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Preparation, quality control and biological characterization of ^{99m}Tc-vincristine

Saira Hina · Samina Roohi · Muhammad Ibrahim Rajoka · Asma Haque · Tanveer Hussain Bokhari · Muhammad Sohaib

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Abstract In present study it is aimed to radiolabel vincristine with ^{99m}Tc and to evaluate bioaffinity of ^{99m}Tc labeled vinc. The optimum conditions required to obtain 99.6 ± 0.4 %, ($n = 5$) radiolabeling yield of ^{99m}Tc-vincristine (^{99m}Tc-vinc) were as follows: pH 4, 5 μg of vincristine sulphate, 6 μg $SnCl_2{\cdot}2H_2O$ as a reducing agent and 10 min incubation time at room temperature. Quality control of ^{99m}Tc-vinc was done by using paper electrophoresis and thin layer chromatography. The radiolabeling yield was confirmed by High performance liquid chromatography using radioactive and UV detector operating at 230 nm. ^{99m}Tc-vinc was stable in vitro for 5 h. Biodistribution and scintigraphy of ^{99m}Tc-vinc was performed in mice and rabbits respectively and that ^{99m}Tc-vinc showed high uptake of it in liver and spleen. Finally ^{99m}Tc-vinc may be the potential imaging agent for liver and spleen.

Keywords ^{99m}Tc-vincristine · Quality control · SPECT imaging · Biodistribution · Scintigraphy

S. Hina (✉) · M. I. Rajoka · A. Haque
Department of Bioinformatics and Biotechnology, Government College University Faisalabad, Faisalabad, Pakistan
e-mail: sairahina@yahoo.com

S. Roohi
Isotope Production Division, Pakistan Institute of Nuclear Science and Technology, P.O. Nilore, Islamabad, Pakistan

T. H. Bokhari
Department of Chemistry, Government College University Faisalabad, Faisalabad, Pakistan

M. Sohaib
Pakistan Institute of Engineering and Applied Sciences, P. O. Nilore, Islamabad, Pakistan

Introduction

Nuclear medicine is unique medical modality that practices radiopharmaceuticals for imaging and therapy. The medical imaging uses molecular probes and radiotracers for diagnosis of tumor metabolism, proliferation and other specific targets thus enabling the early detection of diseases [1]. The imaging modalities for detection and characterization are ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), Single Photon emission Tomography (SPECT) and positron emission tomography (PET) [2]. ^{99m}Tc as a routinely SPECT imaging radiotracer, various ^{99m}Tc-labeled compounds have been prepared for imaging purposes and some of them are routinely used in diagnostic nuclear medicine [3–14]. For tracing the abnormalities of liver and spleen, the goal of scintigraphy is to empower the concerned physician to image hepatic and/or splenic tissue and thus helpful for determining the size and shape of the liver and spleen as well as for detecting functional abnormalities of the reticulo endothelial cells of these organs [15, 16]. ^{99m}Tc has become the most major radioisotope for SPECT medical imaging due to its ideal properties of short suitable half-life (6 h), 140 keV γ-rays emissions best suitable for scintigraphy and low radiation burden [17]. Most of the ^{99m}Tc-radiopharmaceuticals employed for imaging show similar pharmacokinetic properties in animals and human. A variety of radiopharmaceuticals have been described for diagnostics such as ^{99m}Tc-UDCA [18], ^{99m}Tc-disofenin (DISIDA), ^{99m}Tc-EHIDA [19], ^{99m}Tc-mebrofenin [20–23], ^{99m}Tc-lidofenin [24], ^{131}I-AFP-MoAb [25] and ^{99m}Tc-MIBI [26], ^{99m}Tc-duramycin, [12] and ^{99m} Tc-labeled bombesin analog [27]. For liver-splenic imaging, the agents labeled with ^{99m}Tc are sulfur colloid [28] and red blood cells [29].

A large number of drugs selectively target actively proliferating cells such as intercalating agents, antimetabolites, mitotic inhibitors and DNA-alkylating agents. Vincristine, a mitotic inhibitor used in cancer chemotherapy is formally known as leurocristine and is a vinca alkaloid from the *Catharanthus roseus*. It is found to treat a large variety of cancers, such as sarcomas, acute leukaemia, breast cancer, malignant lymphoma, acute erythraemia, Hodgkin's disease, and testicular cancer. Vincristine is a cell cycle-dependent compound that is administered via intravenous infusion and is used to inhibit cell cycle progression at M-phase [30–32].

In this work, the labeling and characterization of ^{99m}Tc-labeled vincristine (^{99m}Tc-vinc) was carried out for liver and spleen imaging in animal models by performing in vitro and in vivo assays followed by scintigraphy.

Materials and methods

Vincristine sulphate was obtained from Lahore Pakistan. ^{99m}Tc was obtained from a locally produced fission based PAKGEN ^{99}Mo/^{99m}Tc generator. All chemicals used were AR grade. The approval for animal's experiments was taken from the Animal Ethics Committee of the Pakistan Institute of Nuclear Science and Technology (Document no. IPDs-H-SOP-04-003).

Synthesis of ^{99m}Tc-vinc

Known amount of stannous chloride dihydrate was dissolved in 0.1 mL of concentrated HCl and diluted with distilled water to get required amount of reducing agent. To the varying amount of ligand (Vincristine sulphate); certain amount of $SnCl_2{\cdot}2H_2O$ and 10 mCi of $^{99m}TcO_4^-$ was added. The pH of the solution was adjusted with the diluted NaOH solution. The mixture was then incubated for different time periods at room temperature (25 °C) for labeling purposes. At least five set of experiments were performed for each point.

Quality control

Electrophoresis of ^{99m}Tc-vinc

Electrophoresis of radiotracer ^{99m}Tc-vinc was studied by using Deluxe electrophoresis chamber (Gelman) system. The phosphate buffer of pH 6.8 was used in this experiment. Whatman No. 1 paper of 30 cm was used marked with L at left side of the strip and R at right side of the strip. The strip was placed in the electrophoresis chamber containing buffer in such a way that left side dip at anode and right side at cathode; one drop of ^{99m}Tc-vinc was poured at the middle of the strip and electrophoresis was run for 45–60 min at a voltage of 300 V. After completion of electrophoresis, the strip was scanned by using 2π scanner to know the charge on ^{99m}Tc-vinc.

Thin layer chromatography of ^{99m}Tc-vinc

Radiochemical yield of ^{99m}Tc-vinc was checked by chromatographic method using Whatman No. 3 paper and ITLC-SG strips (Gelman Science). Free $^{99m}TcO_4^-$ in the preparation was determined by using Whatman No. 3 paper as the stationary phase and acetone as mobile phase. Reduced and hydrolyzed activity was determined by using instant thin layer paper chromatography (ITLC-SG strips) as the stationary phase and 0.5 M NaOH as a mobile phase. The distribution of labeled, free and hydrolyzed compounds on chromatographic strips was measured by a 2π Scanner (Berthold, Germany). Alternatively, the strips were cut into 1 cm segments and counted by a gamma-counter.

High performance liquid chromatography of ^{99m}Tc-vinc

HPLC of ^{99m}Tc-vinc was studied by using D-200 Elite HPLC system. Sodium Iodide crystal detector was used for radioactivity measurement. The column of C-18 (waters, μ-Bondapak^{TM}C18, 3.9 × 300 mm) was used as stationary phase and a mixture of acetonitrile and water were used as mobile phase in the ratio 80:20 (v/v %). The flow rate of the mobile phase was adjusted up to 1 mL per minute. UV detector was used for detection purpose and work was done at wavelength of 230 nm, while gamma detector (NaI) was used for monitoring of ^{99m}Tc activity.

In vitro stability study of ^{99m}Tc-vinc

After choosing suitable vincristine sulphate/^{99m}Tc ratio and pH, the complex was incubated for 24 h at room temperature. To observe the stability of the complex ^{99m}Tc-vinc after 30 min, 1, 2, 4, 6 and 24 h, the complex was spotted on paper strips, developed and scanned likewise by virtue of which in vitro stability of the labeled preparation was ascertained.

In vitro stability in normal human serum

1.8 mL of human serum was mixed with 0.2 mL (2 mCi) of ^{99m}Tc-vinc and incubated at 35 °C. 0.2 mL aliquots were withdrawn during the incubation at 1, 4 and 24 h and subjected to chromatography for determination of ^{99m}Tc-vinc, reduced/hydrolyzed ^{99m}Tc and free $^{99m}TcO_4^-$.

Biological distribution of ^{99m}Tc-vinc in mice

The biological distribution study was done using nine Swiss Albino mice divided into three groups (three animals in each group) weighing 30–35 g. Each anesthetized animal was injected in tail vein with 0.4 mL containing ~74 MBq (2 mCi) of ^{99m}Tc-vinc. The mice were sacrificed after anesthesia and biodistribution was determined. The sample of blood (1 mL) was taken by cardiac puncture, weighted and activity in total blood was calculated by assuming blood volume = 6.5 % of body weight. The whole animals were then weighed and dissected after 1, 4 and 24 h. Samples of muscle, liver, spleen, lungs, kidney, stomach, femur, heart and brain were removed, weighed and content of radioactivity was measured using a gamma counter. Corrections were made for background radiation and physical decay while performing the experiment. The results were expressed as the % uptake of injected dose per gram organ tissue.

SPECT-imaging

The imaging study was performed using Swiss Albino mice and healthy rabbits with weight range of 30–35 and 2.0–2.5 kg respectively. ^{99m}Tc-vinc (2 mCi) was injected intravenously into the tail of mice while ^{99m}Tc-vinc (3 mCi) was administered in the marginal ear vein of rabbit. The animal was sedated by one mL of intramuscular diazepam injection and was immobilized on gantry table under the head of gamma camera projecting the dorsal view of the animal. The energy window of 20 % was set on 140 keV. Images were acquired on 256 × 256 matrix size for 5 min each. Whole body static images were taken at 1, 4 and 6 h in rabbit while 1, 4 and 24 h in mice after ^{99m}Tc-vinc injection. Single headed Siemens Integrated Orbiter Gamma Camera System interfaced with high-resolution parallel-hole collimator was used to acquire digital images. (Macintosh® Operating System 7.5 Software used on the ICON™ Workstation).

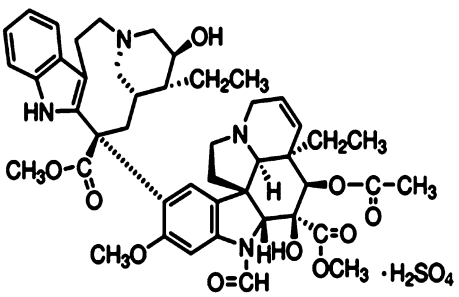


Fig. 1 Structure of vincristine sulphate

Results and discussion

The Vincristine contains the sulphate salt of vinca alkaloid from the *C. roseus* formerly Vincarosea. It has molecular formula $C_{46}H_{56}N_4O_{10}$ as shown in (Fig. 1).

Synthesis of ^{99m}Tc-vinc

The synthesis of ^{99m}Tc-vinc was performed to determine the best conditions ensuring high radiochemical yield, high purity, and stability of ^{99m}Tc-vinc. The examination of the effect of the different parameters on the labeling yield such as amount of vincristine, pH of the reaction mixture, amount of $SnCl_2{\cdot}2H_2O$, and reaction time was studied. The effects of pH are shown in Fig. 2. At low pH (2–3) the labeling efficiency was 60–80 %, while at pH 4 the labeling efficiency of ^{99m}Tc-vinc was ~100 %. In basic media 7–8 the labeling efficiency was decreased (~50 %). Hence further experiments were performed at pH 4.

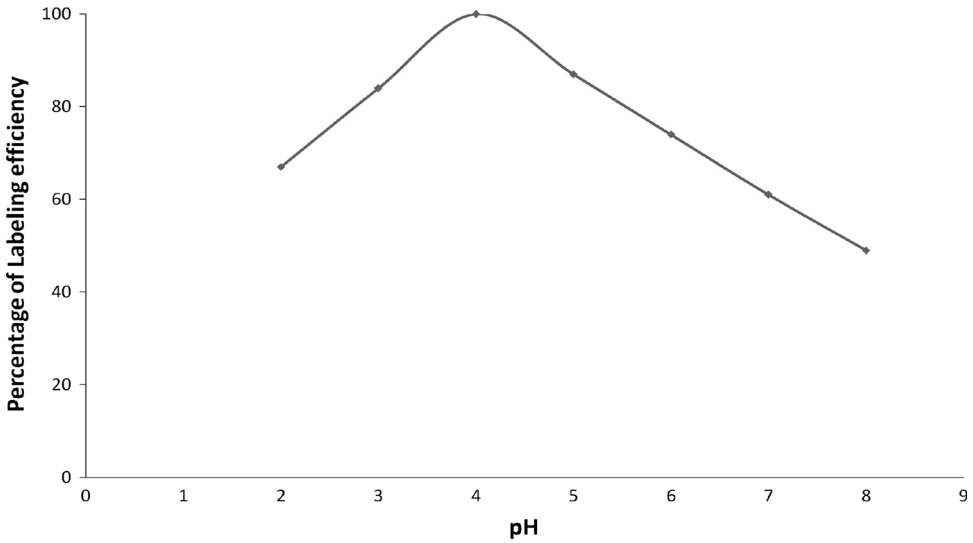


Fig. 2 Effect of pH on labelling efficiency of ^{99m}Tc-vinc

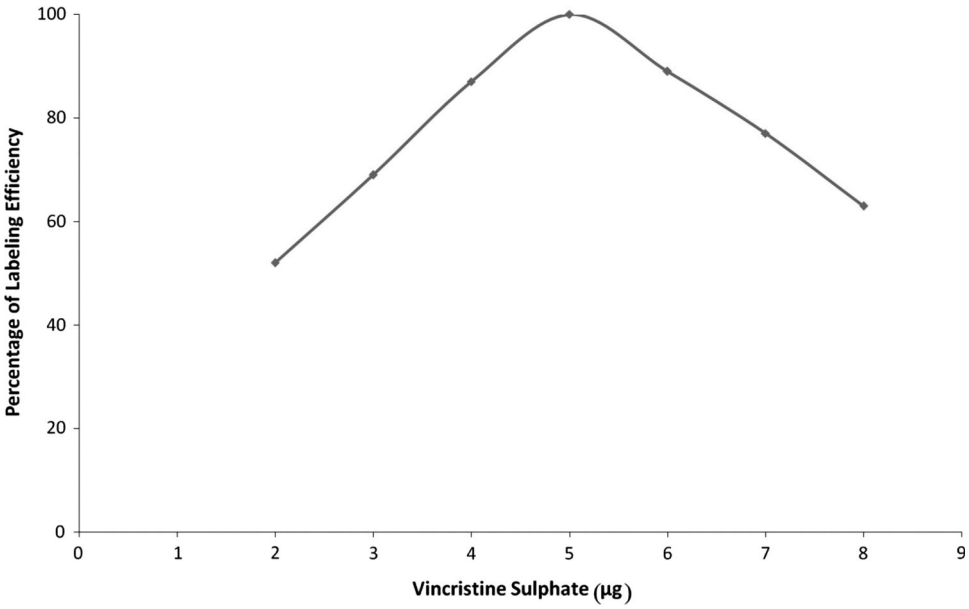


Fig. 3 Effect of amount of stannous chloride on labelling efficiency of ^{99m}Tc-vinc

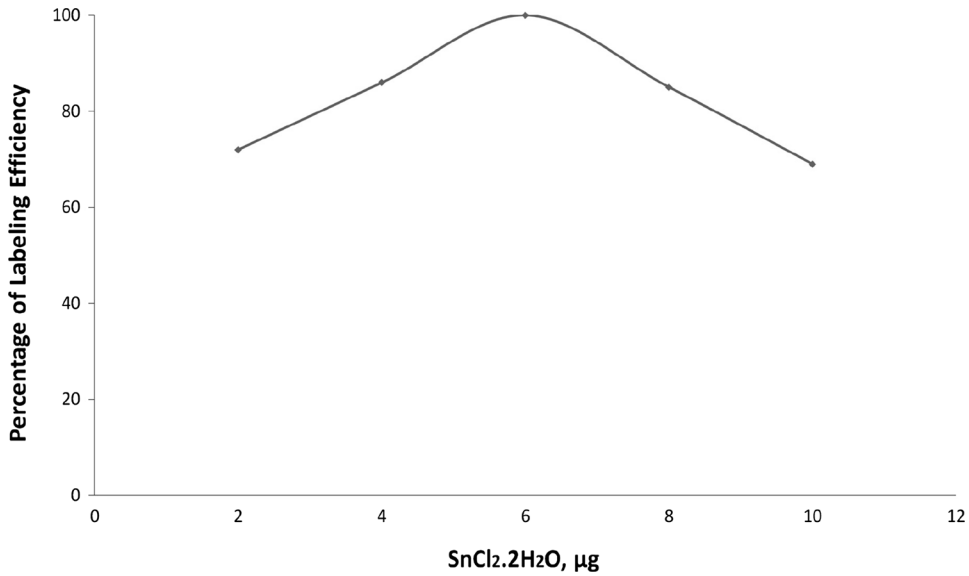


Fig. 4 Effect of amount of ligand on labelling efficiency of ^{99m}Tc-vinc

The amount of reducing agent, $SnCl_2{\cdot}2H_2O$, which gave the highest labeling efficiency, was 4–8 and 6 µg of $SnCl_2{\cdot}2H_2O$ was chosen (Fig. 3) to avoid colloid formation. Basically preparation of the variety of ^{99m}Tc radiopharmaceuticals involves reduction of ^{99m}Tc from 7+ to lower-valence state, which enables its chelation by compounds of diagnostic purposes. The complexation of ^{99m}Tc with 5 µg vincristine at pH 4 with 6 µg of $SnCl_2{\cdot}2H_2O$ gave a maximum labeling efficiency of 99.6 ± 0.4 within few minutes (Fig. 4). Labeling yield at different time intervals 5, 30 min, 1, 2, 4 and 6 h after the initiation of reaction came out to be 97.458 at initial 5 min and 100 % was maintained till 5 h. Graphical representation of these results is depicted in Fig. 5. The final formulation for the radiotracer ^{99m}Tc-vinc was: Vincristine sulphate 5 µg; $SnCl_2{\cdot}2H_2O$ 6 µg; pH ~4; ^{99m}Tc 370 MBq (10 mCi) and reaction mixture volume 1.5 mL. With the development of molecular biology based medicine, a transition is being carried out to incorporate into diagnostic interpretation information because of biochemical perturbations existing in the disease. Biomedical imaging technique can help to diagnose tumors, optimize drug development, and suggest response to a therapeutic modality [33].

Quality control and stability of ^{99m}Tc-vinc

The electrophoresis illustrate that complex is neutral in nature (Fig. 6). Labeling efficiency, radiochemical purity

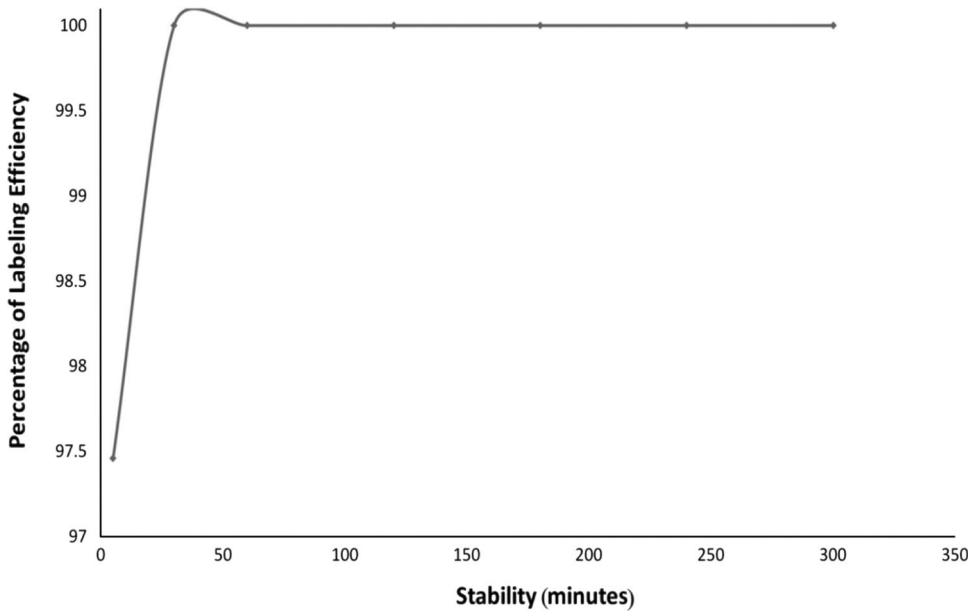


Fig. 5 Stability of the ^{99m}Tc-vinc at room temperature

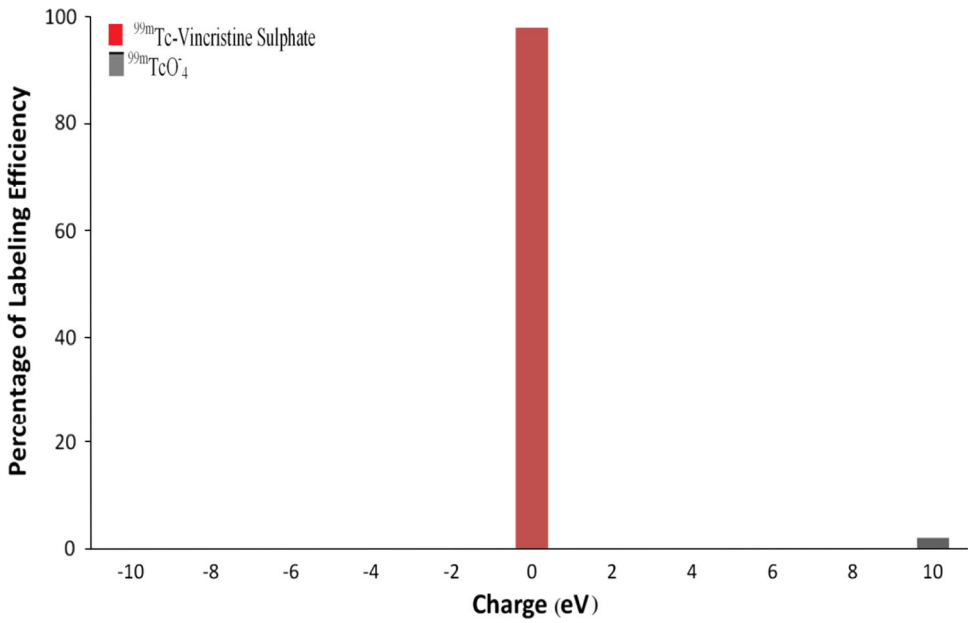


Fig. 6 Electrophoresis result of ^{99m}Tc-vinc

and stability were assessed by a combination of ascending chromatography and instant thin layer chromatography impregnated with silica gel. In paper chromatography using acetone as the solvent, free $^{99m}TcO_4^-$ moved towards the solvent front (Rf = 1), while ^{99m}Tc-vinc and reduced/hydrolyzed ^{99m}Tc remained at the point of spotting. In ITLC-SG chromatography using 0.5 M NaOH as solvent, reduced/hydrolyzed ^{99m}Tc remained at the point of spotting, whereas ^{99m}Tc-vinc and free $^{99m}TcO_4^-$ moved towards the solvent front. HPLC results of inactive ligand illustrate that ligand is >90 % pure (Fig. 7) HPLC analysis of ^{99m}Tc-vinc illustrate that ~100 % ^{99m}Tc binds with available ligand (Fig. 8). When the preparation (labeled radiopharmaceutical) was incubated with normal human serum at 35 °C, no significant increase in free $^{99m}TcO_4^-$ or reduced/hydrolyzed ^{99m}Tc was seen up to 24 h. The total impurities were found to be <5 % (Fig. 9).

Biodistribution and SPECT imaging in animals

Biodistribution of ^{99m}Tc-vinc in various organs of the mice at 1, 4 and 24 h after intravenous administration is

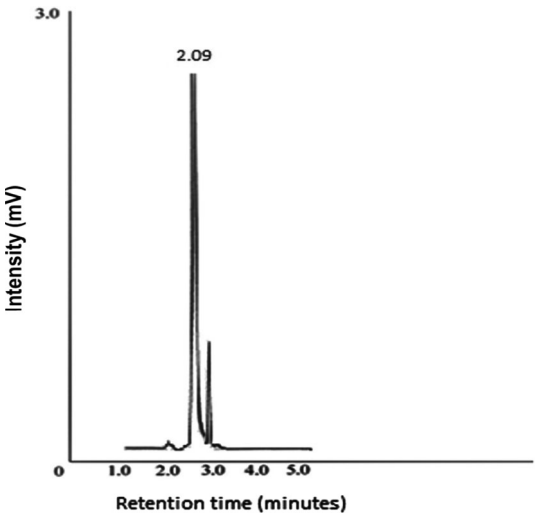


Fig. 7 HPLC analysis (UV detector) showing the purity of vincristine

presented in Table 1. The in vivo behavior of the ^{99m}Tc-vinc was expressed as percentage of injected dose per gram organ tissue (%ID/gram organ tissue). ^{99m}Tc-vinc is accumulated in spleen (~8 %), liver (>18 %), and kidney (>19 %) after 1 h post administration. Spleen showed significant uptake of ^{99m}Tc-vinc being the organ system with high cell turns over. The activity uptake of stomach was low, 0.8 % (60 min post injection), indicating that ^{99m}Tc-vinc was stable inside the body. The ^{99m}Tc-vinc was rapidly distributed after intravenous injection as shown by the renal elimination, although liver and spleen uptake was significant. Vincristine is cleared through hepatobiliary pathway with varying degree of renal extraction and liver retention like all ^{99m}Tc-iminodiacetic acid complexes [34]. The retention of ^{99m}Tc-vinc in liver may be attributed to its metabolism in liver. The study shows that uptake of a radiotracer is dependent on several factors, such as the nature of the radiotracer, blood flow and pH indicating a

Fig. 8 HPLC analysis illustrate the percentage labeling of vincristine with ^{99m}Tc

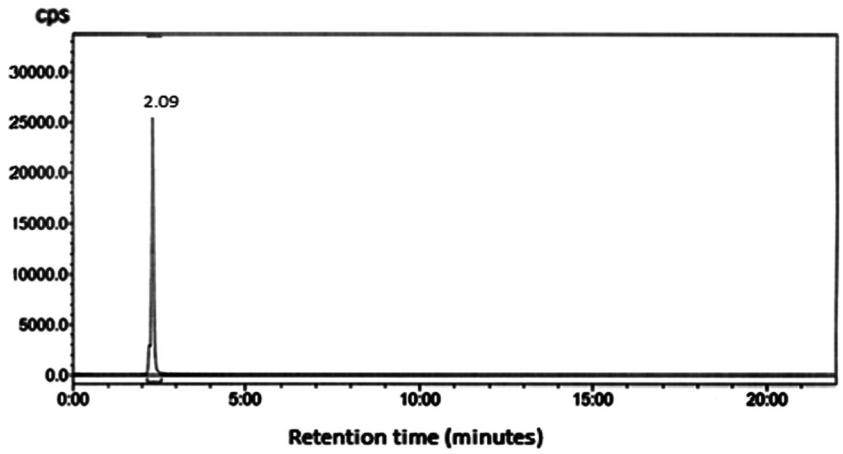
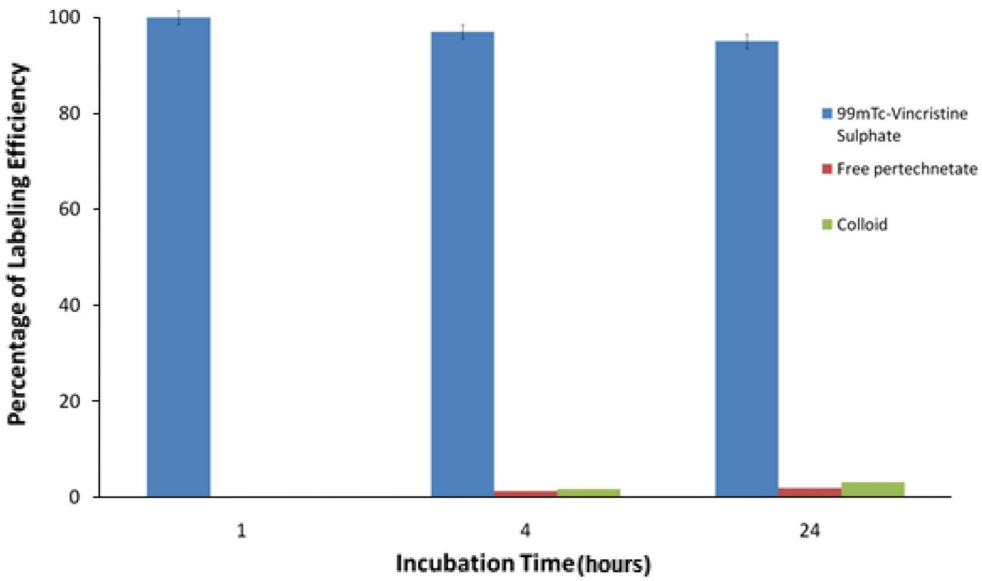


Fig. 9 In vitro stability of ^{99m}Tc- vinc in normal human serum



slow transfer of charged metabolites formed across the cell membrane. The two hydroxyl groups of vincristine play a crucial role in pharmacodynamics. After the transport inside the cell, the hydroxyl groups can be phosphorylated by cellular deoxyguanosine kinase [35]. Vincristine is a very important commercially available clinical medicine with known pharmacokinetics, pharmacodynamics and toxicity. The large activity of ^{99m}Tc-vinc in spleen suggests that ^{99m}Tc-vinc can target highly proliferating cells. The whole body SPECT imaging results agree well with in vivo biodistribution studies of ^{99m}Tc-vinc. The scan showed a high activity in liver, spleen and normal distribution in the whole body after 1 h administration of the ^{99m}Tc-vinc in mice and rabbits as depicted in Figs. 10a and 11a respectively. The activity was gradually increased in liver and slightly decreased in spleen with the passage of time (Fig. 10b, c). The scintigraphic images thus suggest that ^{99m}Tc-vinc possesses excellent characteristics for promising application as a novel splenic imaging agent in mice and rabbits. The high hydrophilic character of ^{99m}Tc-vinc is in accordance with its predominant renal clearance.

Table 1 Biodistribution data of ^{99m}Tc-vinc in percent injected dose per gram organs at 1, 4, and 24 h after intravenous administration in mice

Organ	Percentage of injected dose per gram organs		
	1 h	4 h	24 h
Liver	18.51 ± 0.5	19.06 ± 0.3	20.67 ± 0.2
Spleen	8.02 ± 0.08	4.54 ± 0.1	2.26 ± 0.09
Stomach	0.18 ± 0.5	0.28 ± 0.04	0.49 ± 0.7
Intestine	3.32 ± 0.09	4.48 ± 0.5	5.26 ± 0.2
Lungs	0.21 ± 0.02	0.22 ± 0.1	0.24 ± 0.06
Kidney	19.97 ± 0.1	15.8 ± 0.05	13.87 ± 0.08
Urine	13.43 ± 0.2	27.18 ± 0.05	48.29 ± 0.6
Heart	0.98 ± 0.1	0.75 ± 0.9	0.68 ± 0.06
Blood	0.96 ± 0.05	0.82 ± 0.02	0.54 ± 0.9
Brain	0.63 ± 0.7	0.41 ± 0.4	0.37 ± 0.02
Body	24.77 ± 0.4	22.09 ± 0.02	21.08 ± 0.5
Bladder	11.53 ± 0.09	6.26 ± 0.02	4.69 ± 0.1
Muscle	1.42 ± 0.08	1.1 ± 0.06	0.9 ± 0.05

Conclusion

In present work ^{99m}Tc-vinc was designed, synthesized and evaluated biologically. Radiolabeling efficiency of ^{99m}Tc-vinc monitored by thin layer chromatography was 99.6 ± 0.4, ($n = 5$). Neutral charge on complex was determined by electrophoresis while HPLC results showed single species. Biological distribution and scintigraphic

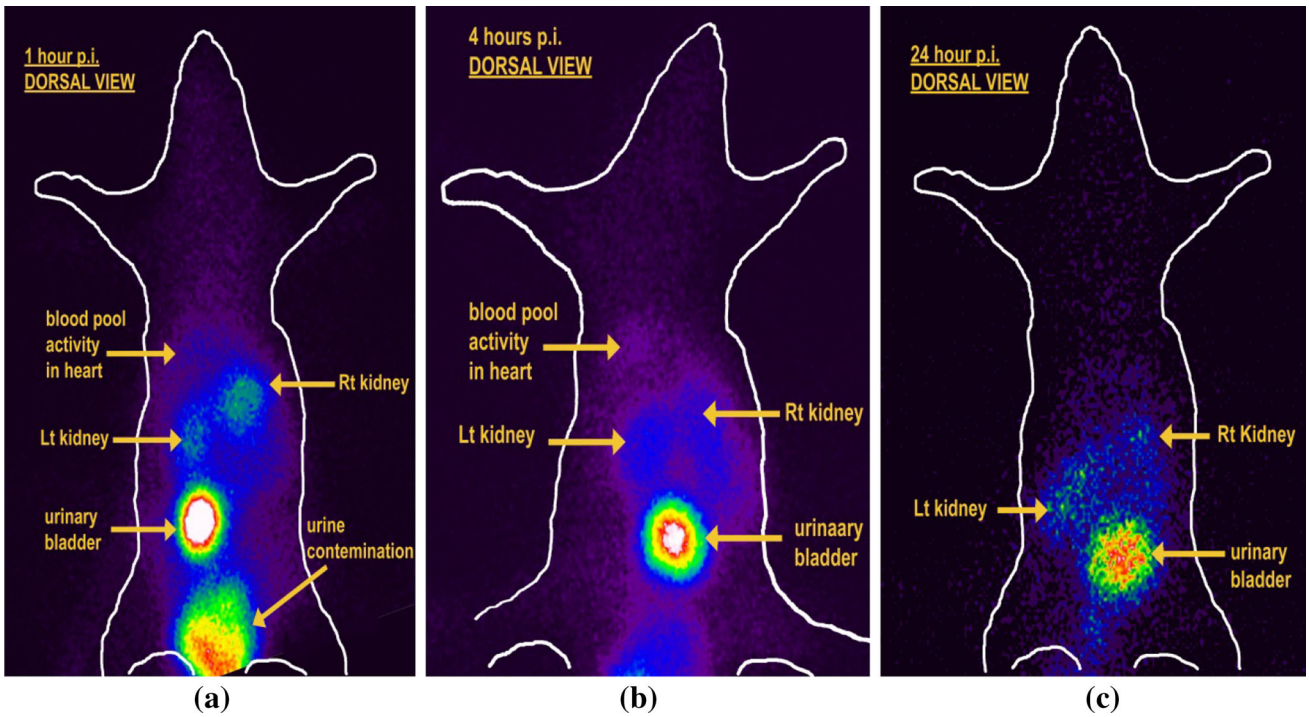


Fig. 10 Whole body gamma camera image of mice injection with ^{99m}Tc-vinc at 1-h post administration (**a**), at 4-h post administration (**b**), and 24 h post administration (**c**)

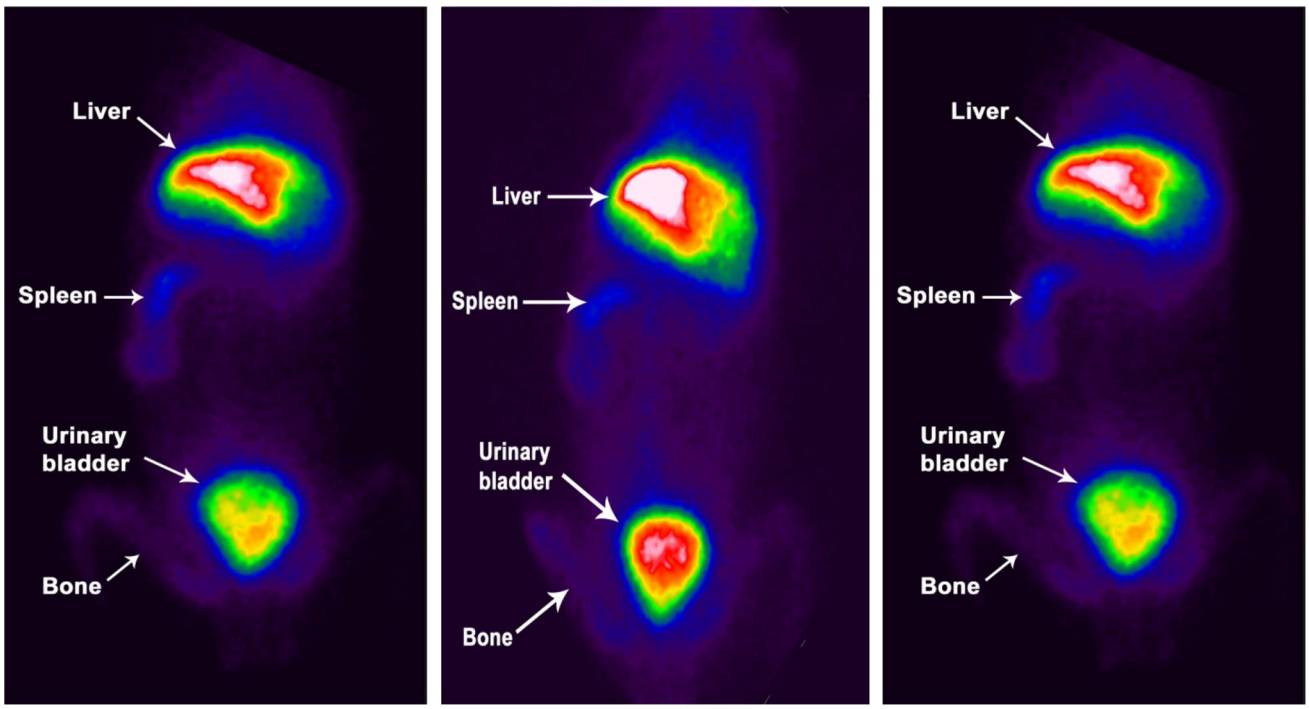


Fig. 11 Whole body gamma camera image of rabbits injected with ^{99m}Tc-Vinc at 1-h post administration (**a**), at 4-h post administration (**b**), and 6-hours post administration (**c**)

studies in normal mice and rabbit indicated higher accumulation of ^{99m}Tc-vinc in liver and spleen. Due to the attractive biological properties, ^{99m}Tc-vinc may serve as functional agent for diagnostic purposes.

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