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DOI
10.1016/j.apradiso.2020.109135

Publication date
2020

Document Version
Final published version

Published in
Applied Radiation and Isotopes

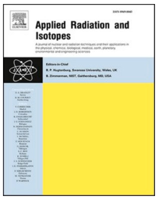
Citation (APA)
Moret, J. L. T. M., Hardens, T. A., van Batenburg, O., Wolterbeek, H. T., van Ommen, J. R., & Denkova, A. G. (2020). ^{64}Cu enrichment using the Szilard-Chalmers effect – The influence of γ-dose. *Applied Radiation and Isotopes*, *160*, Article 109135. https://doi.org/10.1016/j.apradiso.2020.109135

Applied Radiation and Isotopes 160 (2020) 109135

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: http://www.elsevier.com/locate/apradiso



^{64}Cu enrichment using the Szilard-Chalmers effect – The influence of γ-dose

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ARTICLE INFO

Keywords:
^{64}Cu
Szilard-Chalmers reaction
Cu-phthalocyanine
Gamma dose influence
High specific activity

ABSTRACT

Cu is an important trace metal which plays a role in many biological processes. The radioisotope ^{64}Cu is often used to study such processes. Furthermore, ^{64}Cu finds applications in cancer diagnostics as well as therapy. For all of these applications ^{64}Cu having high specific activity is needed. ^{64}Cu can be produced in cyclotrons or in nuclear reactors. In this paper we study the effect of gamma dose on the production of ^{64}Cu according to the Szilard-Chalmers reaction using Cu(II)-phthalocyanine as a target. For this purpose, irradiations were performed in the nuclear reactor of the Delft University of Technology using a novel irradiation facility helping to limit the dose produced by gammas present in the reactor pool. The obtained ^{64}Cu activity yield was in general above 60% in accordance to the theoretical expected value. An increase in gamma dose has no significant influence on the obtained activity yield but increases the loss of Cu from Cu(II)-phthalocyanine up to 0.9% and hence decreases the specific activity that can be obtained. However, without optimisation, when reducing the gamma dose specific activities in the order of 30 TBq/g can be achieved.

1. Introduction

Cu is a trace element important in numerous biological processes like neurotransmitter synthesis and iron metabolism (Kim et al., 2014), but it is also involved in tumour angiogenesis and neurodegenerative diseases (Laura et al., 2013). ^{64}Cu is an radioactive isotope of Cu with a half-life of 12.7 h, decaying either by electron capture (44%) and β^+ (17.5%) to stable ^{64}Ni or by β^- (38.5%) to stable ^{64}Zn (Laboratory, 2000). Because of these decay characteristics ^{64}Cu can be used in imaging i.e. in positron emission tomography (PET) and/or in radionuclide therapy (Chakravarty et al., 2016; Laura et al., 2013). For these applications a specific activity of at least 1 TBq/g is needed (Kim et al., 2014).

^{64}Cu can either be produced by proton activation in a cyclotron or by neutron activation in a nuclear reactor. In proton activation nickel targets are bombarded with a beam of 15.5 MeV protons (McCarthy et al., 1997), allowing for the ^{64}Ni(p,n)^{64}Cu reaction to take place. After irradiation ^{64}Cu has to be separated from the Ni target. The advantage of this method is that non-carrier added ^{64}Cu is produced. However, special targets and cooling are needed (Le et al., 2009). In neutron activation either Zn or Cu targets can be used. The ^{64}Zn(n,p)^{64}Cu reaction needs fast neutrons to take place, which are available in irradiation facilities situated in the core of nuclear reactors (McCarthy et al., 1997). In those facilities often only small volumes can be irradiated, making this production less likely to meet regular clinical demands (Chakravarty et al., 2016). Furthermore, long lived ^{65}Zn is co-produced as waste. For the ^{63}Cu(n,γ)^{64}Cu reaction thermal neutrons are needed. Although many reactors exist where this production route can be implemented, the specific activity of the produced ^{64}Cu is low. Using enriched targets and high flux reactors leads to higher specific activity, but increases costs. Moreover, as natural Cu contains 69.18% ^{63}Cu (Laboratory, 2000), using enriched targets only allows for a factor of maximum 1.5 increase in SA.

The problem of low specific activity ^{64}Cu can be overcome by utilising the recoil effect that occurs during (n,γ) reactions. In 1934 L. Szilard and T.A. Chalmers (Szilard and Chalmers, 1934a, b) already showed that enriched ^{125}I can be produced using natural targets and chemical effects due to nuclear transformations. During neutron activation the energy of the excited state is distributed between the emitted prompt gamma and the newly formed product nucleus. (Fig. 1). The recoil energy of the product nucleus can be calculated using the following equation: $E_r = 537\frac{\overline{E}_\gamma^2}{M_r}$, in which E_r is the recoil energy of the product nucleus in eV, $\overline{E}_\gamma$ the average energy of the prompt gamma in MeV and M_r the mass of the recoiling atom in u. If the recoil energy is

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https://doi.org/10.1016/j.apradiso.2020.109135
Received 9 December 2019; Received in revised form 4 March 2020; Accepted 17 March 2020

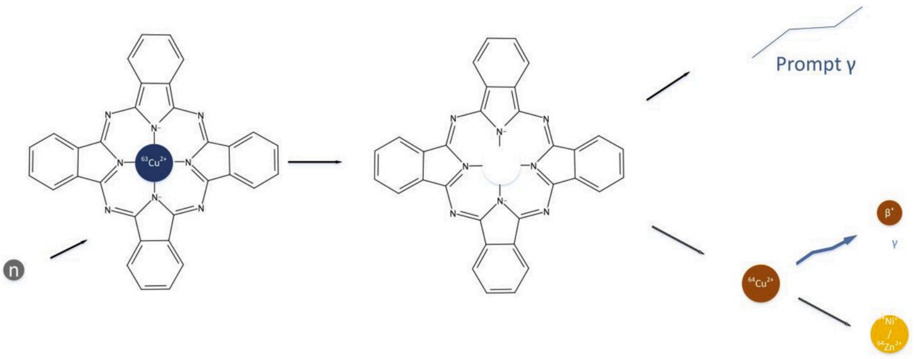

Fig. 1. Schematic representation of the recoil effect induced by neutron activation of Cu-phthalocyanine. Upon neutron activation a nucleus in exited state is formed, which lowers its energy by directly emitting a prompt gamma. When this prompt gamma is energetic enough the daughter will recoil from the complex. This recoil effect can be used to produce enriched radionuclides. The formed ^{64}Cu will decay by electron capture, beta plus or beta minus decay.

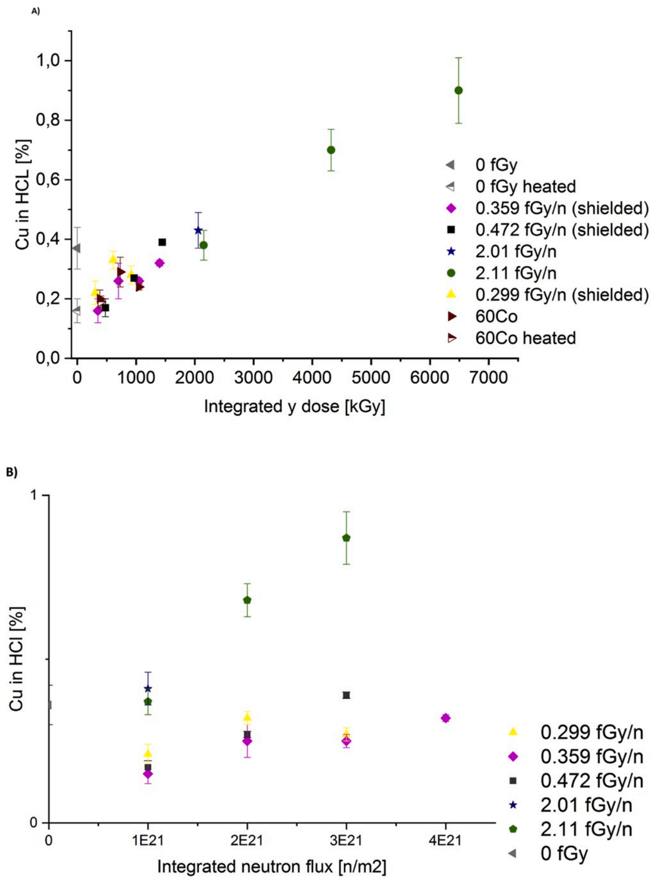

Fig. 2. A) The release of Cu found in the HCl phase as function of the integrated y dose and B) the release of Cu found in the HCl phase as function of the integrated neutron flux. Cu(II)-phthalocyanine mass was 20 ± 0.2 mg. Error bars correspond to experimental uncertainties of n = 3, except for the 0.359 fGy/n sample that received 700 kGy. There the error bars are based on n = 8. The samples receiving 0.472 fGy/n, 0.359 fGy/n and 0.299 fGy/n were irradiated in a lead shielded facility, while the samples receiving 2.01 fGy/n and 2.11 fGy/n were non-shielded.

higher than the energy of chemical bonds (typically in the order of eV (Song and Le, 2017)) the product nucleus will be released from its chemical environment (Yoshihara and Sekine, 2011). Provided that the recoiling atoms and the target are in different chemical form, the enriched isotope can easily be collected.

In 1986 E.L. Hetherington et al. (1986) reported that they could achieve specific activities up to 40 TBq/g Cu using 250 mg Cu (II)-phthalocyanine targets utilising the Szilard-Chalmers effect for an irradiation of 12 h with a neutron flux of $5*10^{17}$ n/m^{2}s. Longer irradiations resulted in lower specific activities. These irradiations were performed in the high flux Australian Reactor (HIFAR), a heavy water nuclear reactor. They concluded that using the Szilard-Chalmers method is an effective way to produce ^{64}Cu in nuclear reactors with a moderate thermal neutron flux, however no explanation was given for the decrease in specific activity. This decrease can possibly be attributed to the destruction of the target due to gamma radiation present in the reactor pool, leading to non-active Cu being released. However, the effect of the gamma dose on the specific activity of Cu-64 using this target or similar has not been researched so far.

The objective of the present paper is to investigate the influence of the gamma dose on the specific activity of ^{64}Cu using Cu(II)-phthalocyanine as a target and a special irradiation facility allowing for decreasing the gamma dose with little loss of neutron flux. Cu(II)-phthalocyanine is chosen because of its known chemical stability (Shapkin et al., 1977).

2. Method

The applied method was based on the procedure described by Hetherington et al. (1986). Samples of 1, 5, 10, 20 and 100 mg of Cu (II)-phthalocyanine (dye content 9, Sigma Aldrich, 11 w% Cu) were irradiated in different facilities having different characteristics at the Hoger Onderwijs Reactor at the Delft University of Technology which we simply numbered as 1 and 2. We also used a special lead shielded facility allowing to change the gamma dose. This facility was denoted with FB3, 6 and 9, where 3, 6 and 9 refer to the cm of lead used. The neutron fluxes and the gamma dose of all facilities are given in Table 1. After irradiation the samples were opened and dissolved in 2 mL 97% H_2SO_4 (J.K. Baker). This solution was slowly transferred into 20 mL MilliQ water (in house Millipore MilliQ system). 12 mL of 20% NH_4OH (J.K. Baker) was added to the Cu(II)-phthalocyanine solution to neutralise the pH. The neutralised solution was transferred onto a 1 g acetic acid buffer conditioned Chelex 100 (100–200 mesh, sodium form, Sigma- Aldrich). A 1 M pH 5 acetic acid buffer was used to condition the Chelex. After all Cu(II)-phthalocyanine solution was passed over the column, the column was rinsed with 8 mL of MilliQ water. Then 16 mL of 1 M HCl (stock solution was made by diluting 30% HCl (Sigma Aldrich)) was passed over the column to remove the trapped Cu-ions. Again, the column was rinsed with 8 mL of MilliQ water. All fractions were collected in separate PE counting vials (Wheatman). Also, the Chelex was transferred to a counting vial. All fractions were measured by gamma spectroscopy (Wallac^2 gamma counter, PerkinElmer). The Cu concentration of all liquid fractions was determined by elemental analysis using ICP-OES (Optima 4300, PerkinElmer). Using this data the

Table 1
The neutron fluxes for the different irradiation facilities of the Hoger Onderwijs Reactor Delft that were used in this work with their corresponding gamma dose rates. The gamma dose was actually a combination of neutron and gamma dose since the two cannot be measured independently. To be able to compare the different facilities and the impact of the gammas, the gamma dose was normalised relative to the thermal neutron flux.

Name of Irradiation facility	Thermal neutron flux [n/m^{2}s]	Epithermal neutron flux [n/m^{2}s]	Fast neutron flux [n/m^{2}s]	Gamma dose rate [Gy/s]	γ Dose per thermal neutron [fGy/n]
FB3	6.22*10^{16}	1.44*10^{15}	4.39*10^{15}	29.33	0.469
FB6	5.64*10^{16}	1.04 *10^{15}	3.28*10^{15}	19.47	0.359
FB9	3.88*10^{16}	6.00*10^{14}	1.94*10^{15}	11.61	0.299
1 (a pneumatic facility)	3.11*10^{16}	7.20*10^{14}	2.60*10^{15}	62.65	2.01
2	2.30*10^{17}	1.74*10^{16}	7.91*10^{16}	485.8	2.11
60Co source	–	–	–	0.210	–

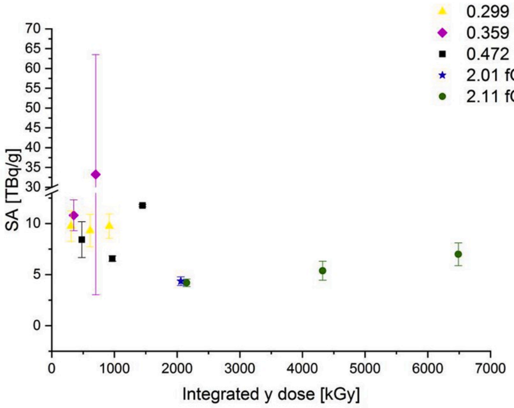

Fig. 3. The specific activity (SA, calculated at the End of Bombardment) as function of the integrated γ dose. Cu(II)-phthalocyanine mass is 20 ± 0.2 mg. Error bars correspond to experimental uncertainty based on n = 3, except for the 0.359 fGy/n that received 700 kGy. There the error bars are based on n = 8. The samples receiving 0.472 fGy/n, 0.359 fGy/n and 0.299 fGy/n were irradiated in a lead shielded facility, while the samples receiving 2.01 fGy/n and 2.11 fGy/n had no shielding.

yield of the reaction was determined according to: $yield = \frac{CPM_{HCl\ fraction(s)}}{\sum_1^i CPM_{i\ fractions}}$, with $CPM_{HCl\ fraction(s)}$ the activity measured in the HCl fractions that contain the freed ^{64}Cu and $\sum_1^i CPM_{i\ fractions}$ the sum of the activity of all the fractions. The enrichment factor of the Szilard-Chalmers method over normal neutron activation was calculated using: $EF = \frac{SA_{SC}}{SA_n}$, with $SA_{SC} = \frac{A_{HCl\ fraction}}{C_{Cu,ICP} * V_{HCl\ fraction}}$ and $SA_n = A_{produced}/m_{Cu}$.

3. Results and discussion

Cu(II)-phthalocyanine is irradiated with neutrons at the Reactor Institute Delft in the facilities shown in Table 1. Samples receiving a 0.299 fGy/n, 0.359 fGy/n or 0.472 fGy/n dose are irradiated in the lead shielded facility. Samples receiving a 2.01 fGy/n or 2.11 fGy/n dose are irradiated in non-shielded facilities. After irradiation bond ruptured ^{64}Cu is separated from the bulk to obtain enriched ^{64}Cu using a Chelex 100 column. During the separation process it is observed that the conditioning of the Chelex is very important. Improperly conditioning caused Cu to leak into the first fraction and thereby lowering the yield obtained. Furthermore, a pH of 1 for the 0.1 M HCl solution is essential to be able to remove $^{(64)}$Cu from the Chelex.

3.1. Influence of the gamma dose on yield and SA

Since the samples receive simultaneously a gamma and a neutron dose irrespective of the facility, we have performed irradiations in a^{60}Co source to determine only the effect of gamma radiation.

Fig. 2A shows clearly that the integrated radiation dose received by the samples influences the amount of Cu that is released from the Cu(II)-phthalocyanine complex. Although there is always a small percentage of Cu that is freed, even if irradiations do not take place, an evident increase of Cu -release is observed as the integrated radiation dose increases. The irradiations performed in the ^{60}Co source show that the gamma dose is most likely responsible for the loss of Cu since the released amount of Cu is comparable to samples that received a comparable integrated radiation dose constituted of both a gamma dose and a neutron dose. Only the non-irradiated, non-heated sample is an outlier with its 0.37 ± 0.07% Cu loss.

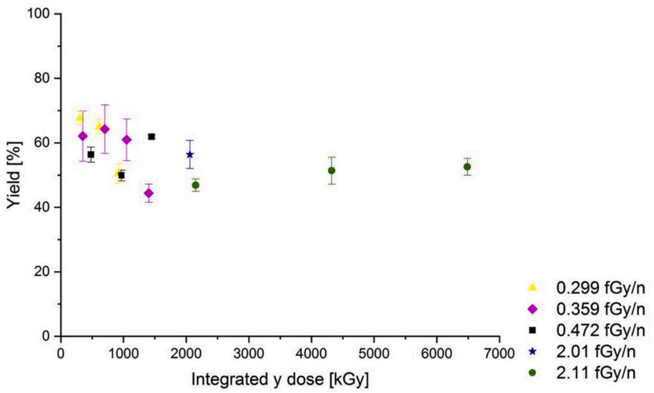

Fig. 4. The ^{64}Cu yield as function of the integrate gamma dose. Cu(II)-phthalocyanine mass is 20 ± 0.2 mg. Error bars correspond to the experimental uncertainty based on n = 3, except for the 0.359 fGy/n sample that received 700 kGy. There the error bars are based on n = 8. The samples receiving 0.472 fGy/n, 0.359 fGy/n and 0.299 fGy/n were irradiated in a lead shielded facility, while the samples receiving 2.01 fGy/n and 2.11 fGy/n had no shielding. Influence of the neutron dose on the yield and SA.

The Cu loss naturally has a direct influence on the SA produced. The effect of the integrated γ dose on the SA is given in Fig. 3. According to expectations, the SA decreases when the integrated γ dose received by the samples increases, up to 2000 kGy. There is no obvious explanation for this observation and further experiments are needed to determine whether there is a clear trend and what its cause is. Furthermore, it can be observed that the lead shielded samples, corresponding to 0.299 fGy/n, 0.359 fGy/n and 0.472 fGy/n, have a higher SA compared to the non-shielded samples, corresponding to 2.01 fGy/n and 2.11 fGy/n, when normalised relative to the neutron flux. This indicates that the lead shielding used to reduce the gamma dose during neutron irradiation has a strong influence on the quality of ^{64}Cu that can be produced. However, the reduction in SA (i.e. factor 2 between the lowest and the highest integrated γ-dose) is not as strong as the Cu loss (i.e. factor 5.6 between the lowest and the highest integrated γ-dose) might have suggested. The SA also depends on the activity produced, which depends on the neutron flux and irradiation time. The samples with the highest integrated gamma dose received four times more neutrons compared to the samples receiving the lowest integrated gamma dose. This has a direct influence on the SA and will compensate for the Cu loss to some extent.

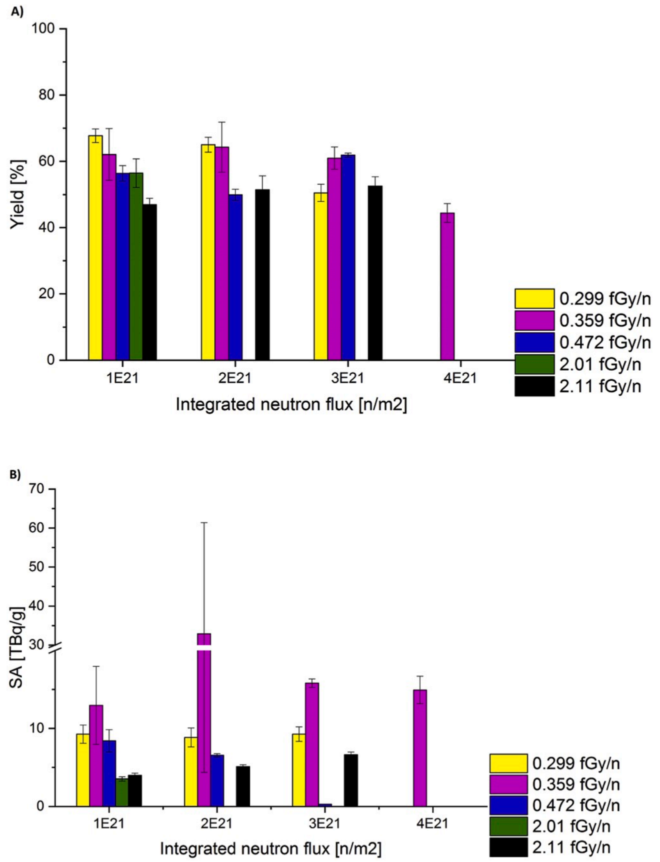

Fig. 5. The influence of different y-dose to neutron ratios as function of the integrated neutron flux on the A) ^{64}Cu yield ($\boldsymbol{yield} = \frac{CPM_{HCl\ fraction(s)}}{\sum_1^i CPM_{i\ \ fractions}}$), B) Specific activity (SA). In all cases the mass of Cu(II)-phthalocyanine was 20 ± 0.2 mg. The irradiation times are taken such that the integrated neutron flux was the same for each facility. Error bars correspond to experimental uncertainty based on n = 3. The 0.473 fGy/n, 0.359 fGy/n and 0.229 fGy/n samples have lead shielding to reduce the gamma dose during irradiation.

The gamma dose does have a small influence on the yield (Fig. 4). The yield of the non-shielded irradiation samples (i.e. 2.01 fGy/n and 2.11 fGy/n) varies between 46% and 56%, while for the other samples it ranges between 58% and 64%. The theoretical yield is calculated to be 60.7%. ^{64}Cu is known to emit many energetic prompt gammas (Tuli, 1999). If the resulting recoil energy from these prompt gammas is high enough, chemical bonds will break (Yoshihara and Sekine, 2011). The Cu bonds in Cu(II)-phthalocyanine are 6.96 eV (Luo, 2009; Sanderson, 1977), so the minimal energy of the prompt gammas required to break that bond is 904 keV. 60.7% of the prompt gammas emitted during neutron irradiation of Cu are 904 keV or higher (Tuli, 1999). The reduction in yield can be caused by reduced solubility or crosslinking of the Cu(II)-phthalocyanine complexes limiting the amounts that can be extracted. The theoretical maximum SA (carrier free ^{64}Cu) that can be reached is 1.4*10^5 TBq/g. However, there will always be some degree of Cu loss due to interactions within molecules, resulting in a lower SA.

When determining the gamma dose in the different irradiation facilities, the determined dose also contains a contribution due to the neutrons. It is impossible to determine these doses independently. Furthermore, the different irradiation facilities have different neutron fluxes. To compensate for the different neutron fluxes the samples are irradiated for the same integrated neutron flux, producing the same amount of activity. The influence of this irradiation time difference is expected to be minimal as saturation activity is reached at much longer irradiation times. (Supplemental information S1) The ^{64}Cu yield, SA, and Cu in HCl phase is determined for four different integrated neutron fluxes (Fig. 5).

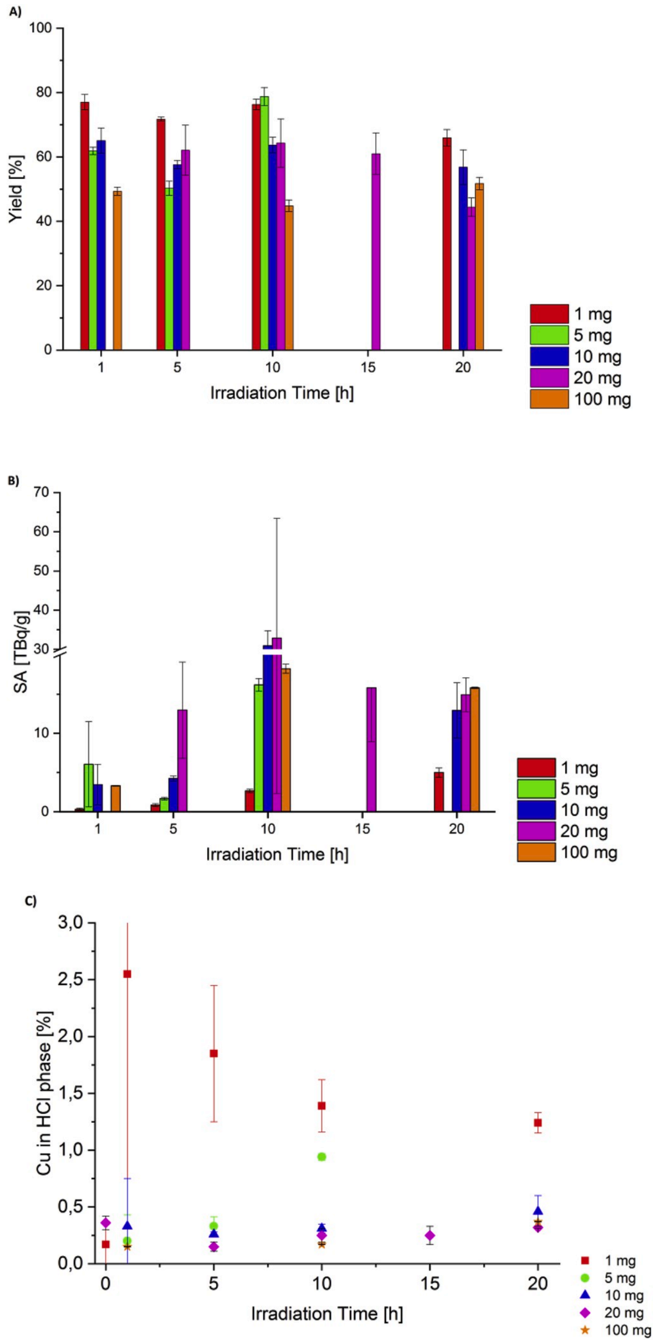

Fig. 6. The influence of neutron irradiation time for different Cu(II)-phthalocyanine masses, at a constant gamma dose to neutron flux 0.395Gy/n, on the A)^{64}Cu yield ($\boldsymbol{yield} = \frac{CPM_{HCl\ fraction(s)}}{\sum_1^i CPM_{i\ fractions}}$), B) Specific activity (SA) and C) Cu in HCl phase. Error bars correspond to experimental uncertainty based on n = 3, except for the 10 h 20 mg, 15 h 20 mg and 100 mg samples. Those error bars are based on n = 8, n = 5 and n = 1 respectively. All samples are dissolved in 2 ml H_2SO_4, except for the 20 h 100 mg sample. That is dissolved in 3 ml H_2SO_4. The amount of Cu in the HCL phase is given as a fraction of the amount of Cu originally present in the sample.

The ^{64}Cu yield is not affected by the increase in integrated neutron flux (Fig. 5 A). As the yield is defined as a fraction of the total activity, it is independent from the activity produced. On the other hand, the SA is affected by the increase in integrated neutron flux (Fig. 5 B). It is expected that at some point the saturation SA is reached. With the increase in Cu loss it is more likely for the SA to decrease, unless the Cu loss and

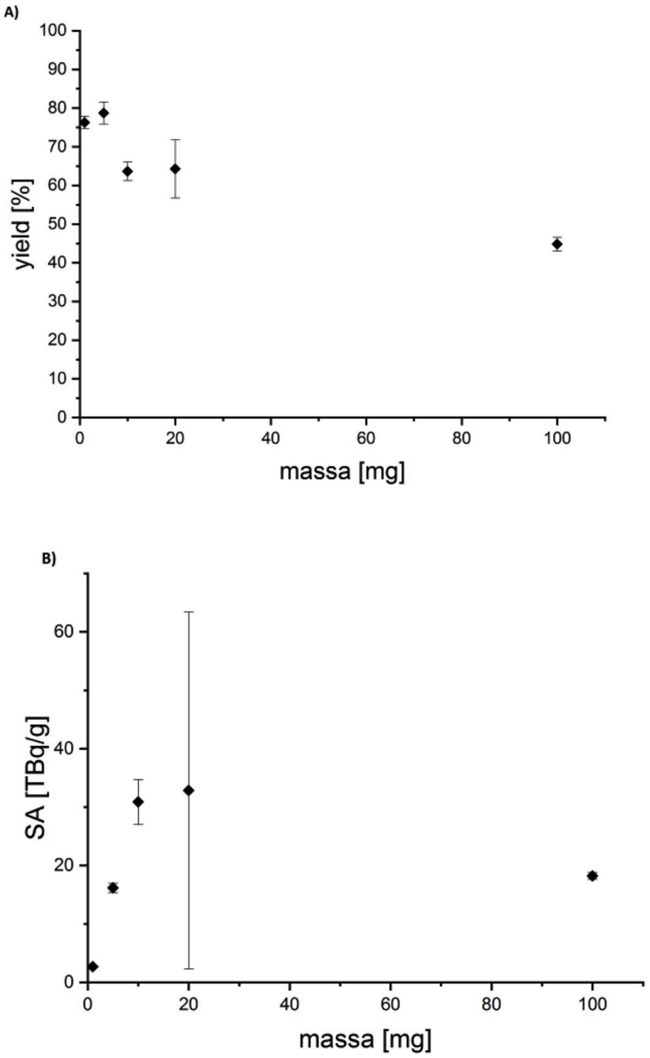

Fig. 7. The influence of mass on the A) yield and B) SA of samples irradiated 10 h in the FB6 facility with a constant gamma dose to neutron flux of 0.395Gy/n. Error bars are based on the experimental uncertainty of n = 3, except for the 20 mg samples. Those are based on n = 8.

the increase in activity are at equilibrium. Furthermore, a clear difference between the shielded samples (0.473 fGy/n, 0.359 fGy/n and 0.299 fGy/n) and the non-shielded samples (2.01 fGy/n and 2.11 fGy/n) is visible. The non-shielded samples have a lower SA and a higher Cu loss compared to the shielded samples, for the same integrated neutron flux. This difference can clearly only be attributed to the gamma dose received by the samples.

Influence of irradiation time and sample mass on yield and SA.

The influence of sample mass is also evaluated as function of irradiation time. The irradiations are performed in the facility having the best results of the previous experiments. The gamma dose divided by the neutron flux is in this case 0.395 fGy/n.

The yields of the different irradiations are above the expected value of 60.7% for most of the masses tested (Fig. 7A), except for the 100 mg samples. The expected yield is an estimate based on the reported probability of the occurrence of the prompt gammas and the energy necessary to break one of the Cu(II)-phthalocyanine bonds. Deviations in either the reported probabilities or bond energies can cause higher than expected yields, as well as release of Cu from the complex. Furthermore, when increasing the Cu(II)-phthalocyanine mass the yield decreases for the same irradiation time. A possible explanation for this decrease in yield could be that the maximum solubility of Cu(II)-phthalocyanine in sulphuric acid is reached. For the samples up to 20 mg this is unlikely because the vials are shaken thoroughly before transferring the solution into water and no relative increased amount of activity was measured in the Chelex phase. However, for the 100 mg samples this is a likely scenario, as the solution became strongly viscous and relatively more activity was found in the Chelex fraction. Increasing the volume of H_2SO_4 to dissolve the 100 mg sample, increased the yield (49.4 ± 1.3% when using 2 ml H_2SO_4 vs 51.8 ± 1.9% when using 3 ml H_2SO_4) Secondly, the Chelex could be saturated, but it is unlikely since it is in a 2–10 fold excess relative to the amount of Cu ions. Moreover, if the Chelex would be saturated an increased amount of activity would be present in the first 2 fractions collected which was not observed.

Table 2
The Cu release from the Cu(II)-phthalocyanine complex when heated for 5 h at 150 °C compared to the release when also irradiated with gammas. The ^{60}Co irradiated samples received a gamma dose of 402 kGy. The samples contained 20 ± 0.3 mg of Cu-phthalocyanine. The experimentally determined standard deviation is based on n = 3.

	Sample Treatment			
	Non-treated	^{60}Co	^{60}Co and heating	Heating only
Cu concentration [mg/l]	0.497 ± 0.096	0.251 ± 0.046	0.217 ± 0.005	0.233 ± 0.009
Cu in HCl phase [%]	0.371 ± 0.074	0.196 ± 0.032	0.192 ± 0.024	0.164 ± 0.038

The specific activity of ^{64}Cu produced increases with the irradiation time and then stabilises for all masses (Fig. 6B). This is expected as with longer irradiation times more atoms get activated and there is only a marginal increase in Cu loss when the samples are irradiated in the lead shielded facility (Fig. 6C). However, these results are contradicted by what is previously reported by E.L. Hetherington et al. (1986). They reported a decrease in SA when increasing the irradiation time. It must be noted that the flux used by E.L. Hetherington et al. was approximately 10 times higher than in this research. This could explain for an important part the differences in the reached specific activity. Furthermore, the shortest irradiation time reported by E.L. Hetherington (Hetherington et al., 1986) was 12 h, while in this research that was 1 h. It is likely that the gamma dose received by E.L. Hetherington's samples is much higher compared to the lead shielded samples in this research, resulting in the different behaviour in SA between their results and the results presented here. For the 10 mg, 20 mg and 100 mg the percentage of Cu found in the HCl phase is only slightly elevated when irradiated for 20 h, where both the neutron dose and gamma dose can have a profound influence. For the 1 mg sample it can be seen that there is a strong increase in Cu dissociation for the irradiated samples compared to the non-irradiated sample.

The enrichment factor (EF) is defined as the factor with which the specific activity is increased using the Szilard-Chalmers method compared to no separation from the target for the same irradiation conditions. An order of magnitude increase is found between the 1 mg and 10 mg samples (Fig. 6B). This can be explained by the fact that for those samples there is also an order of magnitude difference between the SAs produced using the Szilard-Chalmers effect.

Influence of temperature on stability and structure.

During neutron irradiation in the various facilities not only the gamma dose plays a role, but also elevated temperatures can have an effect. To determine whether the different temperatures of the irradiation facilities have an influence on the amount of Cu released from the Cu(II)-phthalocyanine complex two sets of samples are heated up to 150 °C for 5 h, of which one set is irradiated with gammas first in the ^{60}Co source to receive a dose of 402 kGy. The results are given in Table 2.

Heating seems to have little effect on the stability of the Cu(II)-phthalocyanine complex. The total thermal energy supplied to the molecules is with $E = k_B * T = 5.84 * 10^{-21} J = 0.036 eV$ at 150 °C not

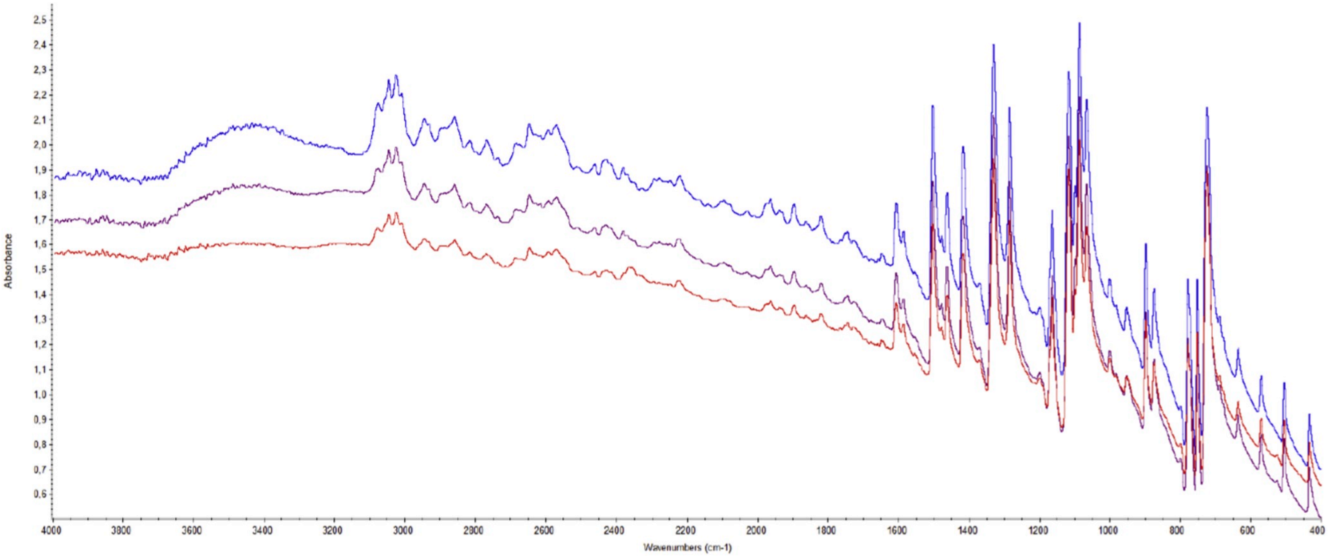

Fig. 8. Result from the FTIR measurements of Cu(II)-phthalocyanine samples receiving an integrated neutron dose of 2.9 $*10^{21}$ n/m^2 and 1052 kGy (blue) or a gamma dose 386 kGy (purple) compared to a control (non – irradiated) (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

enough to break the bonds. Literatures shows that also higher temperatures show little change in the structure (Hassan and Gould, 1992). Hassan et al. (Hassan and Gould, 1992) shows that when heating Cu (II)-phthalocyanine crystal films to temperatures above 300 °C the Cu (II)-phthalocyanine would sublimate and leave a blue film. At temperatures of 240 °C the crystals can change from the α – to the β-form, with the only difference between the forms is a difference in the overlap with their neighbouring molecules (Cruickshank et al., 2012). The α – form is known to be less sensitive to irradiation while the β-form shows a higher sensitivity to irradiation (Yoshihara and Ebihara, 1966). Due to neutron irradiation the temperature in the irradiation facilities can reach up to 60 °C.

In an attempt to visualise the effect of irradiation on the structure of the Cu(II)-phthalocyanine samples are analysed using infrared spectroscopy (FTIR). However, no change is measured between the irradiated samples and control sample, as can be seen in Fig. 8. FTIR is a bulk measurement method, while irradiation effects mostly take place at molecular level. Therefore, it is concluded that compared to the bulk, the damaged molecules are severely outnumbered.

4. Conclusions

Cu(II)-phthalocyanine complexes can be used in the production of high specific activity ^{64}Cu using the Szilard-Chalmers effect. Irradiations in the different facilities showed that the gamma dose in those facilities does have an influence on the Cu released from the complex and so has an influence on the SA produced. The higher the gamma dose in the facility the lower the SA. SA from 6.99 TBq/g (6488 Gy) to 33 TBq/g (700 Gy) are obtained. The decrease in SA is caused by an increase in Cu released from the phthalocyanine due to the gamma dose received. Reducing the gamma dose can be obtained by using a lead shielding during irradiation. The temperature in the facilities is not likely to have an effect on the SA produced.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

J.L.T.M. Moret: Data curation, Formal analysis, Writing - original draft. **T.A. Hardens:** Formal analysis. **O. van Batenburg:** Formal analysis, Supervision. **H.T. Wolterbeek:** Formal analysis. **J.R. van Ommen:** Funding acquisition, Supervision. **A.G. Denkova:** Supervision, Writing - review & editing.

Acknowledgements

This research is part of a project funded by the STW and IDB – Holland BV. under project number 13306. Baukje Terpstra, Mehmet Sarilar and the HOR-operators are thanked for the numerous irradiations performed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apradiso.2020.109135.

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