Development of A New Radiogallium Porphyrin Complex as A Possible Tumor Imaging Agent

Yousef Fazaeli[1], Amir R. Jalilian[1,*] and Ali Khalaj[2]

[1]*Radiation Application Research School, Nuclear Science and Technology Research Institute (NSTRI), Karaj, Iran, P.O.Box: 31485-498*

[2]*Department of Nuclear Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

Abstract: *Introduction:* Developing imaging agents based on novel porphyrin pharmacophores is of great interest based on interesting biological/pharmacological performance when labeled with various radionuclides.

Method: [^{67}Ga] labeled 5,10,15,20-tetrakis (pentafluorophenyl) porphyrin ([^{67}Ga]- TFPP) was prepared using [^{67}Ga]$GaCl_3$ and 5,10,15,20-tetrakis (pentafluorophenyl) porphyrin (H_2TFPP) for 60 min at reflux condition followed by stability tests, partition coefficient determination as well as bio distribution tudies in wild type and tumor bearing animals using scarification and SPECT imaging.

Result: The complex was prepared with acceptable radiochemical purity (>97% ITLC, >98% HPLC, specific activity: 13-14 GBq/mmol) and stability in final formulation and human serum for 24 h. The partition coefficient was 0.69 (log P). The tumor:blood and tumor:muscle uptake ratios were 24.5 and 61.25 respectively after 48 h demonstrating significant tumor-imaging property of the tracer. Also confirmed by SPECT imaging. **Conclusion:** The tracer can be an interesting tumor imaging agent due to high specific uptake and rapid excretion through the urinary tract.

Keywords: Porphyrins, Ga-67, Biodistribution, Imaging agent, SPECT.

1. INTRODUCTION

Developing new radiopharmaceuticals based on new pharmacophores is still a major area of research in the nuclear pharmacy. In this regard, ligands with low toxicity, biocompatibility, and significant tumor avidity are of great importance in oncological nuclear medicine. Porphyrins are good examples of potential tumor imaging agents for nuclear, magnetic and optical diagnosis when labeled with appropriate metals due to the tetrapyrrole moiety. For instance, Motexafin gadolinium used in MRI and [1] BOPP used in boron-neutron capture therapy [2] are main two applications of porphyrins in medicine. the development of new combined nuclear medicine modalities with higher resolution and dual imaging characteristics such as SPECT/CT, PET/CT and PET/MRI has attracted great efforts in developing diagnostic radiolabeled porphyrins in the recent literature including ^{99m}Tc-porphyrin conjugates [3], ^{99m}Tc-porphine[4], ^{111}In-*m*-tetraphenyl porphine [5] and ^{111}In/^{64}Cu-fluoroporphyrins [6, 7]. However based on superior imaging qualities of PET cameras and the development of efficient PET generators including ^{68}Ge/^{68}Ga with long shelf-life, developing radiogallium imaging ligands for ultimate PET (Positron emission tomography) imaging is of great interest [8, 9]. In this regard, suitable physical properties and availability of gallium-67 [10] suggest a robust radiogallium model for feasibility studies in the development Ga-68 labeled homologs.

In continuation of recent efforts in developing ultimate radiolabeled porphyrins with desired pharmacological properties [11], the idea of developing a possible tumor-imaging agent using SPECT by incorporating ^{67}Ga into a suitable porphyrin ligand, *i.e*. 5,10,15,20-tetrakis (pentafluorophenyl) porphyrin H_2TFPP was investigated (Figure **1**).

In this work we report, synthesis, radiolabeling, partition coefficient, quality control and biodistribution studies (using SPECT and scarification) of ^{67}Ga-TFPP in wild-type and tumor-bearing rodents is reported. The time/activity diagrams for the labeled compound in vital organs have been plotted compared to gallium cation.

2. MATERIALS AND METHODS

Enriched zinc-68 chloride with a purity of more than 95% was obtained from Ion Beam Separation Group at Agricultural, Medical and Industrial Research School (AMIRS). Production of ^{67}Ga was performed at the Nuclear Medicine Research Group (AMIRS) 30 MeV cyclotron (Cyclone-30, IBA). Other chemicals were purchased from the Aldrich Chemical Co. (Gemany); and the ion-exchange resins from Bio-Rad Laboratories (Canada). NMR spectra were recorded at room

*Address correspondence to this author at the Nuclear Science and Technology Research Institute (NSTRI), Tehran, Iran, P.O.Box: 14395-836; Tel: ++98-21-88221103; Fax: ++98-21-88221103; E-mail: ajalili@aeoi.org.ir

E-ISSN: 2408-9788/15

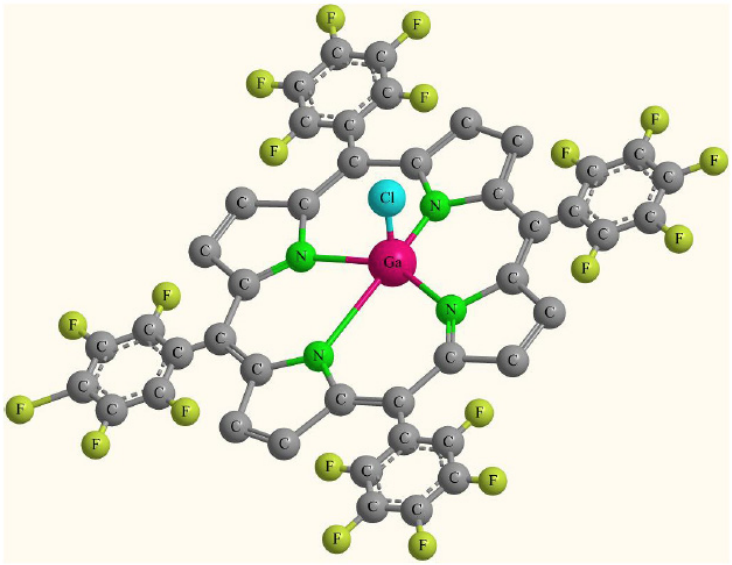

Figure 1: A possible molecular formula for ^{67}Ga-H_2TFPP.

temperature on a Bruker AVANCE 300-MHz operating at 300.0, 75.0 and 23.3 MHz, respectively, and the spectra are referenced to $SiMe_4$. Infrared spectrum was measured on a Perkin-Elmer 781 spectrometer using a KBr disc. Mass spectrum was recorded by a Finnigan Mat TSQ-70 Spectrometer. Thin layer chromatography (TLC) for cold compounds was performed on polymer-backed silica gel (F 1500/LS 254, 20 × 20 cm, TLC Ready Foil, Schleicher & Schuell®, Germany). Normal saline and sodium acetate used for labeling were of high purity and had been filtered through 0.22 μm Cativex filters. Instant thin layer chromatography (ITLC) was performed by counting Whatman No. 2 papers using a thin layer chromatography scanner, Bioscan AR2000, Bioscan Europe Ltd. (France). Analytical high performance liquid chromatography (HPLC) used to determine the specific activity, was performed by a Shimadzu LC-10AT, armed with two detector systems, flow scintillation analyzer (Packard-150 TR) and UV-visible (Shimadzu) using Whatman Partisphere C-18 column 250×4.6 mm, Whatman, NJ (USA). Analytical HPLC was also used to determine the specific radioactivity of the labeled compound. A standard curve was generated to calculate the mass of the final solution. Biodistribution data were acquired by counting normal saline washed tissues after weighting on a Canberra™ high purity germanium (HPGe) detector (model GC1020-7500SL). Radionuclidic purity was checked with the same detector. For activity measurement of the samples a CRC Capintech Radiometer (NJ, USA) was used. All calculations and tissue countings were based on the 184 keV peak. Animal studies were performed in accordance with the United Kingdom Biological Council's Guidelines on the Use of Living Animals in Scientific Investigations, 2nd ed.

2.1. Production of ^{67}Ga

^{68}Zn(p, 2n)^{67}Ga was used as the best nuclear reaction for the production of ^{67}Ga. Other impurities could be removed in the radiochemical separation process. After the target bombardment process, chemical separation was carried out in no-carrier-added form. The irradiated target was dissolved in 10 M HCl (15 ml) and the solution was passed through a cation exchange resin (AG 50W, H+ form, mesh 200-400, h: 10 cm, Ø: 1.3 cm) which had been preconditioned by passing 25 ml of 9 M HCl. The column was then washed by 25 ml of 9M HCl at a rate of 1 ml/min to remove copper and zinc ions. To the eluent 30 ml water plus about 100 ml of a 6 M HCl solution was added. The latter solution was loaded on another exchange resin (AG1X8 Cl^- form, 100-200 mesh, h: 25 cm, Ø: 1.7 cm) pretreated with 6 M HCl (100 ml). Finally, the gallium-67 was eluted as [^{67}Ga]$GaCl_3$ using 2 M HCl (50 ml); the whole process took about 60 min.

2.2. Quality Control of the Product

2.2.1. Control of Radionuclide Purity

Gamma spectroscopy of the final sample was carried out counting in an HPGe detector coupled to a Canberra™ multi-channel analyzer for 1000 seconds.

2.2.2. Chemical Purity Control

This step was carried out to ensure that the amounts of zinc and copper ions resulting from the target material and backing in the final product are acceptable regarding internationally accepted limits. Chemical purity was checked by differential-pulsed anodic stripping polarography. The detection limit of our system was 0.1 ppm for both zinc and copper ions.

2.3. Preparation of Tetraphenyl Porphyrin (H_2TFPP)

This compound was prepared according to the reported method using freshly distilled pentafluoro benzaldehyde , pyrrole and propionic acid followed by oxidation [12]. UV (CH_2Cl_2) λ_{max} (ε) = 412,506,584 nm. ^{1}HNMR : -2.91 (NH), 9.40 (βH) .^{19}FNMR: -136.9 (d), 151.7(t), -161.8 (m),

2.4. Preparation of [^{67}Ga]-TFPP

The acidic solution (2 ml) of [^{67}Ga]$GaCl_3$ (111 MBq, 3 mCi) was transferred to a 3 ml-borosilicate vial and heated to dryness using a flow of N_2 gas at 50-60°C. Fifty micreolitres of TFPP in absolute ethanol (5 mg/ml ≈409 n moles) was added to the gallium-containing vial followed by the addition of acetate buffer pH 5.5 (450 microliteres). The mixture refluxed at 100°C for 60 min. The active solution was checked for radiochemical purity by ITLC and HPLC. The final solution was then passed through a 0.22 μm filter and pH was adjusted to 5.5-7.

2.5. Quality Control of [^{67}Ga]-TFPP

2.5.1. Radio Thin Layer Chromatography

A 5 μl sample of the final fraction was spotted on a chromatography whatman No. 2 paper, and developed in mobile phase mixture, 10% NH_4OAc and methanol 1:1.

2.5.2. High Performance Liquid Chromatography

HPLC was performed with a flow rate of 1 ml/min, pressure: 130 kgF/cm^2 for 20 min. HPLC was performed on the final preparation using a mixture of water:acetonitrile 3:2(v/v) as the eluent by means of reversed phase column Whatman Partisphere C_{18} 4.6 × 250 mm.

2.6. Determination of Partition Coefficient

Partition coefficient (log *P*) of [^{67}Ga]-TFPP was calculated followed by the determination of *P* (*P*= the ratio of specific activities of the organic and aqueous phases). A mixture of 1 ml of 1-octanol and 1 ml of isotonic acetate-buffered saline (pH=7) containing approximately 3.7 MBq of the radiolabeled gallium complex at 37°C was vortexed 1 min and left 5 min. Following centrifugation at >1200*g* for 5 min, the octanol and aqueous phases were sampled and counted in an automatic well-type counter. A 500 μl sample of the octanol phase from this experiment was shaken again two to three times with fresh buffer samples. The reported log *P* values are the average of the second and third extractions from three to four independent measurements.

2.7. Stability Tests

The stability of the complex was checked according to the conventional ITLC method [13]. A sample of [^{67}Ga]-TFPP (37 MBq) was kept at room temperature for 2 days while being checked by ITLC at time intervals in order to check stability in final product using above chromatography system. For serum stability studies, to 36.1 MBq (976 μCi) of [^{67}Ga]-TFPP was added 500μl of freshly collected human serum and the resulting mixture was incubated at 37°C for 5 h, aliquots (5-μl) were analyzed by ITLC.

2.8. Induction of Fibrosarcoma Tumors in Mice

Tumor induction performed by the use of poly aromatic hydrocarbon injection in rodents as reported previously [14]. For tumor model preparation, 10 μl of 3-methyl cholanthrene solution in extra-virgin olive oil (4 mg/ml) was injected subcutaneously to the dorsal area of the mice. After 14-16 weeks, the tumor weighed 0.2-0.4 g and was not grossly necrotic. Tumor tissues of some random animals were sent for pathological tests and were diagnosed as fibrosarcoma.

2.9. Biodistribution in Wild-type Rats and Swiss Mice Bearing Fibro Sarcoma Tumor

The distribution of the radiolabelled complex among tissues was determined for wild-type rats and Swiss mice bearing fibro sarcoma tumor immediately after imaging. The total amount of radioactivity injected into each mouse was measured by counting the 1-ml syringe before and after injection in a dose calibrator with fixed geometry. The animals were sacrificed using animal care protocols at selected times after injection (2 to 24h), the tissues as well as the tumor parts were weighed and rinsed with normal saline and their specific activities were determined with a HPGe detector equipped with a sample holder device as percent of injected dose per gram of tissues.

2.10. Imaging of [^{67}Ga]-TFPP in Wild-type Rats and Swiss Mice Bearing Fibro Sarcoma Tumor

Images were taken 2, 4 and 24 hours after administration of the radiopharmaceutical by a dual-head SPECT system. The mouse-to-high energy septa distance was 12 cm. Images were taken from both normal and tumor bearing mice. The useful field of view (UFOV) was 540 mm×400 mm.

3. RESULTS

3.1. Production

Gallium-67, in form of $GaCl_3$, was prepared by 24 MeV proton bombardment of the ^{68}Zn target at Cyclone-30 on a regular basis. The target was bombarded with a current intensity of 170 μA and a charge of 1400μAh. The chemical separation process was based on a no-carrier-added method.

Radiochemical separation was performed by a two-step ion exchange chromatography method with a yield of higher than 95%. Quality control of the product was performed in two steps. Radionuclidic control showed the presence of 93(40%), 184(24%), 296(22%), 378(7%) keV gamma energies, all originating from ^{67}Ga and showed a radionuclide purity higher than 99% (E.O.S.). The concentrations of zinc (from target material) and copper (from target support) were determined using polarography and shown to be below the internationally accepted levels, *i.e*. 0.1 ppm for Zn and Cu [15, 16].

3.2. Radiolabeling

Chromatographic system was used for the detection of the radiolabeled compound from the free gallium cation. Using 10% NH_4OAc and methanol 1:1 mixture, free gallium remains at the origin of the paper as a single peak, while the radiolabeled compound migrates to higher R_f (0.64) (Figure **2**).

Although the ITLC studies approved the production of radiolabeled compound, HPLC studies demonstrated the existence of radiolabeled species using both UV and scintillation detectors.

A more fast-eluting compound at 2.2 min (scintillation detector) related to 2.4 min peak (UV detector) demonstrated a more hydrophilic compound while the second peak eluted and 2.8 min (UV detector) demonstrated non labeled ligand with a more lipophilic property. Free Ga cation eluted at 1.02 minutes (not shown) (Figure **3**.).

3.3. Partition Coefficient of [^{67}Ga]-TFPP

As expected, the lipophilicity of the [^{67}Ga]-TFPP compound is rather high. The measured octanol/water partition coefficient, *P*, for the complex was found to depend on the pH of the solution. At the pH.7 the logP was 0.69.

3.4. Stability

The chemical stability of [^{67}Ga]-TFPP was high enough to perform further studies. Incubation of [^{67}Ga]-TFPP in freshly prepared human serum for 2 days at

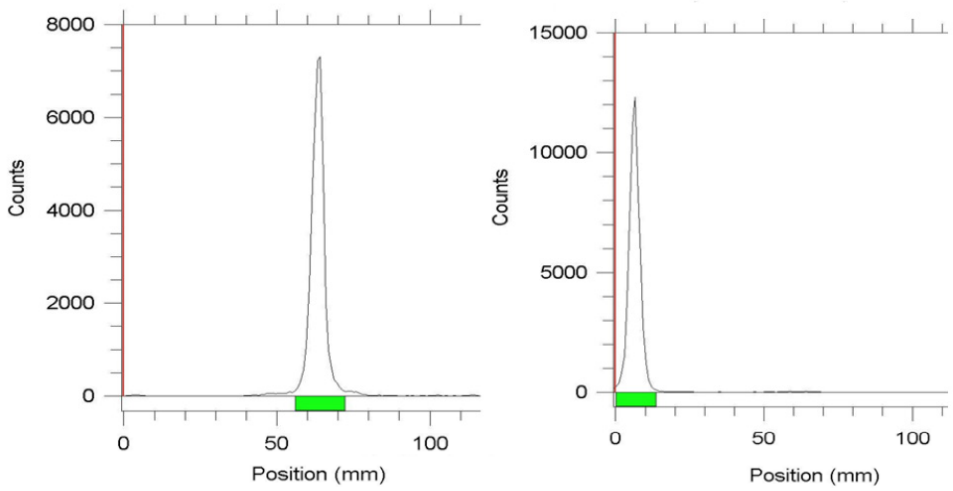

Figure 2: Radiochromatograms of the radiolabeled compound (left) and free gallium cation (right) using 10% NH_4OAc and methanol 1:1 mixture on Whatman paper No.2.

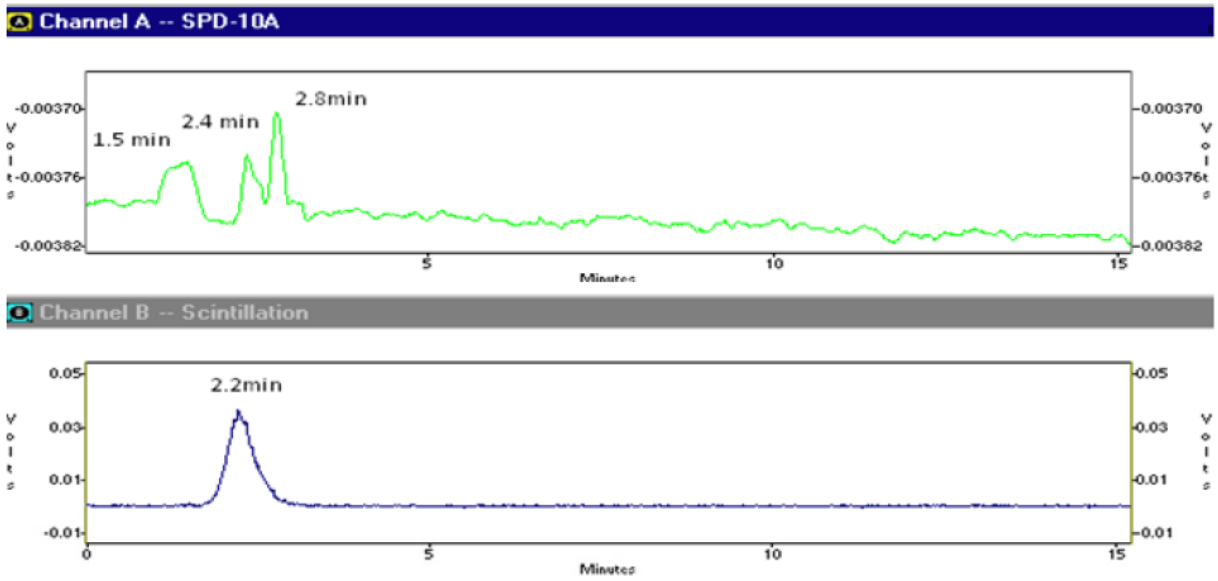

Figure 3: HPLC Radiochromatograms of the radiolabeled compound using UV detector (up) and scintillation detector (down) using a mixture of water:acetonitrile (40:60) on a reverse phase column.

37°C showed no loss of ^{67}Ga from the complex. The radiochemical purity of complex remained at 98% for 2 days under physiologic conditions.

3.5. Biodistribution in Normal Rats

For better comparison biodistribution study was performed for free Ga^{3+}. The %ID/g data are summarized in Figure **4**. As reported previously, ^{67}Ga is excreted majorly from gastrointestinal tract (GIT), thus colon and stool activity content are significant while blood stream activity is high at 2-4 h followed by reduction in 24.

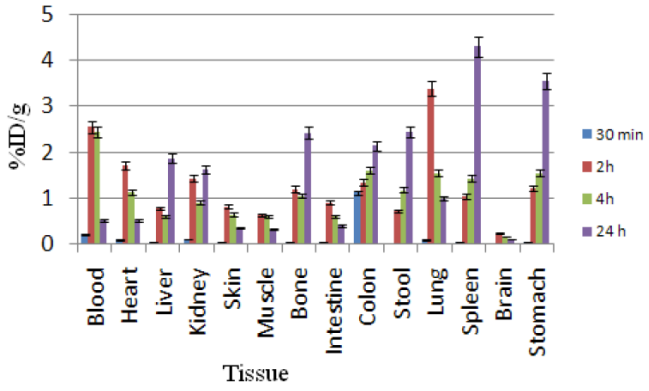

Figure 4: Percentage of injected dose per gram (ID/g %) of $^{67}GaCl_3$ in rat tissues at 0.5, 2, 4 and 24h post injection.

Bone uptake is also observed after 24 h post injection. The radiolabeled compound biodistribution is also demonstrated in Figure **5**. Due to presence of fluorine groups and water solubility of porphyrin compounds the major activity in 2 hours post injection is present in lung, liver and spleen thus the major route of excretion for the labeled compound is urinary tract. Thus the excretion of these two organs has a similar path.

On the other hand, due to relative lipophilicity of the compound, a major portion of the activity is excreted through hepatobiliary tract.

4. DISCUSSION

Because of the engagement of NH polar functional groups in its structure, labeling of H_2TFPP with gallium cation affects its chromatographic properties and the final complex is more lipophilic. Chromatographic systems including HPLC and ITLC were used for the detection of the radiolabeled compound from the free gallium cation. Although the ITLC studies approved the production of radiolabeled compound, HPLC studies demonstrated the existence of radiolabeled species using both UV and scintillation detectors. Both methods demonstrated the formation of a more lipophil complex with respect to retention times and retention factors. The lipophilicity of complex was also confirmed by partition coefficient data.

Comparison of vital organs uptake for ^{67}Ga-TFPP and $^{67}GaCl_3$ demonstrates kinetic pattern difference for both species. ^{67}Ga cation is accumulated in the liver in

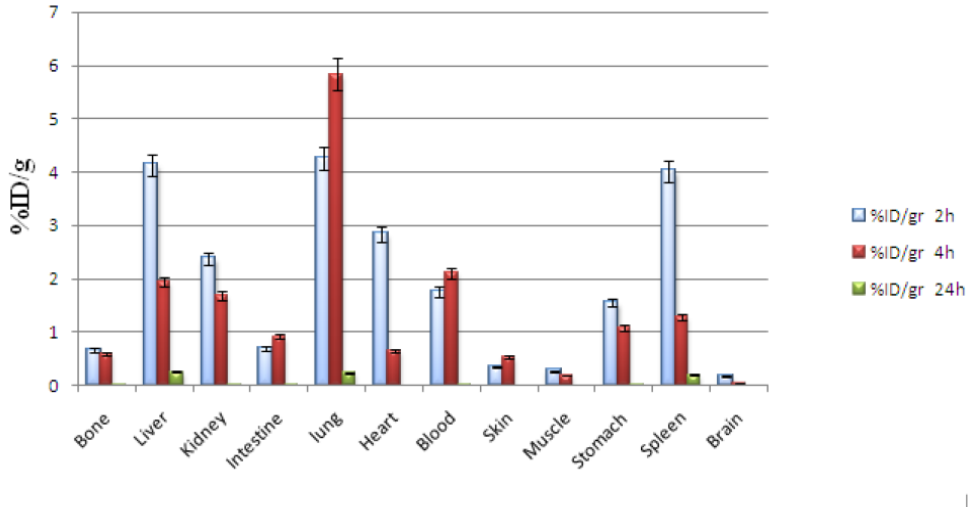

Figure 5: Percentage of injected dose per gram (ID/g %) of [^{67}Ga]-TFPP in rat tissues at 0.5, 2, 4 and 24h post injection.

the first 24h post injection slightly, while ^{67}Ga-TFPP first major excretion route is through the liver (Figure **6**).

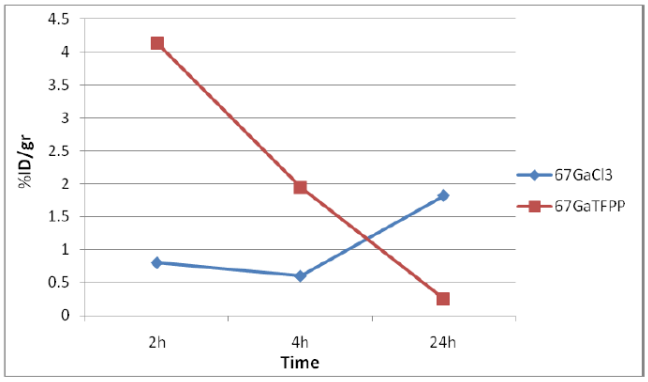

Figure 6: Comparative liver activities (%ID/g) for ^{67}Ga-TFPP and $^{67}GaCl_3$ in wild-type rats from 2-24h post injection.

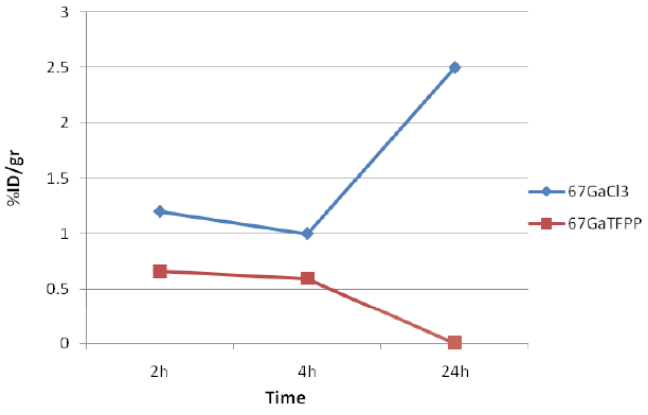

Figure 7: Comparative bone activities (%ID/g) for ^{67}Ga-TFPP and $^{67}GaCl_3$ in wild-type rats from 2-24h post injection.

As shown earlier, ^{67}Ga cation is slightly absorbed in the skeletal system (2.5-3%) while the labeled compound almost shows no uptake in the bone (Figure **7**).

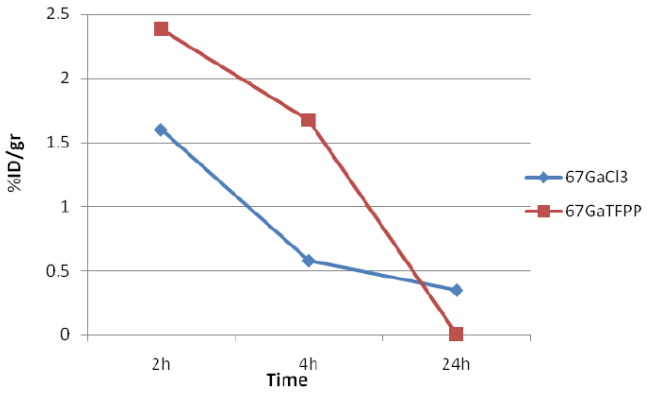

Figure 8: Comparative kidney activities (%ID/g) for ^{67}Ga-TFPP and $^{67}GaCl_3$ in wild-type rats from 2-24h post injection.

Since the urinary tract is a major route of excretion of the porphyrins, and presence of fluorine groups increases the solubility of ligand in water, kidney is another excretory organ and shows low activity for the labeled compound esp after 24h (Figure **8**).

No significant difference in blood activity content is observed for free Ga cation and labeled compound. (Figure **9**.)

Since the gallium cation can be trapped in blood cells due to the high content of thio-proteins, the spleen activity content is drastically higher in this organ after 24h compared to the radiolabeled compound (Figure **10**).

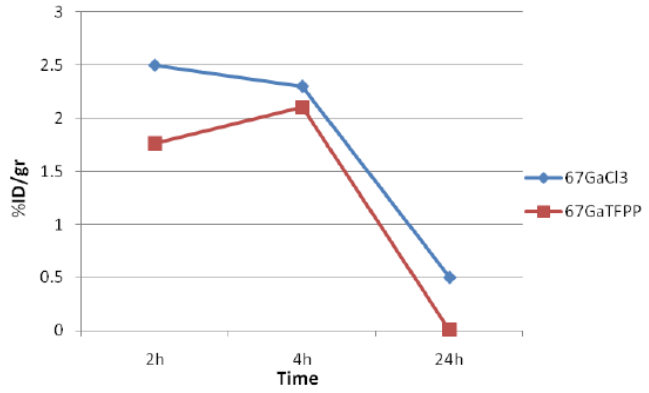

Figure 9: Comparative blood activities (%ID/g) for ^{67}Ga-TFPP and $^{67}GaCl_3$ in wild-type rats from 2-24h post injection.

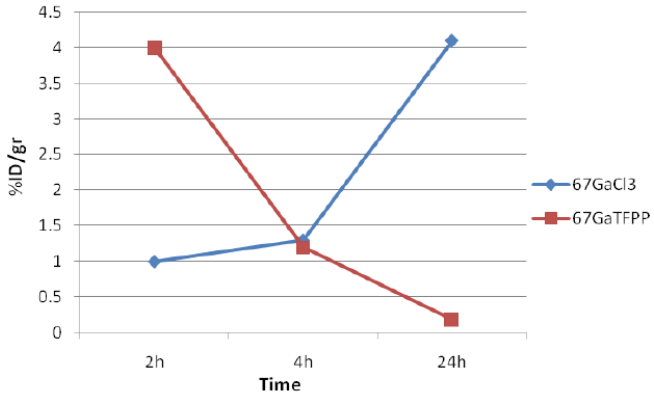

Figure 10: Comparative spleen activities (%ID/g) for ^{67}Ga-TFPP and $^{67}GaCl_3$ in wild-type rats from 2-24h post injection.

Results of the biodistribution studies revealed good tumor uptake (2.005192 %ID/g) within 1h after injection and it remained almost better than other organs in 24h after injection as expected. The %ID/g data are summarized in Figure **11**. The ratio of tumor to blood 2h and 24h post injection are 8.22 and 18.03 respectively. The ratio of tumor to muscle 2h and 24h post injection are 8.22 and 18.03 respectively 15.37 and 38.15 respectively.

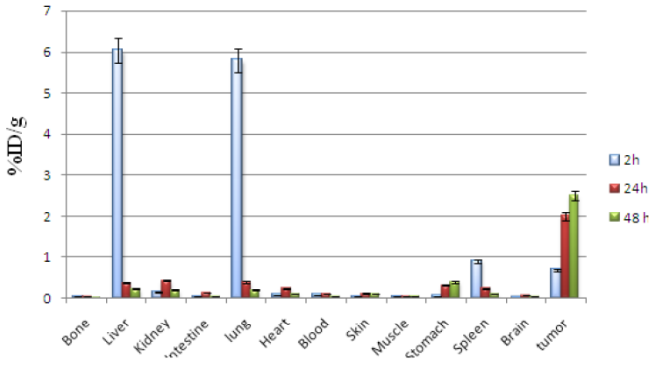

Figure 11: Percentage of injected dose per gram (ID/g %) of [^{67}Ga]-TFPP in rat tissues at 2, 24 and 48 h post injection.

The tumor:tissue uptake ratios usually calculated for diagnostic agents considering two tissues, *i.e*. blood and muscle responsible for background activity, demonstrated the increasing imaging value of the tracer by time as shown in Table **1**., showing the significant tumor imaging property of the tracer.

Table 1: Tumor:Tissue Uptake Ratios of ^{67}Ga-TFPP in 2-24h p.i

Ratio/Time	2h	24h	48h
Tumor: blood	8.22	18.03	24.5
Tumor: muscle	15.37	38.15	61.25

^{67}Ga-TFPP imaging in the wild-type rats showed a distinct accumulation of the radiotracer in the chest region all the time after injection. Most of the activity is washed out from the body after 24h and the picture

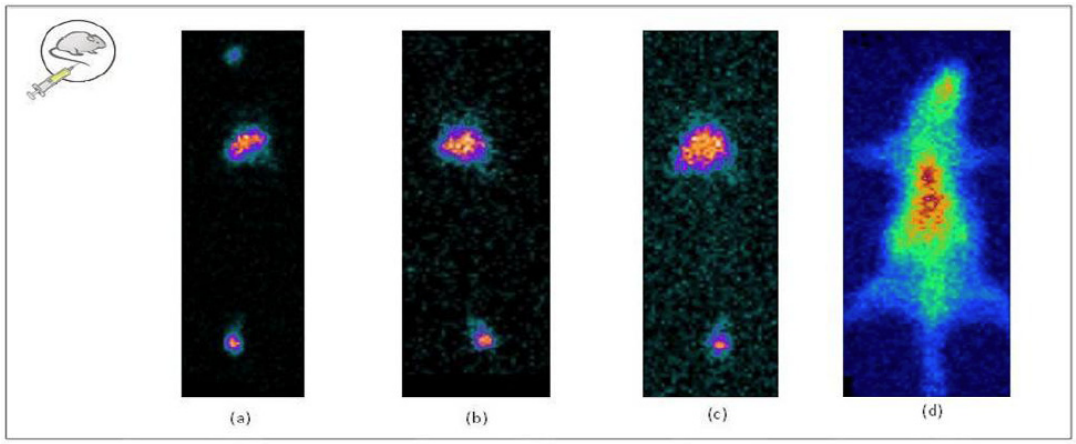

Figure 12: SPECT images of ^{67}Ga-TFPP in wild type rats 2, 4 and 24 h (**a-c** resp.) post injection compared to the ^{67}Ga cation image (**d**).

contrast weakened. While a typical Ga-67 scan is usually high chest and abdomen activity accumulation remaining at least 48 hours in the rat body.

As shown in Figure **13**, in a good accordance with ^{67}Ga-TFPP imaging in normal rats the swiss mice bearing fibro sarcoma tumor showed accumulation of the radiotracer in the chest region and tumor after injection. Most of the activity is washed out from the body after 24h and the rest remains in tumor.

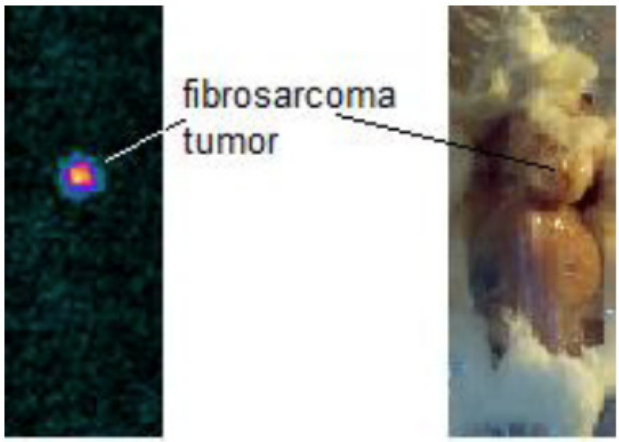

Figure 13: SPECT images of ^{67}Ga-TFPP in mice bearing fibro sarcoma tumor 24 h post injection compared to the anatomical site.

5. CONCLUSIONS

Total labeling and formulation of [^{67}Ga]-TFPP took about 30-60 min (RCP >97% ITLC, >98% HPLC, specific activity: 13-14 GBq/mmol). The complex was stable in final formulation and human serum at least for 24 h. At the pH.7, the logP was 0.69. The biodistribution of the labeled compound in vital organs of wild-type rats was studied using scarification studies and SPECT imaging up to 24 h.

A detailed comparative pharmacokinetic study performed for ^{67}Ga cation and [^{67}Ga]-TFPP. The tumor:blood and tumor:muscle uptake ratios were 24.5 and 61.25 respectively after 48 h demonstrating significant tumor-imaging property of the tracer value of the tracer. SPECT imaging also confirmed the results in 24h. The tracer can be an interesting tumor imaging agent due to high specific uptake and rapid excretion through the urinary tract. It is suggested that ^{67}Ga-TFPP could be a possible SPECT tracer, however considering the well targeted treatment of this compound in chest region, fast wash-out and the short half life gallium-68,^{67}Ga TFPP can be a suitable candidate for tumor imaging applications and future ^{68}Ga-PET studies and less use and therefore less imposed radiation doses to patients.

AUTHORS' STATEMENTS

The authors declare no conflict of interest. The results described in this paper were part of student thesis.

ACKNOWLEDGEMENTS

The authors thank Research Deputy of Tehran University of Medical Sciences, for the financial support of this investigation. Authors also wish to thank Mr S. Daneshvari for conducting animal studies.

REFERENCES

[1] Thomas SR, Khuntia D. Motexafin gadolinium injection for the treatment of brain metastases in patients with non-small cell lung cancer. Internat J Nanomed 2007; 2: 79-87.

[2] Kahl SB, Koo MS. Synthesis and properties of tetrakiscarborane-carboxylate esters of 2, 4-bis (-dihydroxyethyl) deuteroporphyrin IX. In: Allen BJ, Moore DE, Harrington BV (eds). Progress in Neutron Capture Therapy for Cancer, New York: Plenum Press; 1992.p. 223-6.

[3] Murugesan S, Shettyc SJ, Srivastava TS, Noronha OPD, Samuel AM. A technetium-99m-labelled cyclam acid porphyrin (CAP) for tumour imaging. Applied Radiat Isotopes 2001; 55: 641-646.

[4] Wang A-Y, Lin J-L, Lin W-C. Studies on the porphine labeled with ^{99m}Tc-pertechnetate. J Radioanal Nucl Chem 2010; 284: 121-28.

[5] Nunn AD. Medical Radionuclides and the Quality of Radiopharmaceuticals, The kinetics of incorporation of ^{111}In into m-tetraphenylporphine. J Radioanal Nucl Chem 1978; 53 : 291-298.

[6] Fazaeli Y, Jalilian AR, Amini MM, Aboudzadeh-Rovais MR, Shafaee K, Mirzai M, Rahiminejad A. Radiosynthesis and Biological Evaluation of [^{111}In]-5, 10, 15, 20-Tetrakis (Pentafluorophenyl) Porphyrin Complex as a Possible Imaging Agent. Intl J Nucl Energ Sci Eng 2012; 2: 28-32.

[7] Fazaeli Y, Jalilian AR, Amini MM, Aboudzadeh MR, Feizi Sh, Rahiminezhad A, Yousefi K. Preparation, nano purification, quality control and labeling optimization of [^{64}Cu]-5,10,15,20-tetrakis (penta fluoro phenyl) porphyrin complex as a possible imaging agent. J Radioanal Nucl Chem 2013; 295: 255-263.

[8] Fazaeli Y, Jalilian AR, Ardaneh Kh, Rahiminejad A, Bolourinovin F, Moradkhani S, Majdabadi A. Development of a 68Ga-fluorinated porphyrin complex as a possible PET imaging agent. Nucl Med Mol Imaging 2012; 46: 20-26.

[9] Fazaeli Y, Jalilian AR, Amini MM, Rahiminejad-kisomi A, Rajabifar S. Bolourinovin F, *et al*. Preparation and preliminary evaluation of [^{67}Ga]-tetra phenyl porphyrin complexes as possible imaging agents. J Radioanal Nucl Chem 2011; 288: 17-24.

[10] Firestone RB, Shirley VS, Baglin CM, Zipkin J. In: Table of isotopes. 8th edition, John Wiley and Sons, p.1447, New York; 1996.

[11] Falk JE. In: Porohyrins and metalloporphyrins. New York, Elsevier Science Publishing; 1975.

[12] Adler AD, Longo FR, Finarelli JD, Goldmacher J, Assour J, Korsakoff LA. simplified synthesis for meso-tetraphenylporphine. J Org Chem 1967; 32: 476.

[13] Fazaeli Y, Jalilian AR, Amini MM, Mirzai M. Radiosynthesis and biological evaluation of ^{111}In-tris [8-Hydroxy-2-methylquinoline] complex as a possible imaging agent. Iran J Nucl Med 2011; 19: 20-27.

[14] DiGiovanni J, Rymer J, Slaga TJ, Boutwell RK.. Anticarcinogenic and co-carcinogenic effects of benzo[e]pyrene and dibenz [a,c]anthracene on skin tumor initiation by polycyclic hydrocarbons. Carcinogenesis 1982; 3: 371-5.

[15] United States Pharmacopoeia 2005; 28 NF 23: p.1009.

[16] United States Pharmacopoeia 2005; 28NF 23: p.1895.

Received on 21-05-2014 Accepted on 24-02-2015 Published on 20-03-2015

http://dx.doi.org/10.15379/2408-9788.2015.02.01.2