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An automated synthesis method for Ga-68 labelled ubiquicidin 29-41

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Introduction
Published methods for radiolabelling of ubiquicidin (UBI) 29-41 to date describe manual processes. Manual labelling of 1,4,7-triazacyclononane-1,4,7-triacetic acid ubiquicidin (NOTA-UBI) with Gallium-68 (Ga-68) has several disadvantages, including unnecessary radiation exposure to operators, and difficulty to meet Good Manufacturing Practice (GMP) requirements. The aim of this study was to develop an automated synthesis method for the labelling of Ga-68 NOTA-UBI.
Materials and methods
Ga-68 activity was eluted from an iThemba Labs Ge-68/Ga-68-generator using 0.6 M HCl. This approach to developing an automated method first duplicated the manual method developed by Ebenhan et al. (2014) using the generator, eluant and consumables available at our PET Centre, followed by adaptations of the radiosynthesis to suit the automated module. Radiolabelling yield and radiochemical purity were determined after each labelling experiment to compare the efficiency of each method and changes to the protocols.
Ga-68 NOTA-UBI was labelled using the following three generator eluate preparations: the Ge-68/Ga-68 generator was eluted using fractional elution and 1.5 M 4-(2-hydroxyethyl) piperazine-1-ethanesulfonic acid (HEPES) was added as buffering agent (method 1); fractional generator elution was done and 1.0 M sodium acetate solution was added as buffering agent (method 2); and a cationic exchange-based pre-purification step was utilized to clean-up the full-scale generator eluate from any possible metal impurities and combined with 1.0 M sodium acetate solution as buffering agent (method 3). The pH of all labelling mixtures was adjusted to range between 3.5 –4.0. Following radiolabeling, a C18-cartridge based separation of Ga-68 NOTA-UBI was performed to free the labelled product from impurities including colloidal Ga-68. This step was performed on all methods. Regardless the methods applied, Ga-68 NOTA-UBI stability and further tests were performed after each radiosynthesis to justify the product validity for human administration.
Results
NOTA-UBI was successfully labelled (n = 23) with Ga-68 using automated procedures for fractional elution and cationic pre-purification and sodium acetate as buffer. The best percentage labelling efficiency (78.9 ± 3.6, n = 7) was obtained using the cationic pre-purification method. The average radiochemical purity for the cationic pre-purification method was 99.0 ± 1.7 (n = 7). When method 1 was used, the HEPES content in the final labelled product exceeded the limit prescribed in the European Pharmacopoeia which limited further use of HEPES buffer in these labelling methods. Stability and validation studies performed on the Ga-68 NOTA-UBI indicated that both the fractional elution and cationic purification methods comply with specifications for batch release of radiopharmaceuticals intended for human use.
Conclusion
An automated synthesis protocol using a Scintomics GRP Module has been successfully developed and tested for robustness and repeatability. Both fractional elution and cationic purification automated methods using sodium acetate as buffer can be utilised for the routine synthesis of Ga-68 NOTA-UBI under GMP conditions, demonstrating high radiochemical yield and purity. An automated cationic pre-purification method using sodium acetate resulted in the best labelling efficiency. HEPES as a buffer was however found not suitable for routine labelling of Ga-68 NOTA-UBI.

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