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Single vial kit formulation for preparation of PET radiopharmaceutical: ^{68}Ga-DOTA-TOC

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Abstract This paper describes the development of a lyophilized cold kit of DOTA-[Tyr^3]-Octreotide (DOTA-TOC) for instant compounding of ^{68}Ga-DOTA-TOC, suitable for diagnosis of neuroendocrine tumors. The work involved formulation of DOTA-TOC kits, optimization of radiolabeling, quality control of ^{68}Ga-DOTA-TOC and animal biodistribution studies. The prepared kits enable a reliable method for preparation of ^{68}Ga-DOTA-TOC of high radiochemical purity and excellent stability. Availability of such kits along with ^{68}Ge/^{68}Ga generators is expected to stimulate the widespread use of ^{68}Ga-DOTA-TOC in nuclear medicine practice in developing countries.

Keywords ^{68}Ge/^{68}Ga generator · ^{68}Ga-DOTA-[Tyr^3]-octreotide · Lyophilized cold kit · PET imaging

Introduction

In recent years, receptor-avid peptides labeled with positron-emitting radionuclides for use in positron emission tomography (PET) imaging have gained significant attention owing to their ability to provide quantitative information about biological processes in vivo [1–6]. Amongst the positron-emitters for radiolabeling of peptides, ^{68}Ga has drawn widespread attention due to its favorable nuclear characteristics ($t_{½}$ = 67.71 min, 89 % β^+, 1.92 MeV max energy), convenient labeling chemistry and availability from ^{68}Ge/^{68}Ga generator system eliminating the need for an onsite cyclotron. There appears to be significant interest in the use of ^{68}Ge/^{68}Ga generator by virtue of its long shelf life (up to 1 year) and the capability to provide ^{68}Ga in the most convenient manner. The 67.71 min half-life of ^{68}Ga is not only compatible with the pharmacokinetics of small tumor-affine peptides but also provides the scope of multiple daily elutions from the generator for preparation of multiple patient doses.

The success of ^{68}Ga radiopharmacy lies in the availability of an efficient ^{68}Ge/^{68}Ga generator capable of providing ^{68}Ga (III) of requisite purity for preparing receptor-targeted peptide radiopharmaceuticals. Recognizing the exciting prospects of the ^{68}Ge/^{68}Ga generator and its potential role in expanding the scope of ^{68}Ga radiopharmaceuticals, significant amount of research has been carried out. These efforts have resulted in the commercial availability of a number of ^{68}Ge/^{68}Ga ionic generators [7–9]. Despite the impressive progress, the promise to perform straightforward radiolabeling of peptides using generator derived ^{68}Ga has not been fulfilled as the ^{68}Ga obtained from commercial generators is of low radioactive concentration, high acidity, unacceptable ^{68}Ge breakthrough and presence of non-radioactive metal ion impurities. Continuing research in this area has paved the way for the development of not only several post elution processing strategies for ^{68}Ga eluate but also automated ^{68}Ga radiolabeling systems for peptides, some of which have been commercialized [10, 11]. While this constitutes a step in the right direction, the high costs associated with the implementation of such strategy has emerged as the major roadblock limiting their widespread use in nuclear medicine practice.

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Rapid advancements in PET imaging using ^{68}Ga radiopharmaceuticals, with all the inherent imaging advantages compared to SPECT, has been largely due to the development of small tumor-affine peptides, most notably those targeting somatostatin receptors. The thoroughly investigated somatostatin analogues are those conjugated with DOTA (1, 4, 7, 10-tetraazacyclododecane-N, N′, N″, N‴ tetraacetic acid). ^{68}Ga-labeled DOTA conjugated somatostatin analogues such as DOTA-TOC, DOTA-NOC and DOTA-TATE are being used routinely in the clinic for diagnosing patients with NETs and are the most frequently used of all ^{68}Ga-labeled radiopharmaceuticals at present [12, 13]. It has been reported that PET imaging with ^{68}Ga-DOTA-TOC is superior to Octreoscan™ due to higher tumor to non-tumor ratios as well as lower renal uptake [13]. Current practices for formulation of ^{68}Ga-DOTA-TOC in hospitals rely mostly on magisterial preparation and compassionate use under the responsibility of prescribing physician. In view of this premise, development of a freeze dried kit formulation for the compounding of ^{68}Ga-DOTA-TOC in conjunction with a ^{68}Ge/^{68}Ga generator is not only an attempt to ensure its cost-effective availability, but may be viewed as a major step forward to promote its widespread use. In the quest for an effective ^{68}Ge/^{68}Ga generator for instant preparation of ^{68}Ga-DOTA-TOC using the formulated kits, we focused our attention on the in-house 'BARC ^{68}Ge/^{68}Ga Generator' based on nanoceria-polyacrylonitrile composite sorbent owing to its capability to provide ^{68}Ga of requisite quality without any post elution processing [14–16].

In this paper, we describe a pharmaceutical grade kit formulation of the somatostatin analogue DOTA-TOC for preparation of ^{68}Ga-DOTA-TOC using ^{68}Ga eluted from the 'BARC ^{68}Ge/^{68}Ga generator' and a detailed evaluation of the quality of kits for possible use in nuclear medicine routine.

Experimental

Materials and instruments

DOTA-TOC was procured from Ana Spec, USA. Common chemicals and reagents such as sodium acetate and suprapure HCl (30 %) were purchased from Fluka, USA and MERCK, Germany respectively. All reagents were prepared using sterile HPLC grade water (Merck, India). Himedia Laboratories, India supplied sterility test kits containing fluid thioglycollate media and soyabean casein media. Endosafe PTS equipment and cartridges (range of sensitivity: 0.5–0.05 EU/mL) were procured from Charles River Laboratories Pvt. Ltd, India. ITLC SG paper was purchased from Agilent technologies, USA while Whatman 3 mm chromatography strips were obtained from Whatman, UK.

A NaI (Tl) scintillation counter (ECIL, India) was used for radioactivity counting measurements. An HPLC system (JASCO, Japan) equipped with a C18 reversed phase column (HiQ Sil, 5 μm, 4 × 250 mm) connected to a UV/visible detector (JASCO, Japan) and a NaI (Tl) radioactivity detector (Raytest, Germany) was used for carrying out HPLC analyses. Lyophilization was carried out using Alpha 1–2 LD plus freeze dryer (Martin Christ, GmBH). 0.22 μ membrane filters (33 mm) were from M/s. Millipore Corporation, USA.

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

Gallium-68 used in this investigation was obtained from a 740 MBq (20 mCi) ^{68}Ge/^{68}Ga generator developed in-house using CeO_2-PAN composite sorbent as the column matrix. ^{68}Ga activity was eluted from the generator with 2 mL of 0.1 N HCl and directly used for radiolabeling [13, 14]. The levels of ^{68}Ge and trace metal contaminants present in the ^{68}Ga solution was estimated using reported procedures [14].

Kit formulation

Before finalizing the optimal buffer as well as the concentration of DOTA-TOC to be used in the final kit formulation, pre-formulation experiments were carried out which included optimization of radiolabeling with ^{68}Ga by varying the reaction conditions such as the amount of peptide, pH, duration of the reaction at 90 °C and the ^{68}Ga activity. Based on the results of the above experiments, stock solution of DOTA-TOC peptide in optimized volume of 0.5 M sodium acetate solution was filtered through 0.22 μ filter. Solution containing 50 μg of DOTA-TOC and 13 mg of 0.5 M sodium acetate was dispensed per vial in sterile glass vials, freeze dried and vacuum sealed under aseptic conditions. DOTA-TOC cold kits and ^{68}Ga-DOTA-TOC were tested for sterility as per Indian Pharmacopeia. The kit components were dissolved in sterile saline and incubated in soyabean casein digest medium at 20–25°C for 14 days and in fluid thioglycollate medium at 30–35°C for 14 days for determining the presence of microorganisms. BET tests were performed using Endosafe PTS system cartridges.

Radiolabeling

Preparation of patient doses of ^{68}Ga-DOTA-TOC involved radiolabeling of 50 μg peptide with $^{68}GaCl_3$ (92.5–148 MBq) from the in-house ^{68}Ge/^{68}Ga generator eluted directly into kit vial using 1 mL of sterile 0.1 N HCl. The reaction vial was incubated at 90 °C for 10 min followed by quality control.

After quality control, 20 μL of 10 mM EDTA was added to the reaction vial for complexing any free ^{68}Ga and facilitating its clearance via renal route by forming ^{68}Ga-EDTA. The preparation was finally sterilized by passing through 0.22 μ filter. The ^{68}Ga-DOTA-TOC complex was characterized by carrying out HPLC on a C18 reverse phase column using gradient elution of Solvent A: H_2O with 0.1 % TFA, Solvent B: acetonitrile (ACN) with 0.1 % TFA (Gradient: 0–4 min: 5 % B, 4–20 min: 5–95 % B, 20–30 min: 95–5 % B, radioactivity detector 400–600 keV). ITLC was carried out using two solvent systems namely 1 M ammonium acetate: methanol (1:1) and 0.1 M sodium citrate. Paper chromatography using 50 % aqueous acetonitrile as mobile phase was also carried out to estimate the radiochemical yield.

Stability of ^{68}Ga-DOTA-TOC was evaluated in saline and human serum respectively at 2 h post preparation. For estimation of stability in serum, 50 μl of the complex was incubated with 500 μL of human serum for 2 h at 37°C. The sample was precipitated with acetonitrile and centrifuged at 3,000 rpm for 5 min. The supernatant was then analyzed by PC, ITLC and HPLC techniques described above. Long term stability of the formulated kits was tested by radiolabeling with ^{68}Ga at periodic intervals up to 8 months and determining the percentage radiochemical yield by chromatography techniques described above.

Bioevaluation studies

Biodistribution studies of ^{68}Ga-DOTA-TOC were performed in normal Swiss mice. All animal experiments were carried out as per the guidelines and approval from the institutional animal ethics committee. The radiolabeled preparation was diluted in sterile saline and ~0.1 mL (3–4 MBq) of the complex was injected in mice via tail vein. The animals injected with ^{68}Ga-DOTA-TOC were sacrificed at the end of 1 h (n = 4). The tissues and the organs were excised and the radioactivity associated with organs/tissues was measured in a flat type NaI (Tl) scintillation counter. The distribution of the activity in the organs was calculated as percentage of injected activity per gram.

Results

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

In order to realize the aim of preparing ^{68}Ga-DOTA-TOC through kit formulation using the in-house ^{68}Ge/^{68}Ga generator, it was necessary to assess the quality of $^{68}GaCl_3$ obtained from the indigenous generator [8]. $^{68}GaCl_3$ availed from the generator not only possesses the required purity but is also of adequate radioactive concentration (~370 MBq/mL). The amount of ^{68}Ge impurity in ^{68}Ga as estimated by the reported procedure was $<10^{-5}$ % of the total ^{68}Ga activity in all the elutions. The levels of chemical impurities present in the ^{68}Ga eluate in the form of Ce, Fe and Mn ions were <0.1 mg/L (0.1 ppm), as ascertained by ICP-AES analyses of the decayed ^{68}Ga samples [9]. Thus, the radionuclidic and chemical purity of the $^{68}GaCl_3$ obtained from the generator was comparable to that obtained from commercial generators [8]. It is pertinent to note that while the ^{68}Ga eluate from commercial generators was subjected to multiple purification steps to obtain clinical grade ^{68}Ga [7, 8] while the in-house developed generator provides $^{68}GaCl_3$ of requisite purity in a single step. Moreover, unlike the commercial generators, the elution performance of the in-house generator remained consistently good over a prolonged period of time [14, 15].

DOTA-TOC kit formulation

Based on the results of the pre-formulation experiments, the optimum amount of the peptide for obtaining >95 % radiochemical yields was determined to be 50 μg with the optimum pH and the time of reaction being 3.5–4.0 and 10 min at 90 °C. Following the reported procedure, four batches of DOTA-TOC freeze dried kits (batch size = 20 vials) with each vial containing 50 μg of the peptide (in 50 μL) and 330 μL of 0.5 M sodium acetate (~13 mg) could be successfully prepared. The formulated kits were found to be of pharmaceutical grade as per sterility tests and BET tests. The levels of bacterial endotoxins were <10 EU/mL, well within the limits of endotoxins specified in pharmacopoeia for clinical grade radiopharmaceuticals. Sterile 10 mM EDTA solution was also provided with the kit as a second component.

Radiolabeling of DOTA-TOC formulation with ^{68}Ga

Greater than 95 % radiochemical yields could be consistently obtained when ^{68}Ga labeling of the formulated DOTA-TOC kits was carried out. This is evident from the HPLC radiochromatogram of ^{68}Ga-DOTA-TOC which has an R_t of 18.2 min in the standardized system (Fig. 1a). Under the same conditions, free ^{68}Ga (III) has an R_t of 3.3 min in the HPLC system. In ITLC using a 1:1 mixture (v/v) of 1 M ammonium acetate: methanol as mobile phase, ^{68}Ga-DOTA-TOC moved towards the solvent front (R_f = 0.9–1.0) while free as well as colloidal ^{68}Ga remained close to the origin (R_f = 0–0.1). In ITLC using 0.1 M sodium citrate as mobile phase, ^{68}Ga-DOTA-TOC remained close to origin while free Ga (III) moved towards the solvent front (R_f = 0.9). In paper chromatography using 50 % aqueous acetonitrile, ^{68}Ga-DOTA-TOC moved towards the solvent front while colloidal ^{68}Ga and free ^{68}Ga (III), remain at the origin (R_f = 0.0). The prepared ^{68}Ga-DOTA-TOC exhibited excellent stability in saline and human serum when studied up to 2 h at 37 °C.

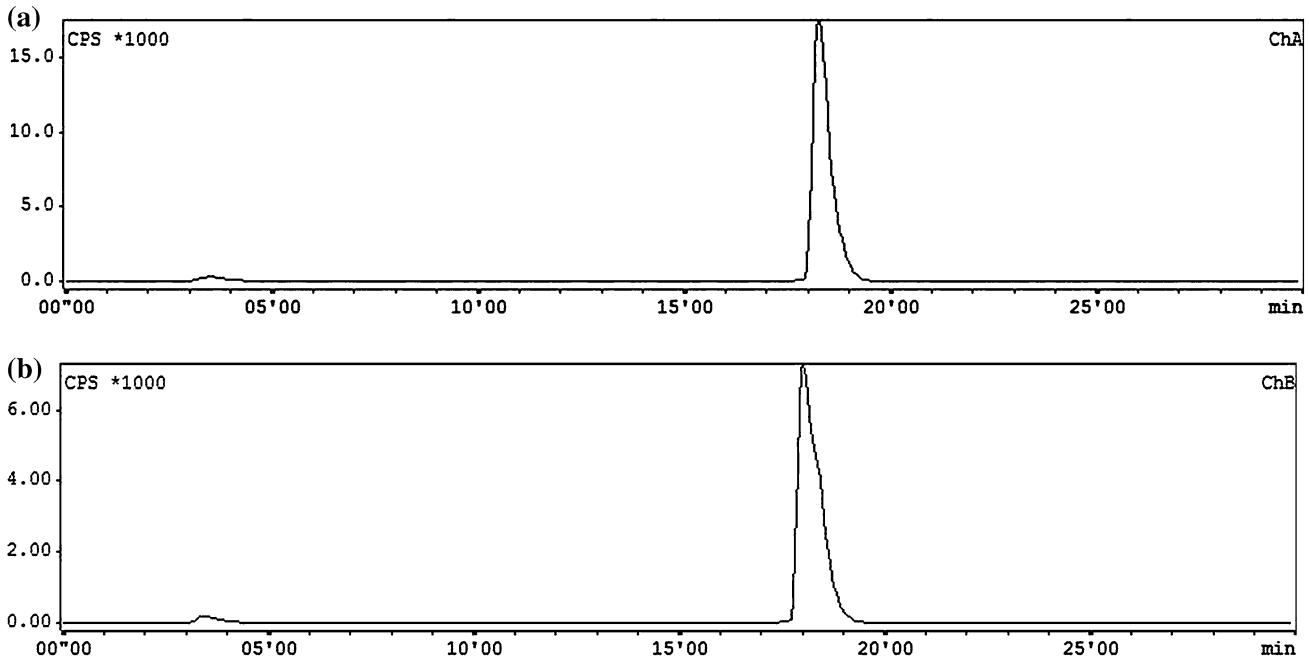

Fig. 1 **a** HPLC radiochromatogram of ^{68}Ga-DOTA-TOC. **b** HPLC radiochromatogram of ^{68}Ga-DOTA-TOC prepared using kits stored at −20 °C for 8 months

No degradation of the radiolabeled peptide was observed in serum and the radiochemical purity remained >98 %. Consistency in ^{68}Ga labeling using the freeze dried kit vials was achieved when tested at periodic intervals up to 8 months with the radiolabeling yields remaining above 95 % at all the time points studied. Fig. 1b depicts the HPLC radiochromatogram of ^{68}Ga-DOTA-TOC prepared using the DOTA-TOC kit vials stored at −20 °C for 8 months while Fig. 2 gives a consolidated profile of the radiochemical yields of ^{68}Ga-DOTA-TOC. Patient doses 55.5–92.5 MBq (1.5–2.5 mCi) of ^{68}Ga-DOTA-TOC could be prepared within 35 min for deployment of the preparation for clinical use, without significant loss of activity due to decay as well as the preparation processes.

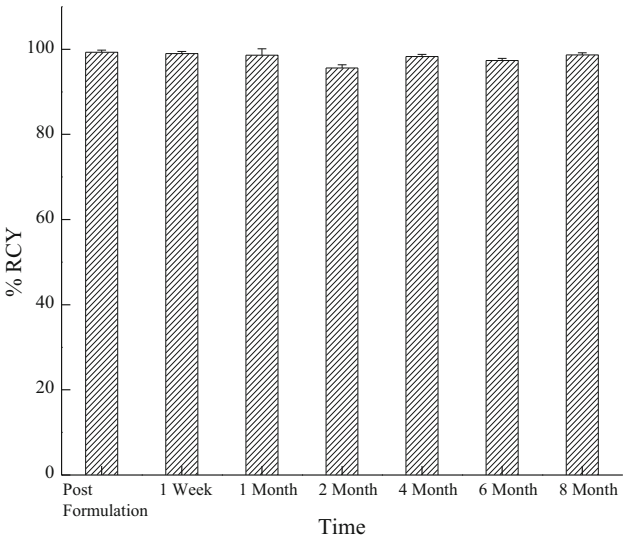

Fig. 2 Radiochemical yields of ^{68}Ga-DOTA-TOC studied over a period of 8 months

Bioevaluation studies

Rapid clearance of ^{68}Ga-DOTA-TOC activity via renal route with no significant retention of radioactivity in blood and other soft tissues was observed at 1 h post injection, which is expected due to the hydrophilic nature of DOTA conjugate. Biodistribution data of ^{68}Ga-DOTA-TOC in Swiss mice is consolidated in Table 1.

Discussion

^{68}Ga-labeled DOTA conjugated somatostatin analogues constitute a successful paradigm for the PET imaging of NETs [1–4]. The multifarious advantages of ^{68}Ga PET in terms of sensitivity, specificity, accuracy, detection rate, acquisition and examination time needs hardly to be reiterated [17]. ^{68}Ga-labeled DOTA somatostatin analogues have made significant strides in the diagnosis, staging prognosis, therapy selection and response monitoring of patients with NETs owing to their ability to accurately visualize NET lesions non-invasively and to avail valuable

Table 1 Biodistribution pattern of ^{68}Ga-DOTA-TOC in Swiss mice at 1 h p.i.

Organ/tissue	%ID/g
Blood	1.2 (0.3)
Liver	1.3 (0.4)
Int + GB	1.0 (0.0)
Stomach	1.2 (0.4)
Heart	0.5 (0.2)
Lung	1.8 (0.3)
Spleen	0.9 (0.5)
Bone	1.6 (1.5)
Muscle	5.7 (0.5)
Kidneys	12.0 (6.7)
Excreta[a]	72.3 (5.7)

n = 4, figures in parenthesis represent standard deviations

[a] Excreta is expressed as %ID

information on somatostatin receptor expression pattern on tumor cells. Pharmacokinetics, blood clearance and target localization rate of this class of peptides are compatible with the half-life of ^{68}Ga. The key to the success of ^{68}Ga-labeled DOTA conjugated somatostatin analogues resides on the continued "fuelling" of the field with cost effective ^{68}Ge/^{68}Ga generators as well as the development and introduction of new radiolabeling strategies. With a view to expand the scope of ^{68}Ga-PET, a simple, reliable and robust kit formulation strategy was developed to fully exploit the potential of ^{68}Ga in the diagnosis and management of patients with NET in routine clinical practice.

Among the ^{68}Ga-labeled DOTA conjugated somatostatin analogues, ^{68}Ga-DOTA-TOC has emerged as the PET radiopharmaceutical of choice for NET owing to its remarkable sensitivity, specificity and accuracy [18]. The utility of ^{68}Ga-DOTA-TOC PET/CT for establishing the extent and progression of NET is highly valuable in the evaluation of patients who may be candidates for peptide receptor radionuclide radiotherapy (PRRT) with ^{90}Y-DOTA-TOC or ^{177}Lu-DOTATATE. Given the success, usefulness and importance of DOTA-TOC [18–22], development of a kit formulation strategy for the preparation of ^{68}Ga-DOTA-TOC is appealing.

Development of kits for small chelator coupled peptides by freeze drying was proposed by Maecke et al. [23]. Although kit type procedures to prepare ^{68}Ga based radiopharmaceuticals using chelators such as NOTA and NODAGA is reported, development of such agents and use in clinical studies is not common as differences in chelators may also influence the pharmacokinetics, affinity and tumor uptake of the agents. In clinical situations where DOTA conjugated peptides are already in use, development of kit formulation strategy for such agents is highly desirable. In order to tap the potential of DOTA conjugated somatostatin analogues, our group has recently explored such a possibility [24, 25].

Preparation of lyophilized DOTA-TOC formulations, radiolabeling with ^{68}Ga and stability studies of ^{68}Ga-DOTA-TOC formulation reported here can be easily translated to the clinic. The developed lyophilized kit formulation strategy for ^{68}Ga-DOTA-TOC is cost effective and could be implemented ubiquitously in a hospital radiopharmacy without any practical hurdles. The total time required for preparation of one patient dose was only 35 min including quality control analysis for optimal utilization of dose in clinical scenario. It is pertinent to mention that the Society of Nuclear Medicine and Molecular Imaging (SNMMI) on November 18, 2013 announced that ^{68}Ga-DOTA-TOC has been granted orphan drug status by the U.S. Food and Drug Administration (FDA) for the management of neuroendocrine tumors (NET). This designation is considered as a significant step forward towards the approval of ^{68}Ga-DOTA-TOC by the US FDA. In-house kit production performed in compliance with regulatory requirements is expected to bring major changes in the current and future clinical use of ^{68}Ga-DOTA-TOC. The reported kit formulation strategy along with 'BARC ^{68}Ge/^{68}Ga Generator' described here can be used for the instant formulation ^{68}Ga-DOTA-TOC at the hospital radiopharmacy. While the present investigation uses ^{68}Ga available from 'BARC ^{68}Ge/^{68}Ga Generator' based on the nanoceria-polyacrylonitrile composite sorbent, similar kit formulation strategy can be adapted with ^{68}Ga obtained from the commercial ^{68}Ge/^{68}Ga generators with the required variations.

Conclusions

This manuscript describes a straightforward kit type labeling procedure for instant preparation of ^{68}Ga-DOTA-TOC for use in hospital radiopharmacy along with ^{68}Ge/^{68}Ga generator systems. The single vial kit consists of DOTA-TOC in sodium acetate, from which ^{68}Ga-DOTA-TOC can be rapidly and reliably compounded by addition of $^{68}GaCl_3$ obtained from a ^{68}Ge/^{68}Ga generator. Consistently good radiolabeling yields could be achieved on ^{68}Ga labeling of the freeze dried kits. The use of such a straightforward kit type labeling procedure for the synthesis of ^{68}Ga labeled peptides will undoubtedly have a bigger impact on the clinical use of ^{68}Ga.

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