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Comparison Study of 18F-FDG Production Utilizing FDG Single Citrate and FDG Duo Citrate Cassette on FASTlab2 Synthesizer at AFIRI, Rawalpindi

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ABSTRACT

Objective: To compare and observe the differences of 18F-FDG produced using FDG citrate and FDG duo citrate cassette on the GE Healthcare FASTlab2 Synthesizer system following standard operating parameters.

Study Design: Quasi-experimental study.

Place and Duration of Study: Armed Forces Institute of Radiology and Imaging, Rawalpindi Pakistan, from Sep 2020 to Aug 2021.

Methodology: Comparison of 18F-FDG produced using FDG citrate and FDG duo citrate cassette on FASTlab2 consists of evaluating the estimated yield uncorrected (EYUC), estimated yield decay corrected (EYDC), radiochemical purity (RCP), synthesis duration and tracer volume in both cassettes. Sixty Batches of each FDG citrate and duo citrate cassettes were utilized to obtain the required results.

Results: Results acquired by comparing the mean yield of FDG citrate and FDG duo citrate cassette were 74.98±8.92% for EYUC and 86.35±10.26% for EYDC for the FDG citrate cassette. At the same time, the mean RCP turned out to be 99.58±1.06% for the citrate cassette and 99.9±0.35 for the duo citrate cassette. The mean synthesis duration of FDG was 24.21±0.76min and 24.75±0.43min for the citrate cassette and duo citrate cassette correspondingly, and the volume of the tracer was 3.5ml for both cassettes.

Conclusion: The results obtained by comparing these two cassettes were within the range of acceptable limits as claimed by the manufacturer, with a single cassette offering more yield as compared to a duo cassette, while the radiochemical purity, pH and volume of the tracer were found to be identical in both cassettes.

Keywords: EYDC (estimated yield decay corrected), FASTlab2, EYUC (estimated yield uncorrected), pH and Volume of the tracer, RCP (radiochemical purity), Synthesis duration.

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INTRODUCTION

18F-FDG is a widespread radiopharmaceutical employed in PET-CT imaging used for diagnosis, staging and restaging of cancer and evaluation of physiological metabolisms within tissues in the body.[1] After FDA approval of FDG in the 1990s, utilization of FDG PET/CT has remarkably increased for imaging purposes in the fields of neurology, cardiology and oncology.[2] Due to the short half-life of fluorine-18-based radiopharmaceuticals, it is compulsory to produce FDG in a radiochemistry lab or nuclear pharmacy close to the clinical imaging center.[3] In the past, FDG was manufactured utilizing electrophilic fluorination of 3,4,6-tri-O-acetyl-D-glucal (TAG) or D-glucal.[4]

The primary difference between the single citrate and duo citrate cassettes is the frequency of batches produced from each cassette, as two consecutive runs could be carried out in the case of duo cassettes without exposure to the workers.[5] In contrast, it is placed to the extreme right in the case of the duo cassette. FASTlab citrate cassette is preferred over the phosphate cassette due to its higher ethanol content which is responsible for radiolysis inhibition and overall stability.[6] Moreover, due to abbreviated new drug application (ANDA) requirements set up by FDA, the citrate cassette is more suitable than the phosphate cassette.[7,8]

The complete procedure is automated and carried out in a shielded and controlled environment, which ensures minimum exposure to the operators working inside a hot lab as radiation workers are exposed to a significant amount of radiation during radiopharmaceuticals manufacturing and dispensing processes.[8,9] This study checks whether significant differences exist between the yield and quality of 18F FDG produced using duo and single citrate cassettes.

METHODOLOGY

The quasi-experimental study was conducted at the Armed Forces Institute of Radiology and Imaging

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(AFIRI), Rawalpindi, Pakistan, from September 2020 to August 2021 after getting approval from the Ethical Committee (certificate number 0062). The sample size was calculated using a WHO calculator with the reported prevalence of 50% of both cassettes.[1]

Inclusion Criteria: All cassettes manufactured and quality certified by GE Healthcare and within the limit of expiry date were included in the study.

Exclusion Criteria: Cassettes from third-party manufacturers and those past the expiry date were excluded from this study.

A total of 120 batches, sixty of each single and duo cassettes, were utilized in this study. A simple convenience sampling technique was used to assemble the data. F18 is produced as fluoride ions from the bombardment of accelerated protons in O18 water. GE Minitrace 9.6 MeV cyclotron can produce up to 2700mci of F18 for 2 hours on 50μA. Fluoride ions are then transported in the form of irradiated water via a transfer line to the radiochemistry module.

Automated radiochemistry modules have overtaken the traditional techniques and homemade systems employed in the 90s for radiopharmaceutical labelling.[9] These systems are supplied with commercially prepared cassettes which are sterile and are manufactured according to GMP, and capable of automated rinsing after the labelling procedure.[10] Fastlab,2 is used in the radiolabelling of radiopharmaceuticals. The irradiated water containing radioactive F18 is transferred from the cyclotron to the synthesizer, which is already on standby to receive activity and start the radiolabelling process.

The Ge Healthcare FASTlab2 synthesizer is supplied with prepared reagents filled cassettes (FASTlab duo citrate cassettes or FASTlab citrate cassettes) consumed during the process. After performing some preliminary steps, the synthesizer is ready to receive the activity from the cyclotron. Radioactive F18 is transferred as liquid 2.7ml to the synthesizer, trapped in the QMA cartridge. At the same time, the residual water is recovered in the vial placed alongside the synthesizer.

Then 0.5ml of eluent mixture (containing kryptofix, Potassium carbonate, Acetonitrile and Water) is passed through the QMA cartridge, and F18 trapped there is moved onto the reactor vessel. After this step, temp in the reactor vessel is increased, and the drying process starts to remove unwanted chemicals from the eluent (Azeotropic drying). This step, 0.1ml of acetonitrile is added to the reactor to facilitate this process.

In the next step, the precursor, i.e., Mannose Triflate 1.7ml, is added to the reactor, and a substitution nucleophilic reaction takes place, resulting in decreased reaction time for synthesis and higher and stable yield a result.[11] In this process trifluoromethane sulfonate group is displaced by radioactive F18 ion resulting in FTAG fluoro 1, 2, 3, 4, 6-tetra-O-acetyl-D-glucose and for the purification of FTAG, it is diluted with 3ml of water then the addition of further 2ml and 4ml of water takes places.

After this step, FTAG is passed on to the tC18 environmental cartridge, and the process is repeated. It is trapped on the cartridge, and free F18 and other impurities are sent to the waste bottle. The reactor vessel is then washed with water to obtain any traces remaining. The next step involved in this process is hydrolysis, which converts FTAG into FDG. In this step, 1ml of 2N NaOH is added to the tC18 environmental cartridge and the acetyl groups by OH ions resulting in the formation of FDG.[12,13]

This FDG produced is alkaline due to the alkaline hydrolysis, so the pH adjustment is significant before administration to the patients. So in the next step, this alkaline FDG is collected in 2ml of water, and 1.70ml of citrate buffer is added to the solution so that pH is adjusted for human administration in the final steps, this FDG is passed on to the tC18 plus cartridge where it retains unhydrolyzed FDG and other impurities and then through the Alumina cartridge where unreacted F18 ions are also retained, and then the final product is transferred to the Phaedra in which clio dispenser is place.

Clio dispensing system is a semi-auto radiopharmaceutical volumetric dispenser. FDG from the FASTlab2 synthesizer is transferred to the Phaedra Hot cell and received in bulk. Commercially prepared kits for clio are utilized in this system. FDG is received in the bulk of the system, where a dose calibrator calculates the mean of the activity received. There is an optional way of dispensing FDG via volume or activity. A volumetric mode of dispensing was utilized in the present study.

The Data was examined using Microsoft Excel-2010, and the independent sample t-test was performed to compare the radiochemical yields uncorrected, decay corrected, radiochemical purities, pHs and synthesis durations of both cassettes. The p-value lower than or up to 0.05 was considered as significant.

RESULTS

After analyzing 60 batches each of FASTlab single citrate cassettes and FASTlab duo citrate cassettes following parameters were used to assess the suitability of both cassettes, namely RYUC (radiochemical yield uncorrected), RYDC (radiochemical yield decay corrected), RCP (radiochemical purity) and synthesis of duration. The mean value for the FASTlab single citrate cassette were 74.98±8.92% for RYUC and 86.35±10.26% for RYDC, while the average results for RYUC and RYDC for FASTlab duo citrate cassette turned out to be 71.316±3.65% and 82.3±4.24% respectively. The differences between the two types of cassettes are given in the Table.

Synthesis of duration was also an essential factor in determining the performance of the cassette used, and there were no vast changes observed in the duration of synthesis with both single and duo citrate cassettes with an average time of 24.21±0.76 and 24.75±0.43 minutes sequentially. The results were significant after applying the t-test for all radiation parameters. The mean values for RCP (radiochemical purity) of both cassettes as both single and duo cassettes produced pure radiochemical compounds with the values of 99.58±1.06% and 99.9±0.35% correspondingly as compared to 99.95%.

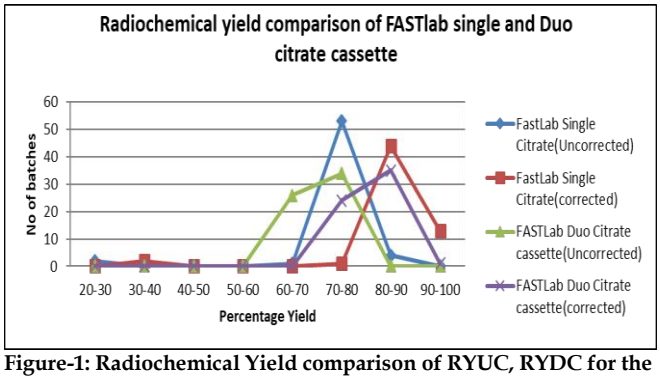

Figure-1: Radiochemical Yield comparison of RYUC, RYDC for the FASTlab Single Citrate Cassette and FASTlab Duo Citrate Cassette

All the QC tests were performed before declaring the batch fit for human use according to European ¨Pharmacopoeia. The average pH for both cassettes was the same, with a value of 5.39. The differences between FASTlab2 single citrate cassettes and FASTlab duo cassettes are given in Figure-1. Layouts of FASTlab single citrate cassette and FASTlab duo citrate cassette are shown in Figure-2 & 3.

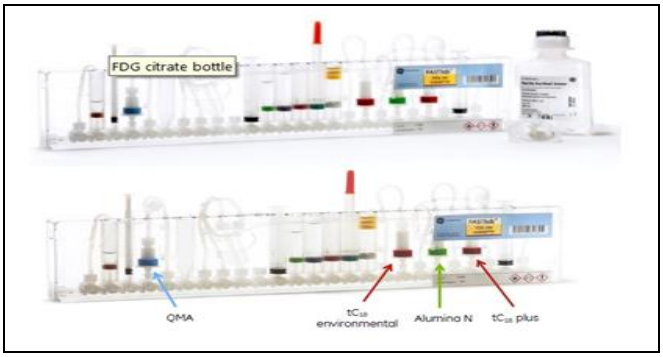

Figure-2: Layout of FASTlab Single citrate cassette

Table: Difference between different Parameters RYUC, RYDC, RCP, pH and Synthesis of Duration

Cassette	RYUC (Radiochemical Yield Uncorrected)%	RYDC (Radiochemical Yield Decay Corrected)%	RCP (Radiochemical Purity) %	pH	Synthesis Duration (min)
Single citrate cassette	74.983±8.92	86.35±10.26	99.58±1.06	5.391±0.34	24.216±0.76
Duo citrate cassette	71.316±3.65	82.3±4.24	99.9±0.35	5.393±0.34	24.75±0.43
Difference	3.667	4.05	-0.307	-0.002	-0.534

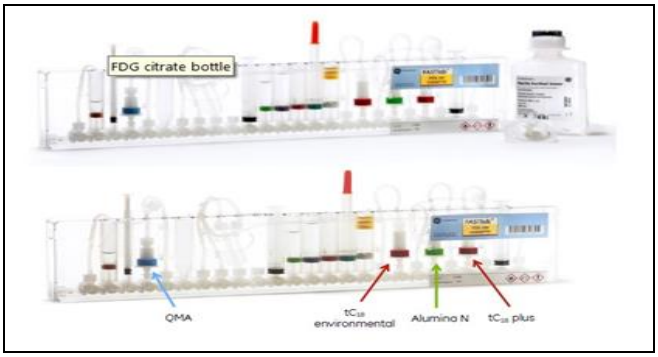

Figure-2: Layout of FASTlab Single citrate cassette

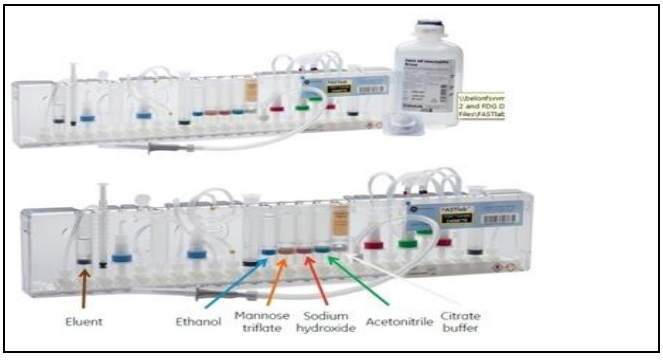

Figure-3: Layout of FASTlab Duo citrate cassette

DISCUSSION

At the Armed Forces Institute of Radiology and Imaging, both FASTlab single citrate cassettes and

FASTlab duo citrate cassettes are being utilized to produce 18F-FDG. The major differences between these cassettes are the number of chemicals in the individual cartridges and the number of productions that could be carried out double in duo cassettes compared to single cassettes. The results obtained from analyzing 60 batches of both cassettes indicated that no significant differences were found in the radiochemical purity of 18F-FDG manufactured from both cassettes.

There were slight differences found in the radiochemical yields of FDG produced from single citrate and duo citrate cassettes which still are within the acceptable range.[14] Synthesis duration was also more or less identical in both cassettes. There was also no considerable variation in the pH of the final product labelled from each cassette type. Furthermore, FASTlab citrate and duo citrate cassettes are preferred over FASTlab Phosphate cassettes due to the former meeting ANDA (abbreviated new drug application) requirements being imposed by FDA1.[15]

One of the advantages of using a FASTlab duo citrate cassette over a single citrate cassette is the cost-effectiveness, as it costs slightly less compared to the latter.[16] However, there are also some limitations of using a duo cassette as the hospital is forced to perform the next synthesis within 24 hours; otherwise, the setup will proceed directly towards cassette rinsing.[17] Another drawback of using the FASTlab duo cassette is that the synthesis module needs to be continuously powered on during the wait time between two syntheses, and nitrogen must be supplied during this whole operation without any hindrance; otherwise, the cassette would be wasted. All the QC tests were performed according to European Pharmacopoeia before passing out the final product. Filter integrity test is another test which is not mentioned in either European or United States Pharmacopeia but is performed to ensure the sterility of the final product.[18]

CONCLUSION

FASTlab2 module is the foremost advanced, efficacious and feasible synthesizer compared to other modules available in the market. There are no whatsoever differences found between the 18F-FDG produced from both the FDG citrate cassette and the FASTlab duo citrate cassette as the parameters like RCP, pH and synthesis of duration are almost identical and only slight deviations were observed between the RYUC and RYDC. Both cassettes were confined to the standards of European Pharmacopoeia, and not a single incident of QC failure occurred during the study. In conclusion, it is up to the institute to decide which kind of cassette it intends to use for production as per convenience.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MA: & RB: Conception, study design, drafting the manuscript, approval of the final version to be published.

AURS: & AJ: Data acquisition, data analysis, drafting the manuscript, approval of the final version to be published.

SAM: & NA: Data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Long JZ, Jacobson MS, Hung JC. Comparison of FASTlab 18F-FDG production using phosphate and citrate buffer cassettes. J Nucl Med Technol 2013; 41(1): 32-34. https://doi.org/10.2967/jnmt.112.112649
2. Sowa AR, Sowa AR, Jackson IM, Desmond TJ, Alicea J, Mufarreh AJ, et al. Futureproofing [18F]Fludeoxyglucose manufacture at an Academic Medical Center. EJNMMI Radiopharm Chem 2018; 3: 12. https://doi.org/10.1186/s41181-018-0048-x
3. Huang Y-Y, Taylor S, Koziorowski J, Chang Y-N, Kao W-H, Tzen K-Y, et al. A two-center study for the quality control of [18 F] FDG using FASTlab phosphate cassettes. Ann Nucl Med 2016; 30(8): 563-571. https://doi.org/10.1007/s12149-016-1097-4
4. Jacobson MS, Dankwart HR, Mahoney DW. Radiolysis of 2-[18F] fluoro-2-deoxy-d-glucose ([18F]FDG) and the role of ethanol and radioactive concentration. Appl Radiat Isot 2009; 67(6): 990-995. https://doi.org/10.1016/j.apradiso.2009.01.005
5. Fawdry RM. Radiolysis of 2-[18F]fluoro-2-deoxy-D-glucose (FDG) and the role of reductant stabilisers. Appl Radiat Isot 2007; 65(11): 1193-201. https://doi.org/ 10.1016/j.ap.2007.05.011.
6. Walters LR, Martin KJ, Jacobson MS,. Stability evaluation of 18F-FDG at high radioactive concen-trations. J Nucl Med Technol 2012; 40(1): 52-56. https://doi.org/ 10.2967/jnmt.111.097287
7. Asti M, Grassi E, Sghedoni R, De Pietri G, Fioroni F, Versari A, Borasi G, Salvo D. Purification by ozonolysis of (18)O enriched water after cyclotron irradiation and the utilization of the purified water for the production of [18F]-FDG (2-deoxy-2-[18F]-fluoro-d-glucose). Appl Radiat Isot 2007; 65(7): 831-835. https://doi.org/ 10.1016/j.apradiso.2007.03.003.
8. Kim ST, Kim J, Park JM. Radiation dose assesment for radiation workers during 18F-FDG synthesis and dispensing activities in hot cells: a proposal to improve the safety of radiation protection measures for workers. Int J Radiat Res 2019; 17(4): 587-593. https://doi: 10.18869/acadpub.ijrr.17.3.587
9. Thompson S, Kilbourn MR, Scott PJ. Radiochemistry, PET imaging, and the internet of chemical things. ACS central science. 2016; 2(8): 497-505. https://doi.org/10.1021/acscentsci. 6b00178
10. Arayne MS, Sultana N, Sajid SS, Ali SS. Cleaning validation of ofloxacin on pharmaceutical manufacturing equipment and validation of desired HPLC method. PDA J Pharm Sci Technol 2008; 62(5): 353-361.
11. Hamacher K, Coenen HH, Stöcklin G. Efficient stereospecific synthesis of no-carrier-added 2-[18F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. J Nucl Med 1986; 27(2): 235-238.

12. Ito S, Sakane H, Deji S, Saze T, Nishizawa K. Radioactive byproducts in [18O]H2O used to produce18F for [18F]FDG synthesis. App Radiat and Isot 2006; 64(1): 298-305. https://doi.org/10.1016/j.apradiso.2005.10.001
13. Liu S, Nie D, Jiang S, Tang G . Efficient automated synthesis of 2-(5-[18F]fluoropentyl)-2-methylmalonicacid ([18F]ML-10) on a commercial available [18F]FDG synthesis module. App Radiat Isot 2017; 123(1): 49-53.
14. Uddin J, Rahman MM, Cho Y-H, Yoon C-S, ln W-J, Park J-B. Evaluation of [18F]FDG Synthesis and Quality Control: Experience in the Seoul National University Hospital (SNUH), Seoul, South Korea. OMICS J Radiol 2021; 10(9): 1-6.
15. Yu S. Review of F-FDG Synthesis and Quality Control. Biomed Imag Interv J 2006; 2(4): e57. https://doi.org/10.2349/biij.2.4.
16. Gallagher BM, Fowler JS, Gutterson NI, MacGregor RR, Wan CN, Wolf AP. Metabolic trapping as a principle of oradiopharmaceutical design: some factors resposible for the biodistribution of [18F] 2-deoxy-2-fluoro-D-glucose. J Nucl Med 1978; 19(10): 1154-1161.
17. Ashtari P. Introducing a novel FDG syhthesis method in Iran based on alkaline hydrolysis. Radiat Phys Eng 2020; 1(1): 7-11. . https://doi.org/10.22034/RPE.2020.57883
18. Chiu C-H, Huang Y-Y, Tsai C-L, Chou T-K, Lo C-H, Tsai K-L, et al. Performance analysis and operational experience of [18 F] FDG production with cassette-type modules in four hospitals of Taiwan. J Radioanalyt Nucl Chem 2020; 326(1): 25-32. http://dx.doi.org/10.1007/s10967-020-07348-6

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