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Research Article

Automated Synthesis of ^{11}C-B-CFT using the CFN-MPS200 Module and its Application in Intracranial PET/MR Imaging of Parkinson's Disease Patients

Zihao Yang, Leilei Yuan, Zhen Qiao, Shu Zhang, Yongzhong Zhang and Lin Ai*

Department of Nuclear Medicine, Beijing Tian tan Hospital, Capital Medical University, China

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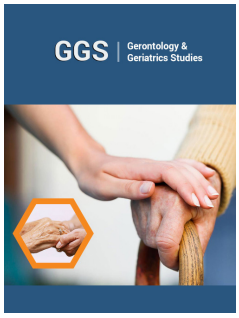

***Corresponding author:** Lin Ai, Department of Nuclear Medicine, Beijing Tian tan Hospital, Capital Medical University, China

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Abstract

Objective: This study aimed to synthesize ^{11}C-methyl-N-2β-methylester-3β-(4-fluoropheny1) nitrilimine (^{11}C-β-CFT) using the CFN-MPS200 automated synthesis module, perform rigorous quality evaluations and subsequently conduct intracranial PET/MR imaging in patients diagnosed with Parkinson's Disease (PD) following intravenous administration of the radiotracer.

Methods: The precursor, 2β-methyl ester-3β-(4-fluoropheny1) desmethy1nortilidine, was utilized for the synthesis of ^{11}C-β-CFT in a solvent-free environment using the Sumitomo CFN-MPS200 automated synthesis module. Comprehensive quality control measures were implemented, including radioactive high-performance liquid chromatography (Radio-HPLC), radioactive thin-layer chromatography (Radio-TLC) and endotoxin testing. Following intravenous administration of the synthesized compound, PET/MR imaging was performed on PD patients.

Results: The automated synthesis of ^{11}C-β-CFT via the CFN-MPS200 module was completed in approximately 15±2 minutes, yielding a decay-corrected production rate of (34±5)% (n=50). The radiochemical purity exceeded 90% and the radioactive concentration was approximately 850±80MBq/mL. The final product is presented as a colorless, transparent solution with a pH ranging from 7.0to8.0PET/MR imaging, conducted 40 to 50 minutes post-injection of ^{11}C-β-CFT in PD patients, demonstrated symmetrical distribution in the bilateral caudate nucleus, putamen and globus pallidus in healthy controls, whereas diminished uptake was observed in these regions among PD patients.

Conclusion: The synthesis protocol for ^{11}C-β-CFT using the CFN-MPS200 multifunctional synthesis module exhibits commendable stability and high yield, with all quality control and toxicity assessment parameters conforming to the standards set forth in the Chinese Pharmacopoeia. These findings confirm that the developed methodology can produce formulations that fulfill the requirements for both research and clinical applications, thereby establishing a foundation for future PET/MR imaging studies in PD

Keywords: Parkinson's disease (PD); PET/MR Imaging agent; ^{11}C-β-CFT; Automated synthesis

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system, characterized by the degeneration of dopaminergic neurons in the substantia nigra and resultant dopamine deficiency in the striatum, with a prevalence reaching up to 3.3% among the elderly population [1]. Numerous studies have established a significant association between PD and dysregulation of the dopamine (DA) system. The dopamine transporter (DAT) functions as a highly sensitive biomarker for assessing alterations in presynaptic dopaminergic neuronal activity [2,3]. DAT, a monoamine-specific transporter situated in the presynaptic membrane of dopaminergic nerve terminals, facilitates the reuptake of dopamine from the synaptic cleft into the presynaptic neuron. Therefore, DAT is a critical modulator of dopamine homeostasis in the brain and has been identified as the most sensitive molecular biomarker for PD [4]. Positron Emission Tomography (PET) has emerged as a critical modality in the molecular imaging of Parkinson's Disease (PD). Among the most extensively investigated dopamine transporter

(DAT) radioligands are the cocaine derivatives N-2β-methylester-3β-(4-fluoropheny1) nitrilimine (β-CFT) and N-2β-methylester-3β-(4-iodopheny1) nitrilimine (β-CIT), both of which exhibit high affinity for DAT [5-7]. Although β-CIT demonstrates superior affinity for DAT, it also binds comparably to other receptors, including serotonin and adrenergic receptors. This results in a diminished striatal-to-background count ratio shortly after administration, producing suboptimal signal-to-noise characteristics. In contrast, while β-CFT has a lower affinity for DAT relative to β-CIT, it exhibits significantly reduced binding to serotonin and norepinephrine receptors. Moreover, β-CFT is characterized by its in vitro stability, low toxicity and minimal risk to human health. It effectively crosses the blood-brain barrier, preferentially binds to presynaptic DAT and accumulates in the striatum, providing a favorable striatal-to-background ratio that facilitates clear imaging outcomes [8,9]. Consequently, upon labeling with the ^{11}C radionuclide, ^{11}C-β-CFT is considered to have considerable clinical application potential. To enhance clinical research in the molecular imaging of Parkinson's Disease (PD), this study focuses on the automated synthesis process of the molecular probe ^{11}C-β-CFT. We developed a disposable tubing system and a corresponding procedural workflow optimized for the CFN-MPS200 automated synthesis module, enabling the stable and efficient production of ^{11}C-β-CFT formulations. In alignment with the standards specified in the Chinese Pharmacopoeia (2020 edition), we established rigorous quality control parameters and testing methodologies for the CFN-MPS200 injection. Building upon this foundation, we conducted clinical trials utilizing PET/MR imaging. The results of this research provide substantial support for the clinical diagnosis and therapeutic application of ^{11}C-β-CFT in patients with PD.

Materials

Reagents

The precursor was sourced from Jiangsu Huayi Technology Co., Ltd., with a chromatographic purity exceeding 99%. Hydrogen iodide (57%) was obtained from Beijing Bailingwei Technology Co., Ltd. Acetone was purchased from China National Pharmaceutical Group Chemical Reagents Co., Ltd. Sterile water for injection and saline were acquired from China Resources Double Crane Pharmaceutical Co., Ltd. Disposable tubing assembly components were supplied by Sumitomo Corporation, Japan. Solid-phase extraction columns were procured from Waters Corporation, USA. Sterile filter membranes were obtained from Merck Millipore, USA. Bacterial endotoxin detection cards (sensitivity range 5-0.05EU/mL) were obtained from Charles River Laboratories, while additional reagents were sourced from Sigma-Aldrich, USA.

Instruments

The HM10 accelerator was provided by Sumitomo Corporation, Japan. The Jasco PU-2086 Plus semi-preparative High-Performance Liquid Chromatography (HPLC) system was acquired from Jasco Co., Japan. The LC-15C analytical HPLC system was purchased from Shimadzu Corporation, Japan. The CFN-MPS200 automated synthesis module was supplied by Sumitomo Corporation, Japan. The HRS2015 Radio-TLC system was sourced from BIOSCAN, USA. The GE Discovery 750w PET/MR system was provided by General Electric, USA. Gas chromatography was performed using an Agilent 7890 system, equipped with a Restek gas chromatography column (0.53mm inner diameter, 1μm polyvinyl alcohol coating) and a hydrogen flame detector. A pH meter of the Onion model from Fisher Scientific, equipped with a microprobe, was utilized. The PTS Endotoxin instrument was obtained from Charles River Laboratories, USA. The CRC-25R radioactivity calibrator was sourced from CAPINTEC, Inc., USA.

Experimental animals

Kunming mice were procured from Xinglong Experimental Animal Breeding Farm in Haidian District, Beijing, comprising five male mice with weights ranging from 19.0 to 22.3g. The animal studies received ethical approval from the Ethics Committee of Beijing Tiantan Hospital.

Patient demographics

This study included five patients diagnosed with mild PD and five healthy volunteers treated at our hospital from January 2023 to June 2024. The cohort consisted of five males and five females, with ages ranging from 52 to 69 years (mean age 60.60 ± 8.54). Inclusion criteria for the PD group encompassed clinically confirmed PD patients who underwent routine neurological assessments. The healthy volunteer group included individuals who received health check-ups at our hospital during the same timeframe. Exclusion criteria encompassed Parkinson's syndrome, Parkinson's disease overlap syndrome, other neurological or psychiatric disorders, severe cardiac, hepatic, renal, or endocrine conditions and a history of sedative or hypnotic medication use. All human imaging studies conducted in this research were approved by the Ethics Committee of Capital Medical University-affiliated Beijing Tiantan Hospital and informed consent was obtained from all participants.

Methods

Radiochemical synthesis route of ^{11}C-β-CFT (Figures 1&2).

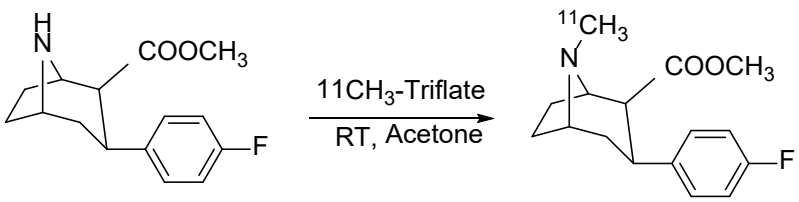

Figure 1: Chemical synthesis route of ^{11}C-β-CFT.

Figure 2: Schematic diagram of the CFN-MPS200 Automated Synthesis Module Program.

Automated synthesis of ^{11}C-β-CFT

The configuration of the disposable tubing utilized for the synthesis of ^{11}C-β-CFT is illustrated in (Figure 3). Initially, 0.5to0.6mL of 57% hydrogen iodide was introduced into vial 1. Both vial 2 and vial 3 contained 8 mL of sterile water for injection, while Vial 4 was filled with 24mL of sterile water for injection. Additionally, 0.4to0.5mL of a lithium aluminum hydride ($LiA1H_4$) solution in tetrahydrofuran (THF) was added to reaction vessel 1(RV1) and 0.2mL of an acetone solution containing 0.33mg of the precursor nor-β-CFT was introduced into reaction vessel 2(RV2).

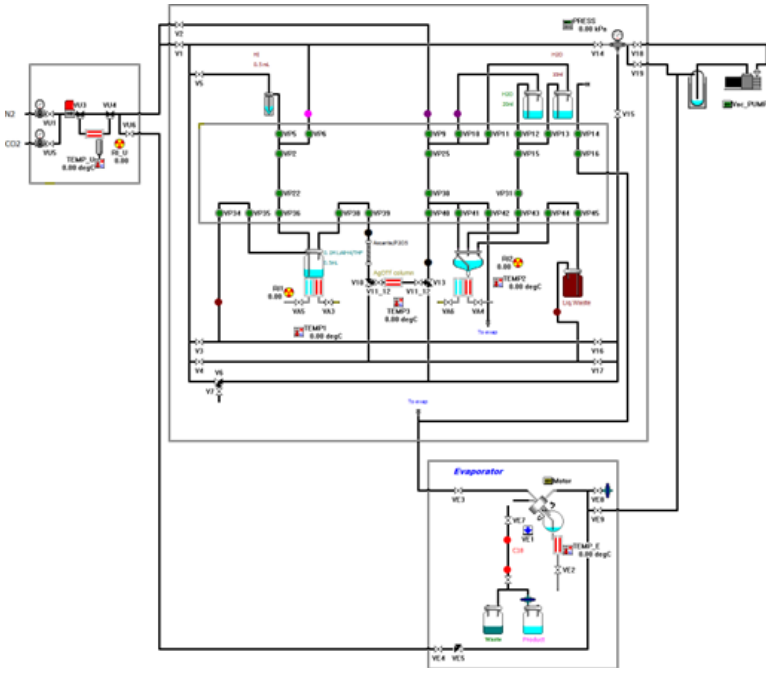

Figure 3: Schematic of the disposable tubing structure and reagent loading for the automated synthesis of ^{11}C-β-CFT using the CFN-MPS200 module.

The automated synthesis program commenced with the operation of the Sumitomo HM-10 cyclotron, wherein a nitrogen-oxygen mixed gas target was subjected to a proton beam of 45μA and 10MeV for 35 minutes. This process facilitated the generation of ^{11}C-CO_2 through the 14N(p,α)^{11}C nuclear reaction. Subsequently, the ^{11}C-CO_2 was transferred via an automated target transfer system to RV1, which contained 0.4to0.5mL of a $LiA1H_4$/THF solution. During this phase, ^{11}C-CO_2 was reduced to ^{11}C-CH_3OH. The heating valve of the module was then activated to gradually evaporate the THF solvent from the reaction vessel. Following complete evaporation, the high-speed air valve was employed to cool RV1 to room temperature.

Next, hydrogen iodide was introduced to react with ^{11}C-CH_3OH, producing ^{11}C-CH_3I. The reaction vessel RV1 was heated to facilitate the volatilization of ^{11}C-CH_3I, which was subsequently directed through a Triflate-Ag column located at position 5, resulting in the formation of ^{11}C-CH_3-Triflate gas. This gas was then conveyed into RV2 under a nitrogen carrier flow, where it reacted with the precursor nor-β-CFT in an acetone solution at ambient temperature for 225 seconds. The reaction was terminated by the addition of 8mL of sterile water from vial 2 into RV2, after which all liquid from RV2 was transferred to vial 4 and captured on two serially connected C18 columns using nitrogen flow. The remaining waste liquid was collected in a waste bottle and the C18 column was subsequently rinsed with 8mL of sterile water from vial 3 to eliminate impurities. The product was then eluted from the C18 column with 1.5mL of anhydrous ethanol into a transfer vial, followed by dilution with 20mL of saline. Finally, the product was filtered through a sterile membrane and transferred to a product vial for future use.

Quality control analysis of ^{11}C-β-CFT injection

The quality control standards for ^{11}C-β-CFT injection were established based on relevant regulations from the Pharmacopoeia of the People's Republic of China (2020 edition) and existing approved formulations, as detailed in Table 1. Following the synthesis, the 0.22μm sterile filter used in production was first rinsed with sterile water. The integrity of the filter was assessed using a bubble point test. Subsequently, 2mL of the formulation solution was extracted from the product vial for quality control analysis. One milliliter of the quality control sample was placed into a sterile vial for sterility testing after decay. The remaining 1mL was transferred into a sterile test tube for additional quality control assessments. The appearance was visually inspected under bright lighting through lead glass. A 20μL aliquot of the sample was diluted 50-fold with endotoxin detection water for endotoxin testing. Five hundred microliters of the sample were measured for radioactive concentration and half-life using a radioactivity counter. A 100μL aliquot was diluted 50-fold with chromatographic-grade water for gas chromatography analysis to detect residual solvents (chromatographic conditions: column temperature 200 °C, injector temperature following column temperature, detector temperature 240 °C, hydrogen flow rate 30mL/min, injection volume 1μL). The pH was measured using a pH meter on a 100μL aliquot. For HPLC analysis, a 20μL aliquot was diluted with a mobile phase of 0.05mol/LNaH2PO4: Acetonitrile (8:2v/v) at a flow rate of 1mL/min, with detection at 207nm, to determine radiochemical identification, radiochemical purity, chemical impurities and the content of ^{11}C-β-CFT, including CH_3-Triflate. The retention time for ^{11}C-β-CFT was referenced at 5.7min, with a corresponding reference compound retention time of 2.9min. Additionally, 20μL of the sample was analyzed by Radio-TLC for radiochemical identification, radiochemical purity, chemical impurities and quantification of ^{11}C-β-CFT, ensuring that the radioactive purity of the product was not less than 90%.

Table 1: ^{11}C-β-CFT injection quality control standards and methods.

Quality Control	Specification	Batch 1	Batch 2	Batch 3
Filter integrity	NLT 50psi	52.46 si	52.07	55.32
Appearance	Clear, faint yellow, free of visible particulate	Pass	Pass	Pass
Half-life	19.2-20.8 min	20.1min	20.4min	19.8min
Radionuclide purity	(511±51) keV	Pass	Pass	Pass
pH	6.9-7.6	7	7.1	7.4
Radiochemical identity	The relative retention time 1.0±0.1	1.03	1.04	1.02
Radiochemical purity	NLT90%	94.32%	92.58%	93.45%
Chemical impurities	NLT 0.5μg.mL-1	0.13μg·mL-1	0.13μg·mL-1	0.13μg·mL=1
Ethanol content	(10±2)% V/V	10	11	10
Eesidual solvent	Acetone NMT 0.041% THF NMT 0.002%	Acetone0.0113%	Acetone0.0124%	Acetone0.0111%
		THF No detected	THF No detected	THF No detected
Endotoxin	NMT 10.0 EU.mL	<2.5EU·mL-1	<2.5EU·mL-1	<2.5EU·mL-1
Sterility	Sterile	Pass (no growth)	Pass (no growth)	Pass (no growth)

Note: *Below the quantitation limit of HPLC detection method 0.08μg·mL-1.

Notes: *Less than the limit of quantitation 0.08μg·mL-1 of the HPLC inspection method. NLT: no less than, NMT: no more than.

Assessment of abnormal toxicity in ^{11}C-β-CFT injection

In compliance with the 2020 edition of the Pharmacopoeia of the People's Republic of China, General Chapter 1141 regarding "Abnormal Toxicity Testing," we conducted an evaluation of the abnormal toxicity of the ^{11}C-β-CFT injection synthesized by the described methodology. The results indicated that all five mice administered the injection survived without exhibiting any abnormal clinical signs over a 7-day observation period. Necropsy findings revealed no significant pathological alterations in the organs of the tested mice. These results substantiate that the production process for the ^{11}C-β-CFT injection did not introduce any exogenous toxic substances or safety concerns.

^{11}C-β-CFT in intracranial PET/MR imaging of PD patients

A total of five patients with mild Parkinson's Disease (PD) and five healthy volunteers were recruited from our hospital between March 2023 and March 2024. Inclusion criteria for the PD group comprised clinically diagnosed PD patients who had undergone routine neurological examinations. The inclusion criteria for the control group involved individuals undergoing health screenings at the same institution during the study period. Exclusion criteria included Parkinson's syndrome, Parkinson's disease overlap syndrome, other neurological or psychiatric disorders, significant cardiovascular, hepatic, renal, or endocrine diseases and a history of sedative or hypnotic medication use. All human and animal

imaging experiments were reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University and informed consent was obtained from all participants prior to the clinical trials.

Imaging methodology: Participants underwent PET/MR brain imaging in the Nuclear Medicine Department of Beijing Tiantan Hospital. The method for acquiring ^{11}C-β-CFT brain images involved intravenous injection of ^{11}C-β-CFT (dosage of 0.15-0.2mCi/kg, with a maximum of 15mCi per patient) via the antecubital vein. Following a resting period of 40-50 minutes in a quiet, dark environment, imaging was conducted for a duration of 10 minutes. During the PET imaging, MRI sequences were acquired simultaneously, including: (1) 3D BRAVO T1-weighted imaging (T1WI) with TE=3.0ms, TR=7.9ms and a slice thickness of 1mm; (2) T2-weighted imaging (T2WI) with TE=140ms, TR=6000ms and a slice thickness of 5mm; (3) T2 FLAIR imaging with T1 =2500ms, TE = 115ms, TR = 6500ms and a slice thickness of 1mm, with a matrix size of 256×256 and FOV = 24cm; (4) Diffusion-Weighted Imaging (DWI) with TE=70ms, TR=5800ms, b=1000 and a slice thickness of 5mm; (5) 3D Arterial Spin Labeling (3D-ASL) with TE=10.71ms, TR=4876ms, PLD=2.0 and a matrix size of 256×256 with FOV=24cm. Following data acquisition, images were transmitted to the AW Volume Share 4 workstation for reconstruction and data analysis.

Image interpretation: PET/MR imaging with ^{11}C-β-CFT was performed on both the control and PD groups. Results indicated a reduced asymmetric uptake of the radiotracer in the bilateral striatum of PD patients, whereas the control group exhibited normal tracer uptake without significant reductions, demonstrating clear imaging.

Result and Discussion

Automated synthesis of ^{11}C-β-CFT

Imaging studies of brain structure and function hold significant value in the clinical diagnosis of Parkinson's Disease (PD) and related movement disorders. The widespread availability of Positron Emission Tomography (PET) has established neuro-molecular imaging as an essential routine technique for diagnosing and differentiating PD and associated movement disorders [10]. While conventional brain MRI and CT scans lack specificity in diagnosing PD, functional MRI is also not suitable as a clinical diagnostic tool for PD [11-13]. In contrast, ^{11}C-β-CFT, a cocaine derivative, exhibits high affinity and can reflect the functional status of dopaminergic neurons in the nigrostriatal pathway, making it a specific imaging agent for PD diagnosis [14]. The development of high-quality imaging agents is crucial for PET research. This study focuses on the synthesis of ^{11}C-β-CFT, which possesses favorable biological properties. Utilizing the CFN-MPS200 synthesis module, we conducted the preparation of this imaging agent. With the disposable tubing system and workflow developed in this study, the total preparation time for ^{11}C-β-CFT injection was 15-18 minutes (n=50). The reaction time of ^{11}C-CO_2 with LiA1H4 was approximately 2 minutes, the addition of hydrogen iodide took 5 seconds and the synthesis of ^{11}CH3-Triflate lasted 226 seconds. The reaction time between $^{11}CH_3$-Triflate and the precursor was 2 minutes, yielding ^{11}C-β-CFT with a radiochemical yield of (32±5) % (decay-corrected n = 50).

In 1992, the research group led by Robert F Dannals [15] first reported the synthesis of ^{11}C-β-CFT using ^{11}C-CH_3 as an intermediate, with an average synthesis duration of 21 minutes; however, this method was manually conducted and yielded a relatively low average radiochemical yield of 20.6% (uncorrected for decay). In 2005, the Zhang Jinming group utilized the Beijing PET Multifunctional Synthesis Module, replacing ^{11}C-CH_3 with $^{11}CH_3$-Triflate, which improved both the yield and radiochemical purity of the product while enhancing its chemical purity. The Tang Ganghua group validated the feasibility of using HBr as a reactant with the same module in 2011, noting that although the reaction proceeded normally, the yield was approximately halved [16]. In 2018, the Yang Nengan group synthesized ^{11}C-β-CFT using the GE Tracerlab FX2-C multifunctional module, obtaining a low yield of only 10% (uncorrected for decay), with a lengthy synthesis time of 40 minutes [17]. In 2010, the Wang Xiaoming group automated the online synthesis of ^{11}C-β-CFT using the GE Tracerlab Fx-pro module, conducting dynamic PET/CT imaging on three normal neonatal pig brains. Notably, this automated process involved the use of dimethyl sulfoxide (DMSO), which is challenging to remove during later drug purification stages and is unsuitable for direct injection into humans, thus limiting its clinical application [18]. The synthesis procedure and yield of ^{11}C-β-CFT using the disposable tubing system in this study are comparable to those reported in the literature.

quality control analysis of ^{11}C-β-CFT injection

The production process of the ^{11}C-β-CFT injection was validated through the continuous production of three batches, all of which met the quality control analysis criteria, as detailed in Table 1. Stability studies demonstrated that when the product solutions from the three validation batches were stored at room temperature for 1 hour prior to a second quality assessment, there were no significant changes in the radiochemical purity or the levels of chemical impurities. This indicates that the ^{11}C-β-CFT injection exhibits good stability when maintained at room temperature for up to 2 hours. Following the completion of process validation, a total of 50 batches of the ^{11}C-β-CFT injection were conducted, with all quality control analysis results confirming compliance [19-21]. Therefore, the ^{11}C-β-CFT formulations produced using the disposable tubing system and its associated protocols are deemed suitable for clinical imaging studies and applications (Figure 4a,4b).

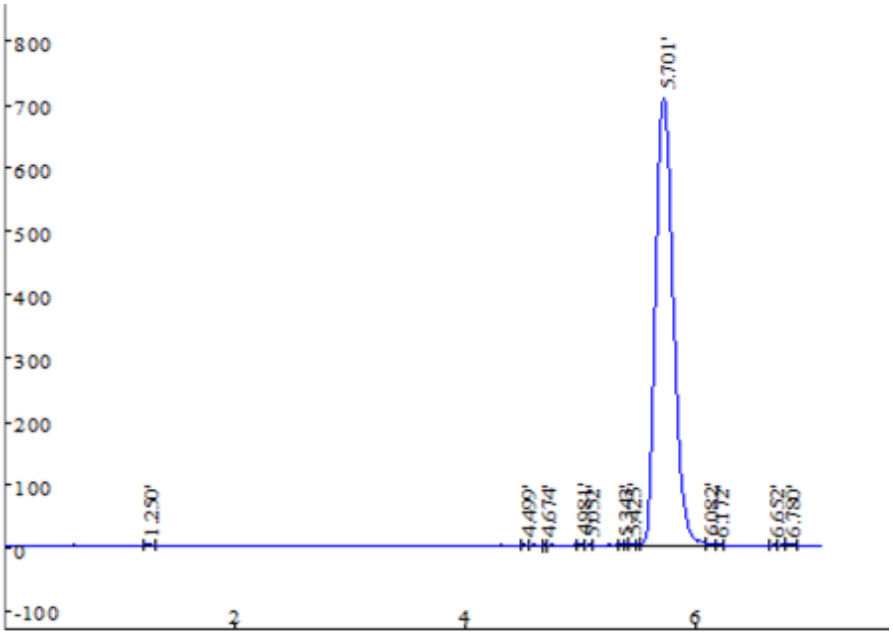

Figure 4a: HPLC radiochemical chromatogram for the quality control analysis of the 11C-β-CFT injectable formulation, exhibiting a retention time of 5.701min.

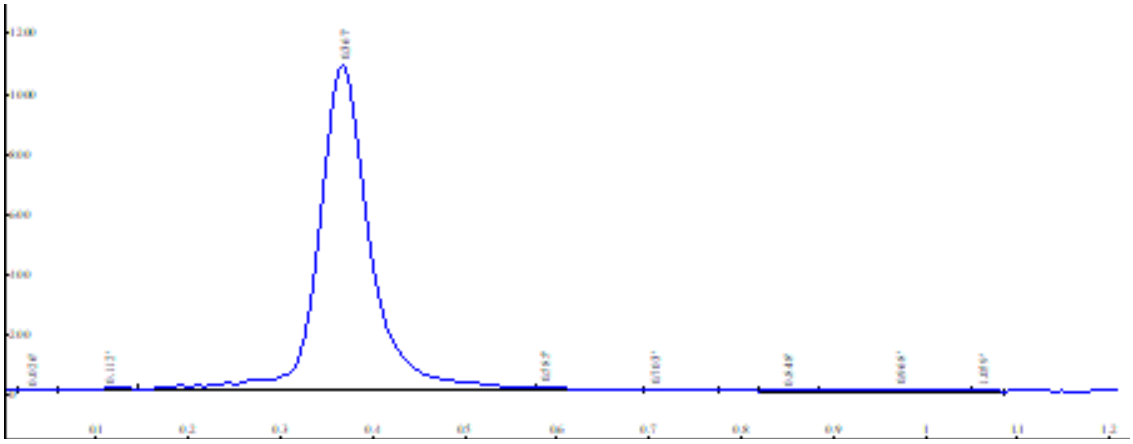

Figure 4b: TLC radiochemical chromatogram for the quality control analysis of the 11C-β-CFT injectable formulation, demonstrating a retention time of 0.367min.

Evaluation of abnormal toxicity of ^{11}C-β-CFT injection

Following the guidelines outlined in the 2020 edition of the Chinese Pharmacopoeia, specifically General Rule 1141 for "Abnormal Toxicity Testing," we assessed the abnormal toxicity of the ^{11}C-β-CFT injection produced using the described methodology. The results indicated that all five mice administered the injection survived for seven days without exhibiting any abnormal clinical signs. Necropsy findings revealed no significant alterations in the organs of the test subjects. These findings substantiate that the production process of the ^{11}C-β-CFT injection did not introduce any exogenous toxic substances or safety concerns [22].

Intra-cranial PET/MR imaging of ^{11}C-β-CFT in parkinson's disease patients

PET/MR imaging utilizing ^{11}C-β-CFT was conducted in both normal volunteers and patients diagnosed with Parkinson's Disease (PD) [23]. The PET imaging results demonstrated a marked reduction in radiotracer uptake within the bilateral striatum of PD patients, indicative of an asymmetric distribution of the tracer. Conversely, the normal control subjects exhibited no significant decrease in radiotracer uptake in the bilateral striatum, resulting in clear and well-defined imaging outcomes (Figures 5 & 6).

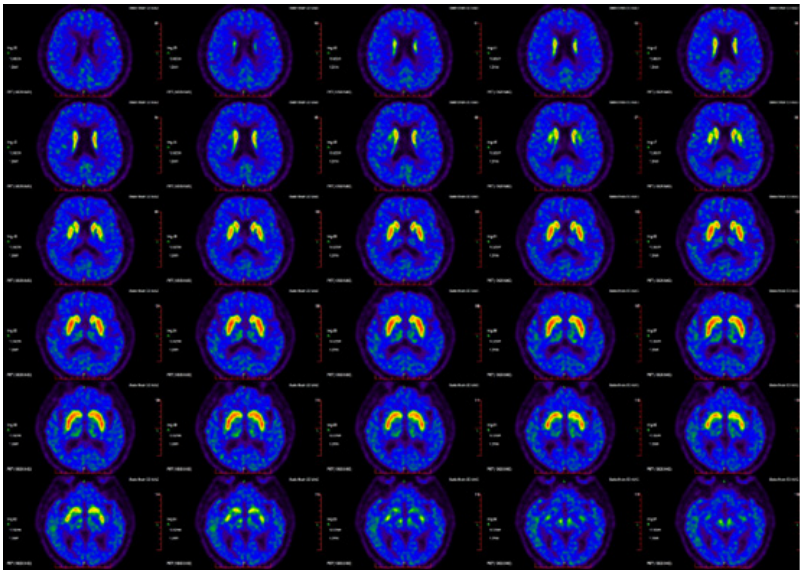

Figure 5: A healthy male subject, aged 55 years, demonstrated a symmetrical distribution of 11C-β-CFT in the bilateral caudate nucleus, putamen and globus pallidus.

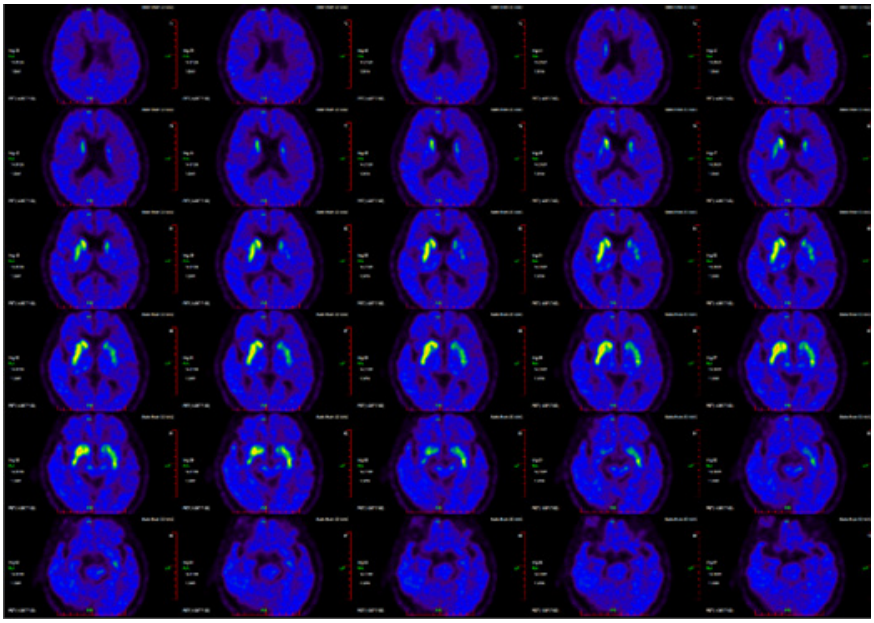

Figure 6: A 61-year-old male patient with a one-year history of Parkinson's disease demonstrated a significant reduction in ^{11}C-β-CFT uptake in the bilateral globus pallidus, with the most marked decrease observed in the left globus pallidus, corresponding to the side of clinical onset.

Conclusion

This study developed a disposable tubing system and corresponding control protocols for the CFN-MPS200 synthesis module, enabling the automated production of the DAT imaging agent, ^{11}C-β-CFT. Quality standards and testing methods for the ^{11}C-β-CFT formulation were established in accordance with the relevant guidelines outlined in the 2020 edition of the Chinese Pharmacopoeia, as well as for other positron-emitting radiopharmaceuticals. The results from 50 production batches confirmed that formulations produced using the disposable tubing system can meet the established quality criteria. Toxicity screening indicated that the production process for the ^{11}C-β-CFT injection did not introduce any unsafe contaminants. PET imaging studies involving healthy volunteers and patients with Parkinson's Disease (PD) demonstrated that the ^{11}C-β-CFT injection prepared in this study is suitable for intracranial PET/MR imaging in PD patients. Utilizing the CFN-MPS200 multifunctional synthesis module allows for rapid and stable production of [^1C]-β-CFT, resulting in a high radiochemical purity. The imaging obtained from PD patients exhibited a favorable signal-to-noise ratio, facilitating effective differentiation between normal tissue and pathological areas.

Acknowledgment

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References

1. Ruppert MC, Greuel A, Tahmasian M (2020) Network degeneration in Parkinson's disease: Multimodal imaging of nigro-striato-cortical dysfunction. Brain 143(3): 944-959.
2. Tarakad A, Jankovic J (2017) Diagnosis and management of Parkinson's disease. Semin Neurol 37(2): 118-126.
3. Lin W, Zuo CT, Wu JJ (2022) Striatal asymmetry index and its correlation with the Hoehn & Yahr stage in Parkinson's disease. Int J Neurosci 132(2): 165-170.
4. Pagano G, Niccolini F, Politis M (2016) Imaging in Parkinson's disease. Clin Med 16(4): 371-375.
5. Mackie P, Lebowitz J, Saadatpour L (2018) The dopamine transporter: An unrecognized nexus for dysfunctional peripheral immunity and signaling in Parkinson's disease. Brain Behav Immun 70: 21-35.
6. Palermo G, Ceravolo R (2019) Molecular imaging of the dopamine transporter. Cells 8(8): 872.
7. Mehta SH, Adler CH (2016) Advances in biomarker research in Parkinson's disease. Curr Neurol Neurosci Rep 16(1): 7.
8. Mehta MA, Montgomery AJ, Kitamura Y (2008) Dopamine D2 receptor occupancy levels of acute sulpiride challenges that produce working memory and learning impairments in healthy volunteers. Psychopharmacology (Bed) 196(1): 157-165.
9. Neumeyer JL, Tamagnan G, Wang S (1996) N-substituted analogs of 2 beta-carbomethoxy-3 beta-(4'-iodophenyl) tropane(beta-CIT) with selective affinity to dopamine or serotonin transporters in rat forebrain. J Med Chem 39(2): 543-548.
10. Booth S, Park KW, Lee CS (2022) Predicting cognitive decline in Parkinson's disease using FDG-PET-based supervised learning. The Journal of clinical investigation 132(20): e157074.
11. Lee JY, Jeon BS, Paek SH (2010) Reprogramming guided by the fused images of MRI and CT in subthalamic nucleus stimulation in Parkinson disease. Clinical Neurology & Neurosurgery 112(1): 47-53.
12. Tuite PJ, Mangia S, Michaeli S (2013) Magnetic Resonance Imaging (MRI) in parkinson's disease. Therapeutic Advances in Neurological Disorders Suppl 1: 001.
13. Saleh S, Swanson KI, Lake WB (2015) Awake neurophysiologically guided versus asleep MRI-guided STN DBS for parkinson disease: A comparison of outcomes using levodopa equivalents. Stereotact Funct Neurosurg 93(6): 419-26.
14. Sun X, Tan X, Zhang Q (2024) ^{11}C-CFT PET brain imaging in parkinson's disease using a total-body PET/CT scanner. EJNMMI Physics 11(1): 40.
15. Dannals RF, Neumeyer JL, Milius RA (1993) Synthesis of a radiotracer for studying dopamine uptake sites in vivo using PET: 2β-carbomethoxy-3β-(4-fluorophenyl)-[N-11C-methyl] tropane ([11C] CFT or [11C] WIN-35,428). Journal of Labelled Compounds and Radiopharmaceuticals 33(2): 147-152.
16. Tang G, Tang X, Deng H, (2011) Efficient preparation of [11C]CH_3Br for the labeling of [11C]CH_3-containing tracers in positron emission tomography clinical practice. Nuclear Medicine Communications 32(6): 466-474.
17. Zhang YF, Wang XM, Cao L (2010) Automatic preparation of dopamine transporter imaging agent ^{11}C-β-CFT and its application in PET/CT brain imaging of newborn piglets. Chinese Journal of Medical Imaging Technology 26(8): 1409-1412.
18. Zhang YF, Wang XY, Cao L (2011) Effects of hypoxic-ischemic brain injury on striatal dopamine transporter in newborn piglets: evaluation of ^{11}C-CFT PET/CT for DAT quantification. Nuclear Medicine & Biology 38(8): 1205-1212.
19. Ouchi Y, Etuji Yoshikawa BA, Hiroyuki Okada BA (2010) Alterations in binding site density of dopamine transporter in the striatum, orbitofrontal cortex and amygdala in early Parkinson's disease: compartment analysis for beta-CFT binding with positron emission tomography. Annals of Neurology 45(5): 601-610.
20. Jinju S, Chao C, Xin peng, Li Weicheng, Zhou Renxiang, et al. (2024) Identification of Parkinson's disease and multiple system atrophy using multimodal PET/MRI radiomics. European Radiology 34(1): 662-672.
21. Xu J, Xu Q, Liu S (2022) Computer-aided classification framework of parkinsonian disorders using ^{11}C-CFT pet imaging. Frontiers in Aging Neuroscience 13.
22. Xin M, Wang Y, Yang X (2024) Exploring the nigrostriatal and digestive interplays in Parkinson's disease using dynamic total-body [^{11}C]CFT PET/CT. European Journal of Nuclear Medicine and Molecular Imaging 51(8): 2271-2282.
23. Sun X, Tan X, Zhang Q (2024) ^{11}C-CFT PET brain imaging in parkinson's disease using a total-body PET/CT scanner. EJNMMI Physics 11: 40.

