Automated [^{68}Ga]DOTA-NOC Production Using a Commercial Synthesizer

PRODUÇÃO UNIPESSOAL UNIVERSIDADE DE COIMBRA

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I. INTRODUCTION

Generator produced ^{68}Ga has boosted interest for radiolabelling small peptides for PET applications as an alternative to ^{18}F- and ^{11}C-radiopharmaceuticals, in particular, for centers without access to a cyclotron(1). From those, [^{68}Ga]DOTA-NOC, a synthetic somatostatin (SST) analog, with high affinity for ssr2, ssr3 and ssr5 receptor subtypes is of major interest for *in vivo* imaging of SST receptor-expressing neuroendocrine tumors(2). Regulatory, as well as radioprotection issues, require process automation for routine use in human studies. Here we report on the development of a fully automated synthesis process for [^{68}Ga]DOTA-NOC production compatible with current GMP requirements.

II. AIMS

Here we describe the development of a simple and reproducible process for Gallium-68 peptide labelling using an automated module with disposable cassettes suitable for a GMP manufacturing process. A commercial synthesizer was used (Synthera®, IBA, Louvain-la-neuve, Belgium) coupled with a standard SnO_2 based ^{68}Ge/^{68}Ga generator (iThemba, LABS, Somerset West, South Africa). Software, test and synthesis method sequences were developed and implemented. Disposable cassettes were adapted from those used for FDG.

III. METHODS

^{68}Ge/^{68}Ga generator elution

- 5-7ml HCl 0.6M
- 1 ml/min

^{68}Ga absorption to SCX

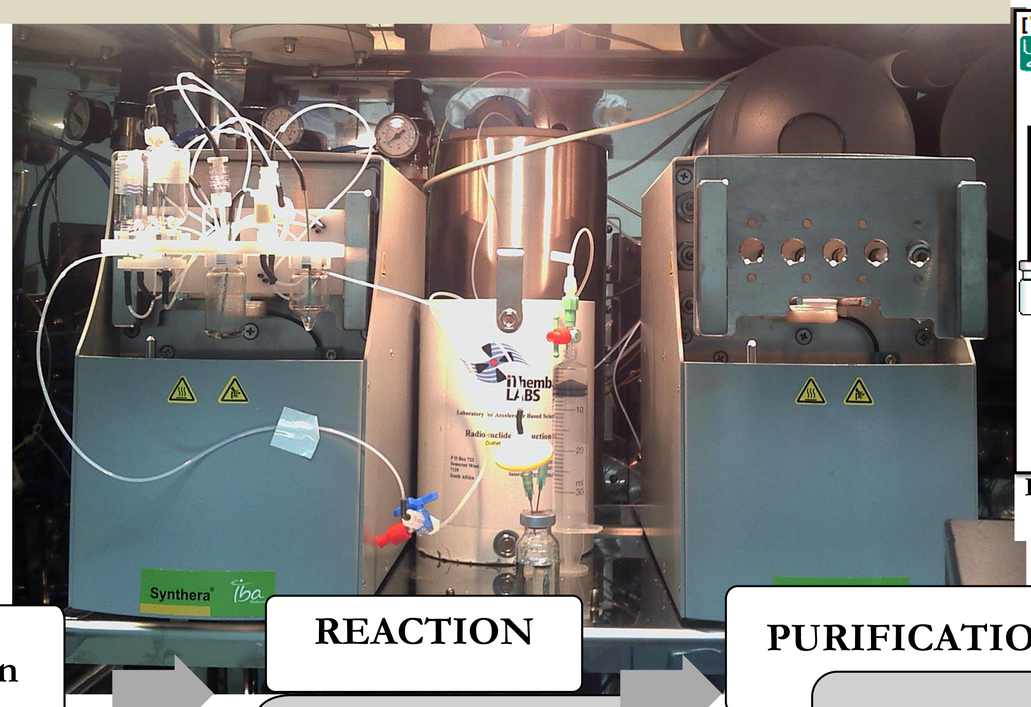
- Cation exchange column

Yield: 96.65±2.66

^{68}Ga deabsorption from SCX

- Acetone(98%)/0.02M HCl (1.2ml)

Yield: 94.81±2.57



REACTION

- 30µg DOTA-NOC peptide
- 1ml HEPES buffer 0,5M (pH=3.9)
- Rtime = 15min.
- Rtemp = 105ºC

RCY (DC): 70.88±19.34

PURIFICATION

- C18 cartridge
- Extraction from C18 with 1ml EtOH
- Dilution with 9ml NaCl 0.9%

FILTRATION

- 0.22µm sterile filter

EOS RCY (DC): 57.26±17.64

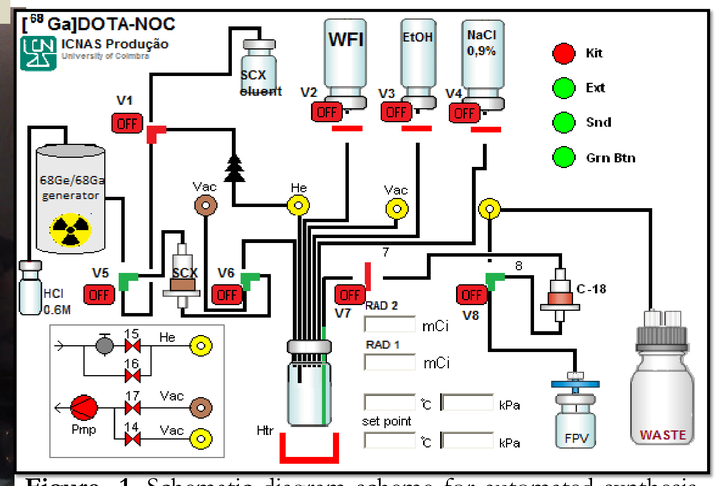


Figure 1. Schematic diagram scheme for automated synthesis of [^{68}Ga]DOTA-NOC on Synthera® V1 module.

IV. RESULTS

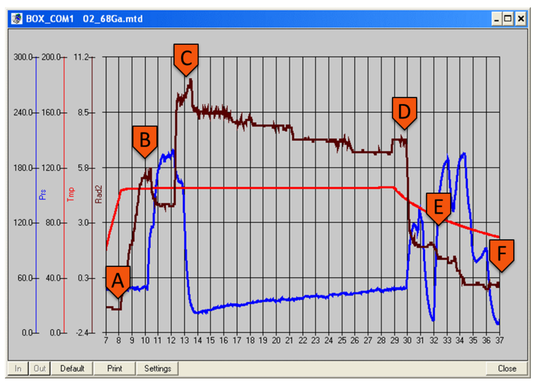


Figure 3. Chart of [^{68}Ga]DOTA-NOC synthesis.
A: generator elution/SCX retention; B: SCX elution; C: Start reaction; D: C18 purification; E: C18 elution; F: EOS.

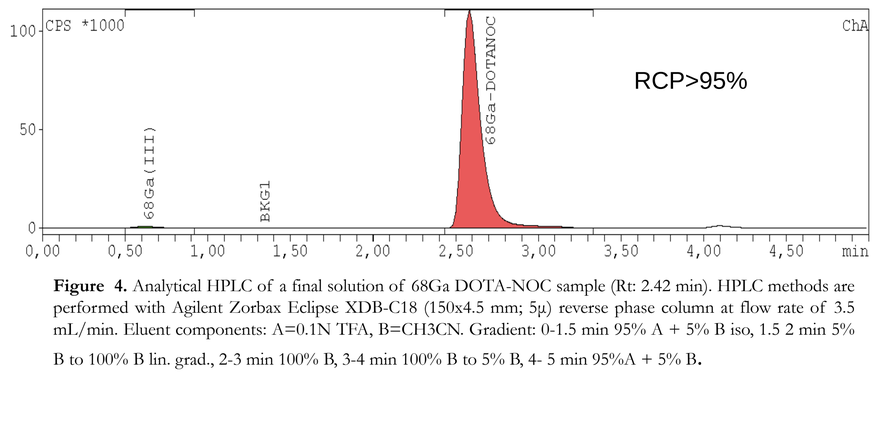


Figure 4. Analytical HPLC of a final solution of 68Ga DOTA-NOC sample (Rt: 2.42 min). HPLC methods are performed with Agilent Zorbax Eclipse XDB-C18 (150x4.5 mm; 5µ) reverse phase column at flow rate of 3.5 mL/min. Eluent components: A=0.1N TFA, B=CH3CN. Gradient: 0-1.5 min 95% A + 5% B iso, 1.5 2 min 5% B to 100% B lin. grad., 2-3 min 100% B, 3-4 min 100% B to 5% B, 4- 5 min 95%A + 5% B.

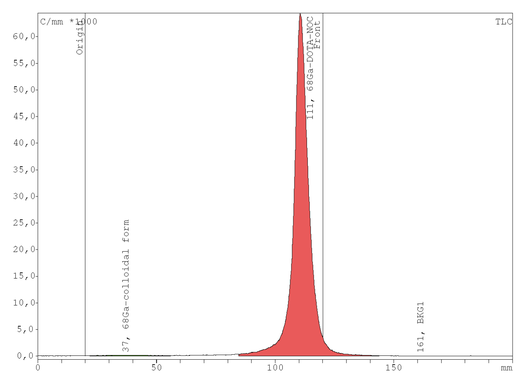


Figure 5. Analytical TLC of a final solution of [68Ga]DOTA-NOC sample (Rf=0.9). TLC was performed with iTLC-SG silica gel plate. Eluent: Ammonium acetate 1M and Methanol (50:50)

TABLE I. Quality test results of [^{68}Ga]DOTA-NOC obtained using pre-purification with SCX column and a C18 cartridge for final purification.

Parameter	Result
Volume	10 ml
Appearance	Clear or colourless
pH	4.96±0.51
RCP (HPLC)	> 97%
RCP (TLC)	> 99%
Acetone	< 50 mg/V
HEPES	< 0.2 mg/V
Sterility	Sterile

V. CONCLUSION

An automated process for [^{68}Ga]DOTA-NOC production using a commercial synthesizer was successfully developed for a reliable and reproducible routine production. The radiochemical yields of final product are reproducible, stable and show excellent quality with high RCP and RNP. With this system and dedicated disposable cassettes (IFP), the synthesis is made with safety and under European GMP guidelines. The process can easily be adapted for the labeling of other peptides and for other radiometals.

References

(1) Boschi, S., et al. (2013). "Overview and perspectives on automation strategies in (68)Ga radiopharmaceutical preparations." Recent Results Cancer Res 194: 17-31.

(2) Di Pierro, D., et al. (2008). "Radiolabelling, quality control and radiochemical purity assessment of the Octreotide analogue 68Ga DOTA NOC." Appl Radiat Isot 66(8): 1091-1096.

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