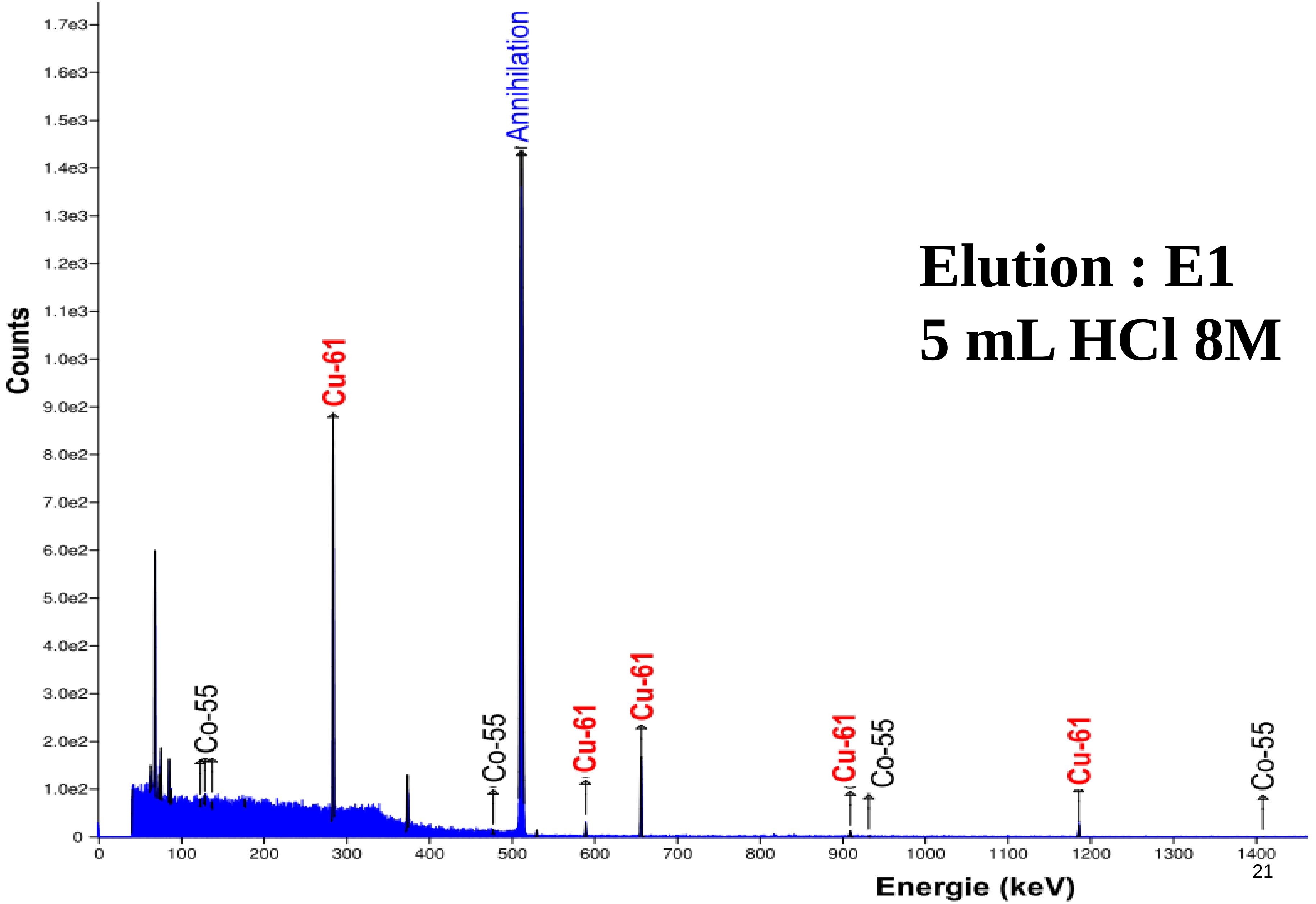




Rinsing : R1

10 mL HCl pH 2

Elution : E1
5 mL HCl 8M



Conclusions II

- ✓ High Cu selectivity
- ✓ Negligible interference of Ni or Zn
- ✓ Fast kinetics
- ✓ Quantative recovery of Cu in elution studies
- ✓ **Very good Cu separation**
- ✓ Ni could be recovered in a small volume of HCl pH 2
- ➢ Cu elution volume still rather large

Optimization of Cu elution volume

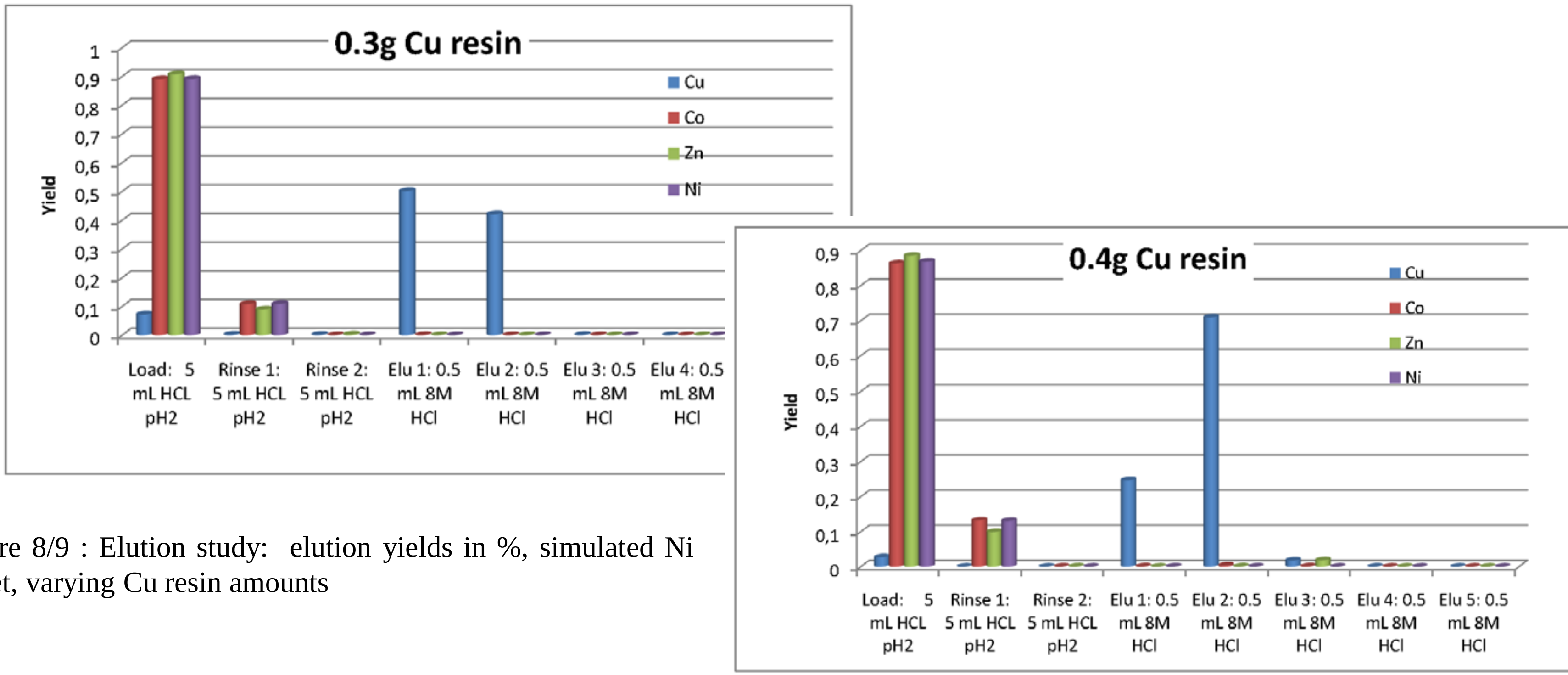
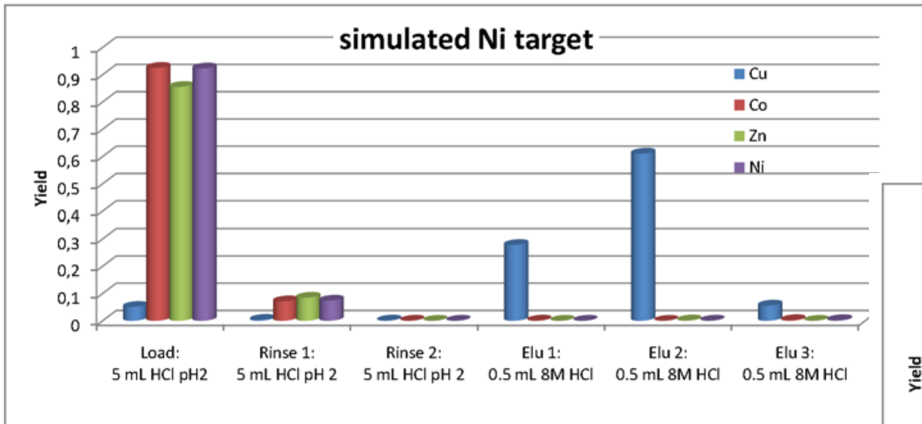


Figure 8/9 : Elution study: elution yields in %, simulated Ni target, varying Cu resin amounts

- Use of smaller columns allows reducing Cu elution volume
  - Quantitative Cu recovery in 1 mL 8M HCl
- No impact on purity

Optimization of Cu elution volume – vacuum-assisted flow



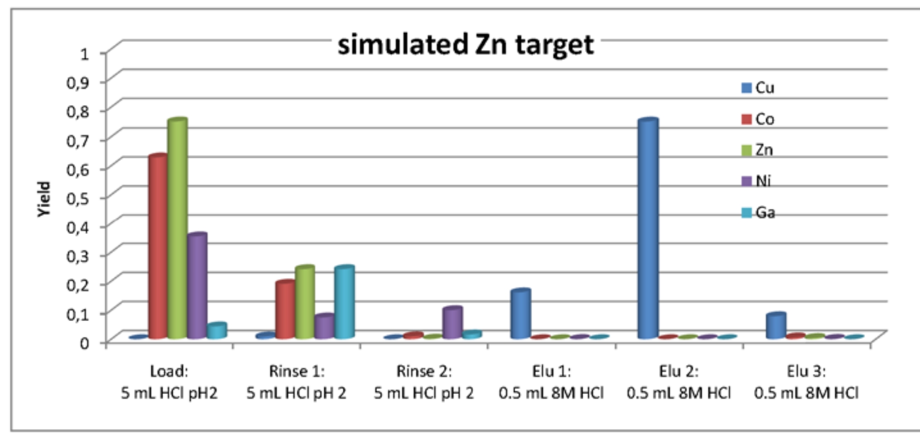


Figure 10/11 : Elution study: elution yields in %, simulated Ni and Zn target, 300 mg Cu resin

- Flow rate: 1 mL/min
- 0.3g columns
- Simulated Ni and Zn targets
- > 90% recovery in 1 mL 8M HCl, quantitative recovery in 1.5 mL
- No impact on purity

Decontamination factors D_f

- Flow rate: 1 mL/min
- 0.3g columns
- Loading solution: elevated amounts of Ni, Zn, Co, Ga and Au in 5 mL HCl pH 2
- Separation as described before
- ICP-MS measurement
- Calculation of deconfactors D_f for Cu fractions
  - Fraction E1 (0.5 mL 8M HCl):
    - D_f: Ni, Co & Zn > 20 000
    - D_f: Au & Ga > 10 000
  - Fraction E2 (0.5 mL 8M HCl):
    - D_f : Ni > 20 000, Co > 40 000, Zn > 70 000, Au > 50 000, Ga > 10 000

Conversion of Cu eluate

- Aim: recovery of Cu in small volume of dilute HCl, water or NaCl solution
- Anion exchange resins (AIX) shows necessary selectivity
- Cu eluate (1mL 8M HCl) from 300 mg Cu resin column directly loaded onto small AIX column
- Rinse with 1 mL 8M HCl
- Elution with 2 x 1 mL H_2O

Conversion of Cu eluate via AIX

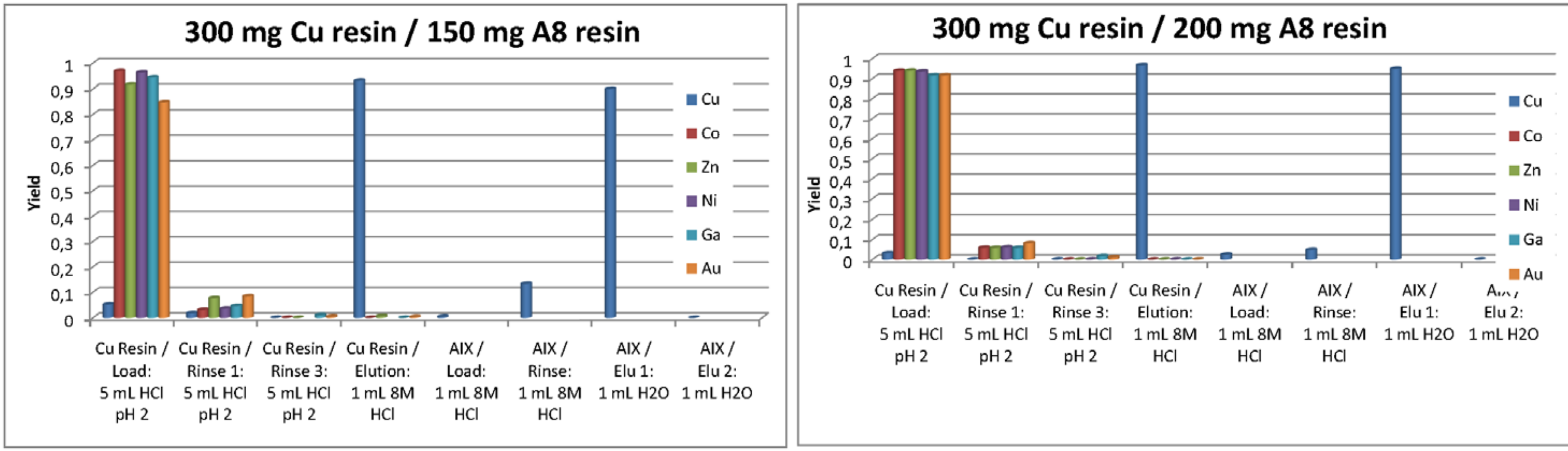
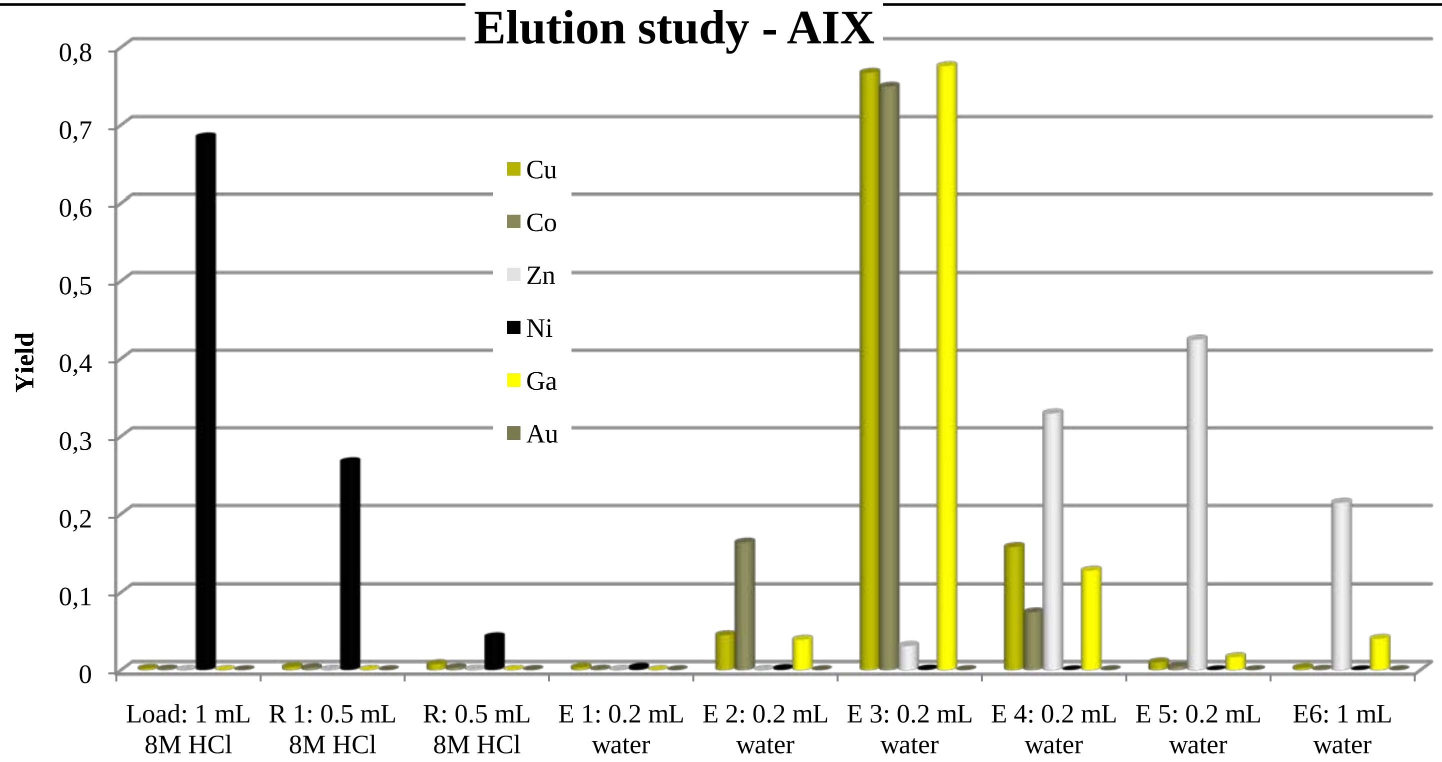


Figure 12/13 : Elution study: elution yields in %, simulated Ni target, 300 mg Cu resin, varying amounts of AIX resin

- Quantitative load of Cu on AIX from 8M HCl , Cu elution in 1 mL H_2O
  - Conversion works well
- 150 mg AIX column shows Cu breaktrough in rinsing step
  - Use of 200 mg AIX columns or more advisable
- Next steps:
  - Smaller elution values possible?
  - Additional purification by AIX step?

Elution study - AIX



- 400 mg AIX
- Cu elution in 0.6 – 0.8 mL water
- Anion echange conversion step gives additional decontamination from Ni, Zn, Au

Optimized method

- Vacuum-assisted flow (1 – 3 mL/min)
- Cu resin (300 mg)
  - Load from 1 - 2 mL HCl pH2
  - Rinse with 5 mL and 3 mL HCl pH 2
  - Load and rinse contain ~100% Ni (important for Ni-64 recovery)
  - Cu elution in 1 – 1.5 mL 8M HCl
- Conversion on AIX
  - Load from 1 – 1.5 mL 8M HCl
  - Rinse with 2 x 0.5 mL 8M HCl
  - Cu elution in 0.6 – 0.8 mL water (or saline solution)
- Cu yield > 95%, high decontamination factors
- Separation time: 18 minutes

Short view to the future

- Cu-DOTA labeling
- Organic impurities content of the Cu fraction
- Recovery of Ni for target preparation
- Optimisation of flowrates
- Ni-64 and/or Zn target irradiation
- Analytical application (concentration and purification of Cu for ICP-MS)

Literature

[1] Qaim, S. M.: Decay data and production yields of some nonstandard positron emitters used in PET. Q. J. Nucl. Med. Mol. Imaging 52, 111–120 (2008).

[2] Smith, Suzanne: Molecular imaging with copper-64. J. of inorganic Biochemistry 98, 1874-1901 (2004)

[3] Aslam, M.N., Sudár, S., Hussain, M., Malik, A.A., Shah, H.A. and Qaim, S.M.: Charged particle induced reaction cross section data for production of the emerging medically important positron emitter 64Cu: A comprehensive evaluation. Radiochim. Acta 97, 669–686 (2009)

[4] Szelecsényi, F., Blessing, G., Qaim, S.M.: Excitation functions of proton induced nuclear reactions on enriched 61Ni and 64Ni: Possibility of production of no-carrier-added 61Cu and 64Cu at a small cyclotron. Appl. Radiat. Isot. 44, 575–580 (1993).

[5] Horwitz, E.P., McAlister, D.R., Bond, A.H., Barrans, R.E. and Williamson, J.M.: A process for the separation of 177Lu from neutron irradiated 176Yb targets. Appl. Radiat. Isot. 63(1), 23-36 (2005)

[6] Dirks, C., Scholten, B., Happel, S., Zulauf, A., Bombard, A., Jungclas, H.: Characterisation of a Cu selective resin and its application to the production of Cu-64 J. Radioanal Nucl. Chem. in press