Securing Gallium-68 availability with liquid target production on mid-energy cyclotrons: Users' experience and scaling up

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Introduction and objectives

It is redundant to say that the use of Gallium-68 (^{68}Ga) has grown exponentially in recent years with about 400 ongoing clinical trials[1] for multiple indications. In this context, an uninterrupted supply of ^{68}Ga is key. Production from liquid targets using mid-energy cyclotrons can be a stable and cost-effective alternative for many centers worldwide. In this paper, several users share their experience on the liquid target production and scaling up of ^{68}Ga through labelling and QC testing in GMP (good manufacturing practices) compliance.

Methods and materials

The ^{68}Ga is produced in a cyclotron via ^{68}Zn(p,n)^{68}Ga nuclear reaction, where an enriched Zinc-68 (^{68}Zn) nitrate solution (^{68}Zn concentration ranging from 33-133 mg/ml) in a conical liquid target is irradiated for about 1h [2]. Subsequently, the irradiated solution is post-processed via two-step solid phase extraction)[3] to obtain [^{68}Ga]GaCl$_3$ (^{68}GaCl$_3$) in ~ 35 min, which is ready to be used for labelling of peptides (DOTA-NOC, DOTA-TOC, DOTA-TATE, DOTA-Ubiquicidin and PSMA-11) in an online, automated process. Quality control of the finished drug product is performed according to current European Pharmacopoeia and a shelf-life is established. When comparing the results among the sites relevant parameters have to be considered such as energy on target (target configuration), current on target, quality of enriched target material, irradiation time, target material concentration.

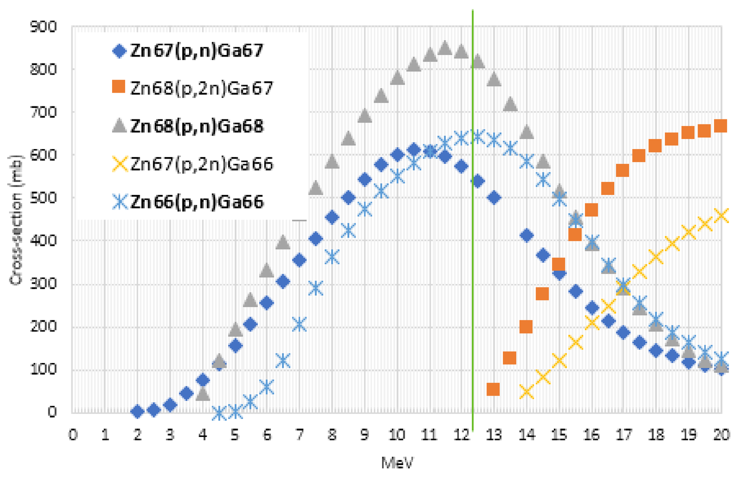


Figure 1: Quality of enriched Zn
^{67,68}Zn(p,n)^{67,68}Ga- ^{67}Zn(p,2n)^{66}Ga

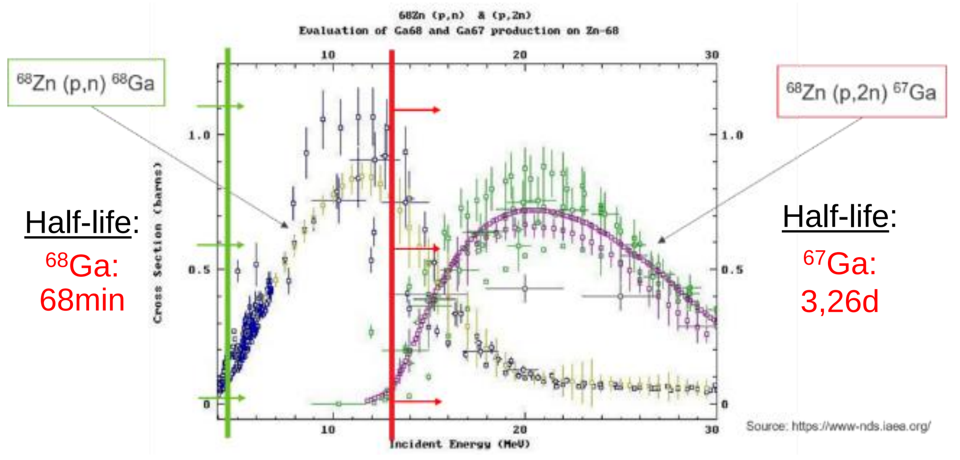


Figure 2: Cyclone® Kiube – Custom Energy 13 to 18 MeV
^{68}Zn(p,2n)^{67}Ga vanishes at E ~ 12MeV

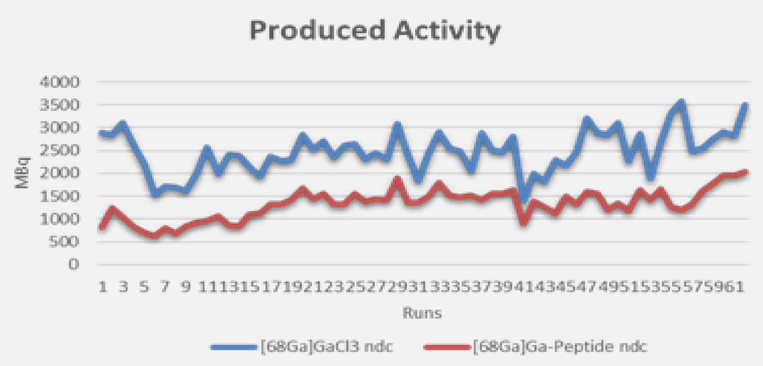
Results

On average, for 1-hour irradiations, sites have been able to produce up to 5.2 GBq of ^{68}Ga at EOB (end of bombardment) when low concentrations of enriched ^{68}Zn (33-45 mg/ml) are used, while for higher concentrations of enriched ^{68}Zn (66-133 mg/ml), up to 13.8 GBq of ^{68}Ga at EOB can be obtained. The purified [^{68}Ga]GaCl$_3$ (end of purification= EOP) resulted between 2.77 GBq at lower concentrations up to 5.4 GBq at the highest concentrations and labelling yields varied from greater than 55% n.d.c (non-decay corrected) to up to 80% n.d.c., depending on the peptide and labelling conditions. Labelling yields can be increased when ascorbic acid is added. The labelled compounds were compliant with current European Pharmacopoeia requirements.

Results from Department of Radiology, Nuclear medicine and Molecular Imaging, Bad Oeynhausen, GERMANY

^{68}Ga-irradiation parameter

Cyclotron energy port: 18 MeV
Beam current :45 µA
Irradiation time:30 – 50 min
Target solution: ^{68}Zn(NO$_3$)$_2$ (99,5%)
Target concentration: 33 – 45 mg/ml
Target config: 250 µm foil



Activity after purification (EOP): 2.5 – 3 GBq (68-81 mCi)

Quality Control Results

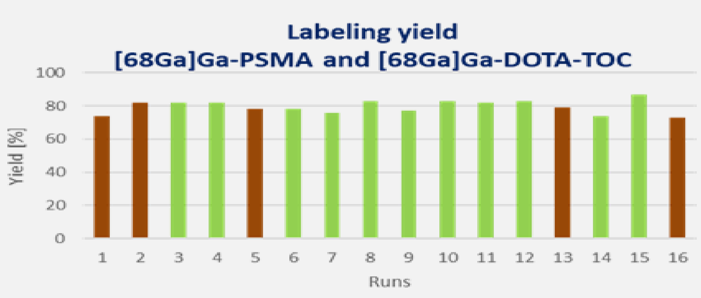
^{68}Ga-Chloride after Purification

pH	0,7 - 1,0
Zn	< 0,1 mg/l
Fe	< 0,1 mg/l
^{67}Ga (2h EOS)	1,7 %
^{66}Ga (2h EOS)	0,08 %

[^{68}Ga]Ga-PSMA-11, [^{68}Ga]Ga-DOTA-TOC

Radiochemical Purity
≥ 95% [^{68}Ga]Ga-PSMA-11
≥ 90% [68Ga]DOTA-TOC
≤ 2 % Free ^{68}Ga

72 successful runs since 2021
60 runs [^{68}Ga]Ga-PSMA-11
12 runs [^{68}Ga]DOTA-TOC;
Average amounts :1.5-1.8 GBq (40-48 mCi); yields n.d.c. up to 80%



Results from the Cyclotron Department, Doctors Hospital, Monterrey, MEXICO

^{68}Ga-irradiation parameters

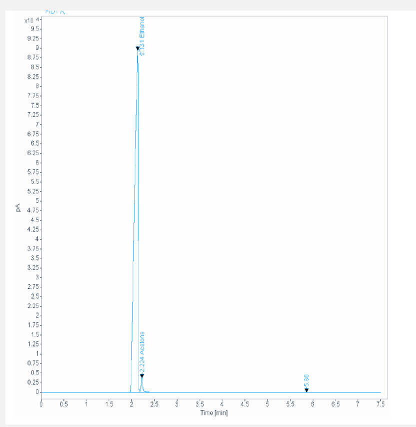
Cyclotron energy port: 18 MeV
Beam current: 45 µA
Irradiation time: 60 min
Target solution: ^{68}Zn(NO$_3$)$_2$ (99,5%)
Target concentration: 33 mg/ml
Target config: 125 µm Nb
n=15

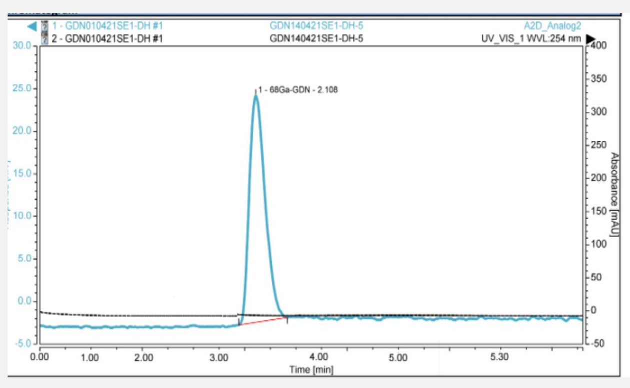
- Produced ^{68}Ga-activity at EOB: 5.2 GBq (140 mCi) (average)
- Activity after purification (EOP) : 2.77 GBq (75 mCi) (average)

- Production on routine of
[^{68}Ga]Ga PSMA-11
[^{68}Ga] DOTA-UBI
[^{68}Ga] Dota-Noc
Average amount: up to 1.7GBq (45 mCi)
Yield n.d.c;= 55-60%

Quality Control Results Labelled Peptide

Specification	Result
pH	7
HEPES	0
Zinc	< 0.1 mg/mL
Radioche. purity	> 99 %
Ethanol	< 10%
Acetone	< 0.5 %
Bacterial endotoxins	< 4 EU/mL

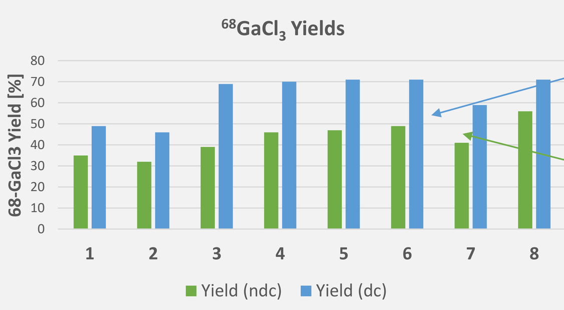




Results from the Department of Radiology, University of Chicago (research collaboration)

^{68}Ga-irradiation parameters

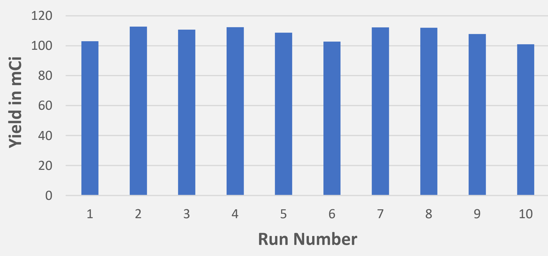
Cyclotron energy port: 18 MeV
Beam current :40 µA
Irradiation time: 66-68 min
Target solution: ^{68}Zn(NO$_3$)$_2$ (99,5%)
Target concentration: 33 mg/ml
Target config: 125 µm Nb



- DC Yields of ^{68}GaCl$_3$: 63 ± 11 %
- Improved yields in later runs: 70% DC
- NDC Yields of ^{68}GaCl$_3$: 43 ± 8 %

Future perspectives:
tests with cold kits for labelling

^{68}Ga Yield, 68 min irradiations (n=10)
Average = 4 GBq (108.3 mCi),
St. Dev. = 0.17 GBq (4.5 mCi)



ICP-MS Analysis: Inductively coupled plasma mass spectroscopy analysis was performed on three (3) samples after total sample decay

Lot Number	Al	Co	Cu	Fe	Ni	Pb	Zn
GACL200114	< 5 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 1 ppm
GACL200115	< 5 ppm	< 0.1 ppm	0.5 ppm	< 0.1 ppm	< 0.1 ppm	< 0.1 ppm	< 1 ppm
GACL200116	< 3 ppm	< 0.1 ppm	< 0.1 ppm	0.2 ppm	< 0.1 ppm	< 0.1 ppm	< 1 ppm

Results from the Institute for Nuclear Sciences Applied in Health (ICNAS), Coimbra, PORTUGAL

Scaling up results

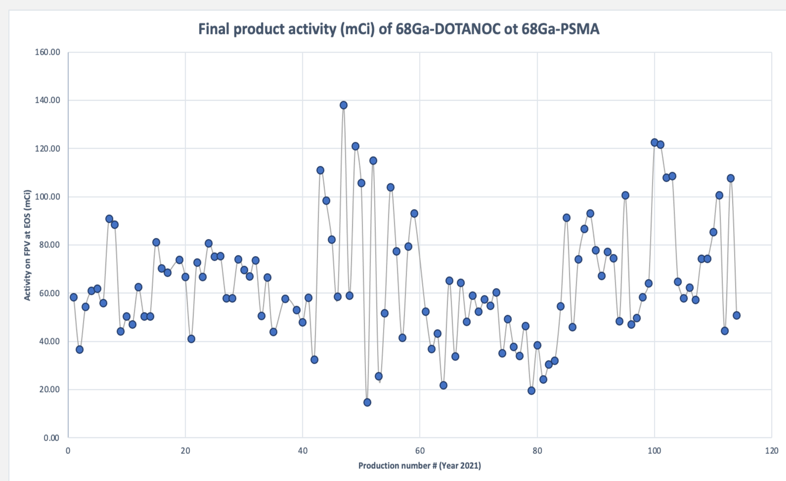
^{68}Zn mg/ml	Cyclotron Energy port	Irr time (min)	Window (µm) Nb	Tgt Curr (µA) range	^{68}Ga [EOB] GBq(mCi)	^{68}GaCl$_3$ [EOP] GBq(mCi)	68Ga-peptide EOS (n.d.c) GBq(mCi)	^{68}Ga-peptides (%,n.d.c.)
133 (n=5)	13 MeV	68	75	50-70	13.8±2.2 (371.6±58.7)	5.4±0.5 (146±13.3)	3.4±0.4 (92.8±11.4)	63.4 ± 3.0 %
100 (n=7)	13 MeV	68	75	71	10.3±0.4 (279.0±11.9)	4.0±1.1 (107.1±30.2)	2.8±0.8 (76.7±21.5)	62.0 ± 9.9 %
66 (n=7)	13 MeV	68	75	>70	7.3±0.4 (197.1±11.7)	3.3±0.5 (89.2±12.2)	2.4±0.3 (64.7±7.1)	66.1 ± 6.1%

Quality Control Results: [^{68}Ga]GaCl$_3$ after Purification

Batch	Half-life(h)	HPGe ^{68}Ga [EOP]	HPGe ^{67}Ga [EOP]	HPGe ^{66}Ga [EOP]	HPGe ^{68}Ga [T=6h]	AAS Fe (µg/ml)	AAS Zn (µg/ml)	AAS Fe [EOP] (µg/GBq)	AAS Zn [EOP] (µg/GBq)	AAS Fe [T=4h] (µg/GBq)	AAS Zn [T=4h] (µg/GBq)	TLC ^{68}GaCl3
GA210217-01	1.15	99.938%	0.025%	0.037%	98.14%	0.04	0.15	0.14	0.51	1.67	5.93	99%
GA210218-01	1.13	99.94%	0.03%	0.03%	98.29%	0.2	0.6	0.3	0.9	3.0	10.08	99%

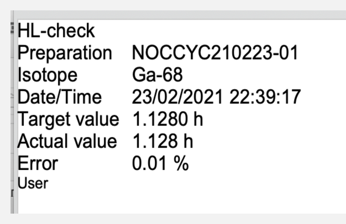
[^{68}Ga]GaCl$_3$ from ICNAS recently obtained a marketing authorization in Portugal.

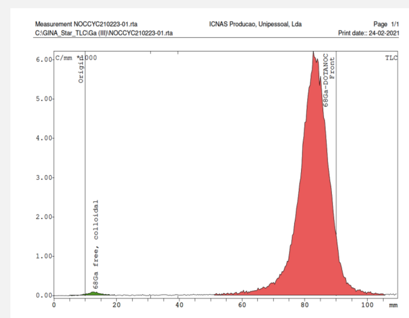
Final product activity (mCi) of [^{68}Ga]GaDOTANOC & [^{68}Ga] GaPSMA-11 (n=114)



Quality Control Results: Labelled Peptide (n=114)

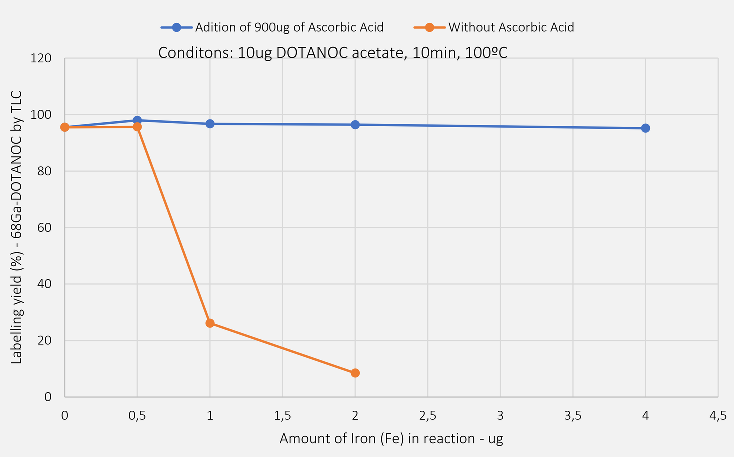
QUALITY CONTROL (N=114 RUNS (2021))	
pH	5 - 7
Zn	< 10 ug/GBq (up to 4h after EOP)
Fe	< 10 ug/GBq (up to 4h after EOP)
^{68}Ga	> 98% (up to 4h after EOP)
^{68}Ga-DOTANOC or ^{68}Ga-PSMA-11	≥ 95 %
Free ^{68}Ga	< 2%
Colloidal ^{68}Ga	< 3%

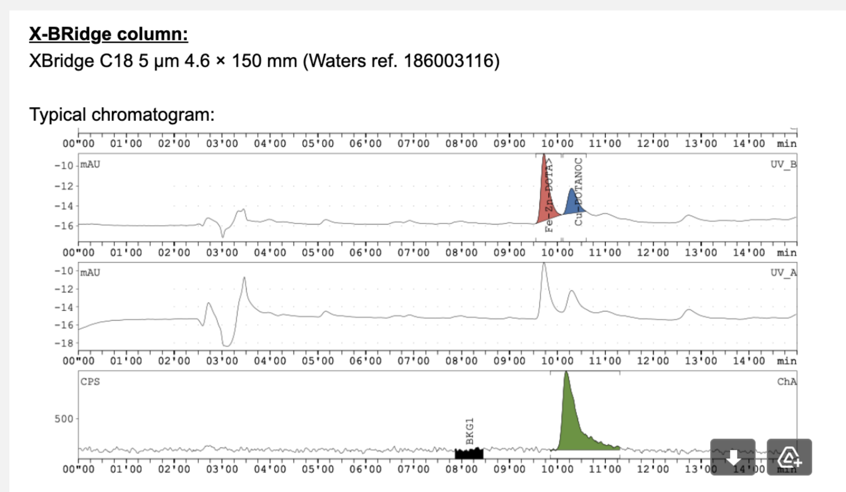




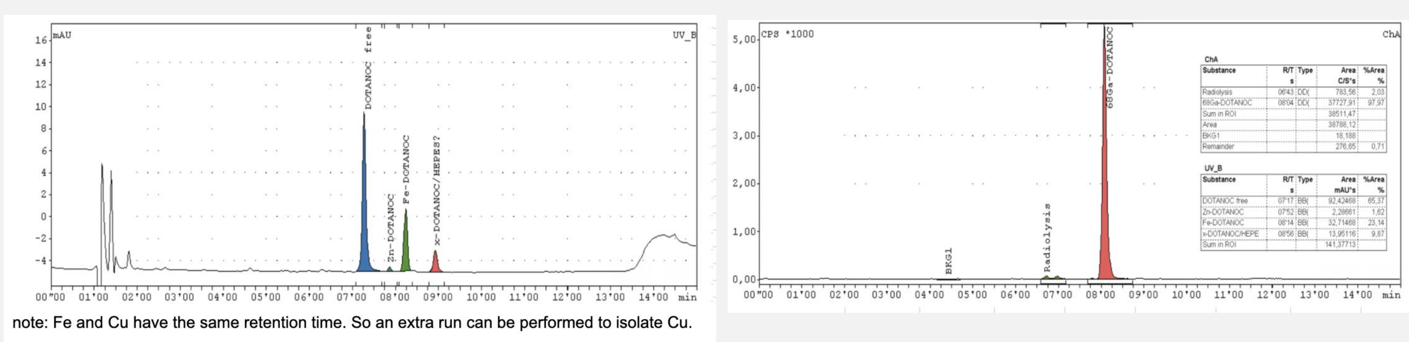
Use of ascorbic acid to reduce Cu^{2+} to Cu^{+} and Fe^{3+} to Fe^{2+} to increase yields and prevent radiolysis

A- tests using ascorbic acid





B- Two different HPLC methods to check for presence of metals



A: Water/0.1%TFA:B: ACN;
Gradient, 0.6ml/min;
243 / 254 nm
ACE column:
ACE® (15 cm x 3.0mm, 3 µm)

Conclusions

Production of ^{68}Ga via liquid targets using mid-energy cyclotrons is performed routinely in several GMP sites worldwide, which provides an economical viable and sustainable alternative to the production of ^{68}Ga for local use and potential distribution when ramping up the manufacturing with higher concentrations of target material.

Bibliography

[1] https://www.clinicaltrials.gov/ct2/results/details?term=gallium+68:search date April, 2021
[2] F. Alves et al, Modern Phys. Lett A, vol 32 (17), 2017.
[3] V. Alves et al, Instruments vol 2 (17), 2018.

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