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QUALITATIVE COMPARISON OF LOCALLY PREPARED ^{99m}Tc-LABELED METHYLENE DIPHOSPHONATE AND ^{99m}Tc-LABELED PYROPHOSPHATE

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Different parameters affecting labeling of ^{99m}Tc with two compounds were studied in order to standardize the procedure for the preparation of ^{99m}Tc -MDP and ^{99m}Tc -PYP. Briefly radiochemical purity, stability, pyrogenicity were studied. Radiochemical purity was checked by paper chromatography. Stability was checked by incubating the labeled products for several hours at room temperature. Pyrogenicity was checked by noting the rectal temperatures after injection of the preparation into the rabbit. The optimized preparations were then injected to the rabbits to compare imaging quality and biodistribution of the agents in the body. Finally the preparations were injected into patients to see the image quality and diagnostic efficacy of the technique. The results show superior image quality and biodistribution with locally prepared ^{99m}Tc-MDP as compared to ^{99m}Tc-PYP although both the preparations were having good radiochemical purity and stability. It is concluded that the locally developed techniques for preparation of ^{99m}Tc-MDP and ^{99m}Tc-PYP are simple, safe and of acceptable quality. The data on biodistribution in these bone agents suggests relatively good target to non-target contrast with ^{99m}Tc-MDP. The image quality with patient scans is also superior with ^{99m}Tc-MDP. This confirms that the homemade ^{99m}Tc-MDP is superior in quality than ^{99m}Tc-PYP. This is in agreement with the previous findings.

Keywords: Radiopharmaceuticals, Bone imaging, Phosphates, Phosphonates, Biodistribution

1. Introduction

Radiopharmaceuticals are important diagnostic tools for the diagnosis of various diseases of bones. They can be useful in detecting bone pathology of unknown origin, suspected malignancy, selection of site for bone biopsy, bone metastasis, tumors, bone trauma fracture, compression fracture in the spine, inflammatory bone disease, soft tissue calcification and site of Paget's disease.

Since the early 1970's a number of such compounds have been introduced for bone imaging. Initially ^{99m}Tc-tripolyphosphate was introduced, which was soon replaced with ^{99m}Tc-polyphosphate. 1-hydroxyethylidene diphosphonate (HEDP), methylene diphosphonate (MDP), hydroxymethylene diphosphonate (HDP) and pyrophosphate labeled with ^{99m}Tc were then introduced with relatively better results in bone imaging [1]. It was shown that ^{99m}Tc-methylene diphosphonate is a superior agent for skeletal imaging due to its better concentration and retention in bone tissue, negligible fecal excretion, fast clearance relative to pyrophosphates and polyphosphates, 1-hydroxyethylidene diphosphonate (HEDP), hydroxymethylene diphosphonate (HDP) and better image quality as early as 2 hrs. after administration and so far ^{99m}Tc-MDP is accepted worldwide.

These compounds can be easily labeled with Technetium-99m, which is easily available isotope in our country. This isotope was discovered in 1937 [2] and is now eluted from a generator system for organ imaging in nuclear medicine. The use of technetium-99m as a tracer in medicine was originally suggested because of its optimum nuclear properties [3]. Since that time it has become the nuclide of choice in many different types of imaging procedures and chemical formulations employed so far.

The use of ready-made imported commercial kits for bone imaging has been very common in nuclear medicine departments of our country in the past. Many of these departments have shifted or are shifting to locally produced radiopharmaceuticals. The homemade imaging agents are cost saving and can be locally prepared by developing simple, good quality and quick techniques. This not only saves foreign exchange but also improves the understanding of our technologists. This study has, therefore, been conducted to achieve this goal.

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Each radiolabeled compound must be tested for radiochemical purity (radiochemical binding) before use in patients. Unless the radiopharmaceutical is efficiently tagged, the accuracy of the patient diagnosis may be compromised [4].

2. Materials and Method

2.1. Principle of labeling with technetium-99m

The structure of pyrophosphates and disphosphonate is shown below :

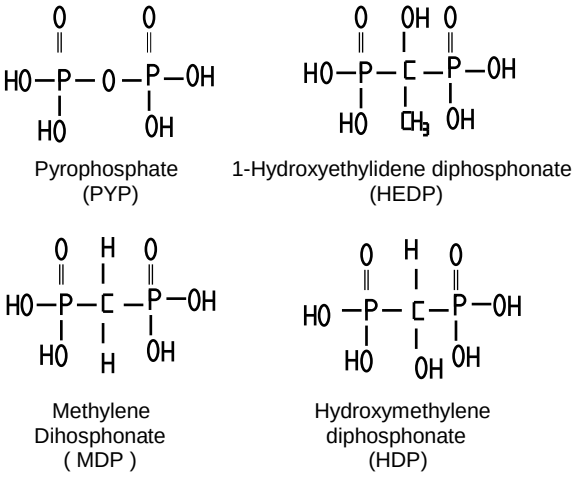


Figure 1. Structures of phosphate compounds.

The labeling of phosphates and diphosphonates with technetium involves reduction of technetium from +7 oxidation state to +4 oxidation state followed by combination of reduced technetium with donor atoms of these compounds. The reduction of technetium is summarized below [5].

$$3Sn^{2+} \rightarrow 3Sn^{4+} + 6e^{-} \quad (1)$$

$$2^{99m}TcO_4^{-} + 16H^{+} + 6e^{-} \rightarrow 2^{99m}Tc^{4+} + 8H_2O \quad (2)$$

Adding the two equations, we get

$$2^{99m}TcO_4^{-} + 16H^{+} + 3Sn^{2+} \rightarrow 2^{99m}Tc^{4+} + 3Sn^{4+} + 8H_2O \quad (3)$$

Equation 2 indicates that $^{99m}Tc^{7+}$ has been reduced to $^{99m}Tc^{4+}$.

Reduced technetium (Tc^{+4}) is highly reactive and can accept lone pairs of electrons from oxygen atoms of methylene diphosphonate and pyrophosphate anions forming coordinate covalent bonds. The result is in the formation of a chelate complex as shown in Fig. 2.

The preparation of ^{99m}Tc-phosphate complexes involves reduction of $^{99m}TcO_4^-$ with Sn^{2+} in an acidic medium and then allowing the reduced technetium to bind to phosphate compounds. The final pH is adjusted to 6 with dilute NaOH. Disphosphonates and pyrophosphates are most commonly available in kit form.

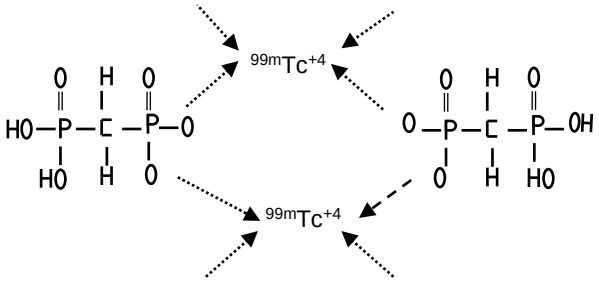


Figure 2. Principle structure of labeling MDP with technetium.

2.2. Materials required / arranged

i. MDP and PYP compound : Sigma, Germany.

ii. Stannous Chloride: ($SnCl_2.2H_2O$) SIGMA/ ALDRICH, Germany.

iii. Sterile Saline: Manufactured by Otsuka, Pakistan Ltd. Company of Otsuka Group. Japan in 1000 ml under brand name PLASALINE (0.9 % Sodium Chloride, for intravenous infusion, B.P).

iv. 1 N NaOH : Dissolved 40 gm of NaOH in 1000 ml of distilled H_2O in flask and made 1 N solution.

v. 3 N HCl: Took 25.55 ml solution of HCl and made volume upto 100 ml with distilled H_2O.

vi. Balance: Sartorius GMBH GOTTINGEN (Germany), Type-H110, Fabr-Nr: 40020112

vii. Vortex machine [Mixer], Made in Germany, Heidolph REAX 2000, No. 541.19000.000, Serial no. 059758019.

viii. Fumehood with shielding facility from radiation: ALLEN-BRADLEY Co. Milwaukee, Wis. (Made in U.S.A).

ix. Radiation Contamination monitor: Model TBM-3, Technical associates CANOGA PARK CALIFORNIA, USA.

x. Radiation dose calibrator: Radioisotope calibrator CRC-30, CAPINTEC, U.S.A. Model CRC-30, S.No. 30169. V/HZ 220/50 Code 8 AMP 3.

This instrument was used to measure activity of ^{99m}Tc, in the eluate. The concentration of radioactivity was calculated by dividing the activity measured over volume of the eluate.

xi. Portable Radiation Dose Rate Meter (survey meter): NE Technology, UK.

xii. Gamma counter. CAP – RIA 16 . CAPINTEC Instrument, INC, Pitsburgh, USA.

xiii. Rabbits for bone scintigraphy were provided by animal house Nishtar Medical College and Hospital, Multan.

xiv. Lab apparatus. pH Paper (MACHEREY-NAGEL.W.Germany), Pipettes (2ml, 10 ml; HBG.W, Germany), Micropipettes. (1ml, 500µl, 250 µl, SOCOREX, Swiss), Beaker (100ml IWAKI.), Disposable Syringes (3ml, 1ml, PARAS), Disposable Gloves, Filter paper (Whatman-1), Millipore Filter Paper (Millipore Corporation, Bedford, MA01730, UK).

2.3. Labeling of methylene diphosphonate with ^{99m}Tc.

A number of combinations of concentrations of MDP and PYP with $SnCl_2$ were tried. Radiochemical binding was checked by paper chromatography.

Preparation of Solutions

Solution-1

Weighed 50 mg of methylene diphosphonate (MDP) and dissolved it in 5 ml of normal saline to prepare a concentration of 2 mg MDP/ml. Mixed thoroughly and stored in refrigerator until use.

Solution-2

Weighed 20 mg of $SnCl_2$. $2H_2O$ and added to it 5 ml of 3N HCl to prepare 4 mg $SnCl_2$ per millilitre. Heated it slowly until clear solution was obtained. Always used freshly prepared solution.

Optimization of procedure of labeling of MDP with ^{99m}Tc.

The procedure of labeling was developed after optimization of various parameters of reaction mixture. The detail is given below:

(a) Optimization of concentration of $SnCl_2$. $2H_2O$

In order to find useable amount of $SnCl_2$ prepared solution-1 (10 mg MDP) was divided in 4 equal parts (in properly labeled four glass vials) each of 1 ml. To these vials 0.25 mg (60 µl), 0.5 mg (120 µl), 1 mg (240 µl) and 2 mg (480 µl) of $SnCl_2$ (solution-2) were added followed by gently mixing the components. Added 20 mCi of ^{99m}Tc to each and performed paper chromatography to find radiochemical binding. Selected the optimum amount of tin at maximum binding (1-2 mg $SnCl_2$; see results section).

(b) Optimization of concentration of MDP

Prepared the serial dilutions of solution-1 in normal saline (by doubling dilution method) resulting in following concentrations of MDP: 2.5 mg/ml, 5 mg/ml, 7.5 mg/ml and 10 mg/ml. Added 0.25 ml (1mg $SnCl_2$) of solution-2 into each dilution followed by addition of 20 mCi of ^{99m}Tc-TcO_4 and performed paper chromatography of each concentration to find radiochemical binding. Selected optimum concentration of MDP from the chromatographic data (it was around 5-7 mg/ml; see results section).

(c) Optimization of pH of MDP/$SnCl_2$ mixture to get maximum radiochemical yield

Effect of pH was studied at six different pH values ranging from 1 to 14. Took six vials and labeled them as 1, 3, 6, 7, 9 or 14. In each vial 1ml of Solution-1 (5 mg MDP) and 0.25 ml of Solution-2 (1mg $SnCl_2$) was taken. Mixed thoroughly and adjusted the pH of each vial with the help of dilute NaOH according to the labels of vials (i.e., 1, 3, 6, 7, 9 and 14). Added 20mCi ^{99m}Tc in each vial and performed the quality control to find the pH value where maximum radiochemical binding occurs (the optimum pH observed was 6; see results section).

(d) Preparation of injectable technetium labeled methylene diphosphonate (MDP) solution.

1 ml of Solution-1 (5 mg MDP) and 0.25ml of solution-2 (1 mg $SnCl_2$) were taken with the help of a pipette in a sterilized clean vial. Mixed thoroughly and adjusted the pH to 6 with dilute NaOH. Measured 20 mCi of ^{99m}Tc using a dose calibrator and added to the above reaction mixture. Mixed well and performed paper chromatography to recheck the radiochemical binding.

(e) Determination of stability of Tc^{99m}-labeled methylene diphosphonate.

To determine the stability of ^{99m}Tc-labeled MDP performed paper chromatography experiments immediately after the preparation of ^{99m}Tc-labeled MDP and serially after every one hour for a period

of 5 hours and noted the time where the radiochemical binding remains the same.

(f) Study of pyrogenicity of radiolabeled MDP.

About 0.5 mCi of ^{99m}Tc-MDP was injected to a rabbit and rectal temperatures were noted to check any pyrogenic reactions for a period of 3 hours.

(g) Method of study of biological distribution of ^{99m}Tc labeled MDP in rabbit.

0.5 mCi of the injectable dose (step d) was injected intravenously through ear vein of preweighed rabbit. After about 2 hours, bone scans from dorsal and ventral side were taken with the help of a gamma camera. The animal was then sacrificed and all the blood was collected in a pre-weighed beaker to find the activity per gram of blood. Different tissues and organs were then removed from sacrificed animal and their weight and activity was measured. Calculated the amount of radioactivity per gram of each tissue or organ from these measurements and compared with the injected activity using following formulas.

A_{inj} = Activity injected/wt of rabbit

A_{accu} = Activity observed/Wt of tissue

%Ar = A_{accu}/A_{inj} (after decay correction)/ X 100

Where

A_{inj} = Activity per gram injected

A_{accu} = Activity per gram accumulated in tissue

% Ar = Relative amount of radioactivity accumulated in tissue.

2.4. Labeling of sodium pyrophosphate with technetium (^{99m}Tc).

Preparation of solutions

Solution-1:

Weighed 50 mg of Sodium pyrophosphate (PYP) and dissolved it in 5 ml of normal saline to prepare a concentration of 4 mg PYP/ml. Mixed thoroughly and stored in refrigerator till use.

Solution-2:

Weighed 20 mg of $SnCl_2$. $2H_2O$ and added to it 5 ml of 3N HCl to prepare 4 mg $SnCl_2$ per millilitre. Heated it slowly until clear solution was obtained. Always used freshly prepared solution.

Optimization of procedure of labeling of PYP with ^{99m}Tc.

The procedure of labeling was developed after optimization of various parameters of reaction mixture. The detail is given below:

(a) Optimization of concentration of $SnCl_2$. $2H_2O$

In order to find useable amount of $SnCl_2$ prepared solution-1 was divided in 4 equal parts (in properly labeled four glass vials) each of 1 ml. To these vials 0.25 mg (60 µl), 0.5 mg(120 µl), 1 mg (240 µl) and 2 mg (480 µl) of $SnCl_2$ (solution-2) were added followed by gently mixing the components. Added 20 mCi of ^{99m}Tc to each and performed paper chromatography to find radiochemical binding/yield. Selected the optimum amount of tin at maximum binding (1-2 mg $SnCl_2$; see results section).

(b) Optimization of concentration of Sodium pyrophosphate (PYP).

Prepared the serial dilutions of solution-1 in normal saline resulting in following concentrations of PYP: 2.5 mg/ml, 5 mg/ml, 7.5 mg/ml and 10 mg/ml. Added 0.25 ml (1mg $SnCl_2$) of solution-2 into each dilution followed by addition of 20 mCi of ^{99m}Tc-TcO_4 and performed paper chromatography of each concentration to find radiochemical binding. (~10 mg/ml; see results).

(c) Optimization of pH of PYP/$SnCl_2$ mixture to get maximum radiochemical yield.

Effect of pH was studied at six different pH values ranging from 1 to 14. Took six vials and labeled them as 1, 3, 6, 7, 9 or 14. In each vial 1 ml of Solution-1 (5 mg MDP) and 0.25 ml of Solution-2 (1mg $SnCl_2$) was taken. Mixed thoroughly and adjusted the pH of each vial with the help of dilute NaOH according to the labels of vials (i.e., 1, 3, 6, 7, 9 and 14). Labeled each vial and added 20mCi ^{99m}Tc in it and performed the quality control to find the pH value where maximum radiochemical binding occurs (the optimum pH observed was 6; see results section).

(d) Preparation of injectable technetium labeled pyrophosphate (PYP) solution.

1 ml of Solution-1 (5 mg PYP) and 0.25 ml of solution-2 (1 mg $SnCl_2$) were taken with the help of a pipette in a sterilized clean vial. Mixed thoroughly and adjusted the pH to 6 with dilute NaOH. Measured 20 mCi of ^{99m}Tc using a dose calibrator

and added to the above reaction mixture. Performed paper chromatography to recheck the radiochemical binding.

(e) Determination of stability of ^{99m}Tc-labeled Pyrophosphate

To determine the stability of ^{99m}Tc-labeled PYP performed paper chromatography experiments immediately after the preparation of ^{99m}Tc-labeled PYP and serially after every one hour for a period of 5 hours and noted the time where the radiochemical binding remains the same.

(f). Study of pyrogenicity of radio-labeled PYP.

About 0.5 mCi of ^{99m}Tc-PYP was injected to a rabbit and rectal temperatures was noted to check any pyrogenic reactions for a period of 3 hours.

(g). Method of study of biological distribution of ^{99m}Tc- labeled PYP in rabbit.

0.5 mCi of the injectable dose (step d) was injected intravenously through ear vein of a rabbit. After about 2 hours bone scans from dorsal and ventral sides were taken with the help of a gamma camera. The animal was then sacrificed and all the blood was collected in a pre-weighed beaker to find the activity per gram of blood. Different tissues and organs were then removed from sacrificed animal and their weight and activity measured. Calculated the amount of radioactivity per gram of each tissue or organ from these measurements and compared with the injected activity using formula as mentioned above.

3. Results

Labeling of methylene diphosphonate with ^{99m}Tc.

Chromatographic data on optimization of concentration of $SnCl_2$ is given in Table 1 and displayed in Figure 3. The optimum concentration of $SnCl_2$ was observed to be 1-2 mg/ml. The data on optimization of concentration of MDP is given in Table 2 and displayed in Figure 4. The optimum concentration of MDP observed in our experiment was 5-7.5 mg/ml.

Table 1. Radiochemical bindings at various amounts of $SnCl_2$.

S. No.	Amount of $SnCl_2$ (mg)	MDP % bound activity	PYP % bound activity
1	2	99.2	97.2
2	1	99.1	98
3	0.5	84.8	78
4	0.25	87.2	79.3

Table 2. Radiochemical binding at various concentrations of MDP and pyrophosphate in the final mixture.

S. No	Conc. MDP & PYP (mg/ml)	% Bound activity (MDP)	% Bound activity (PYP)
1	10	89.6	98
2	7.5	99.3	96
3	5	99.1	97.4
4	2.5	60.8	74.4

The results on optimization of of pH of MDP/$SnCl_2$ mixture are given in Table 3 and shown in Figure 5. The optimum pH from experiments on pH was around 6. The chromatographic findings on final injectable preparation showed more than 99% binding of the radioisotope with the compound.

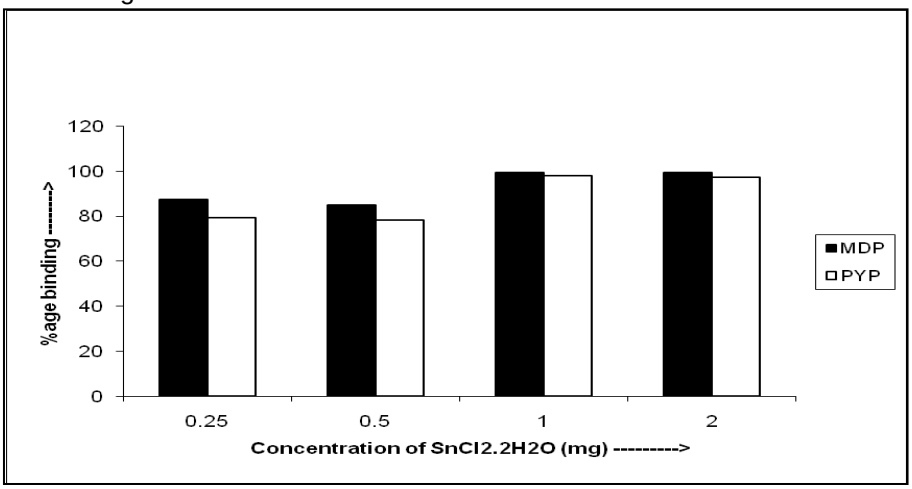


Figure 3. Percent binding versus amount of stannous chloride.

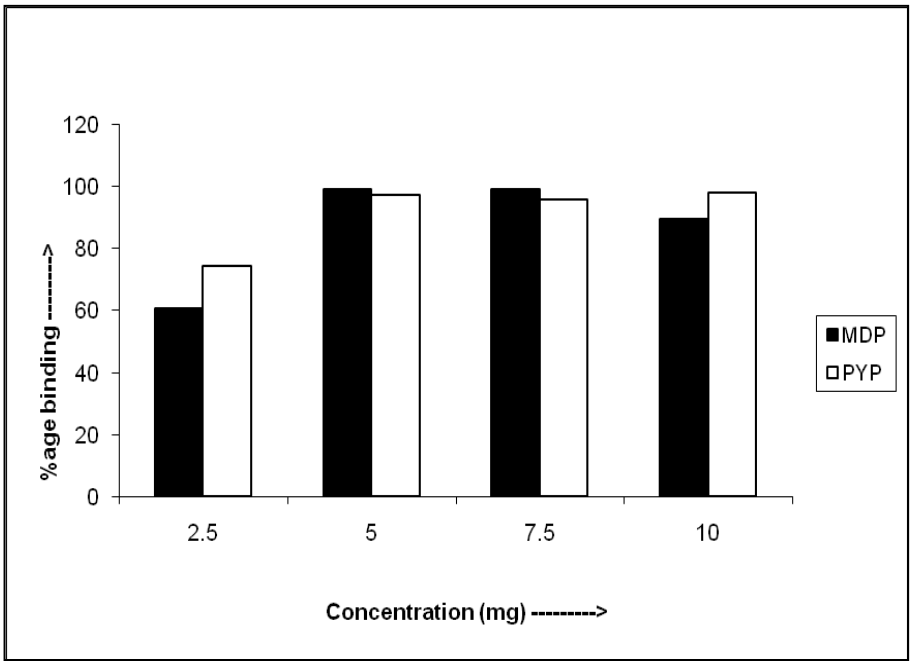


Figure 4. Percent binding versus concentration of MDP and PYP in the final mixture.

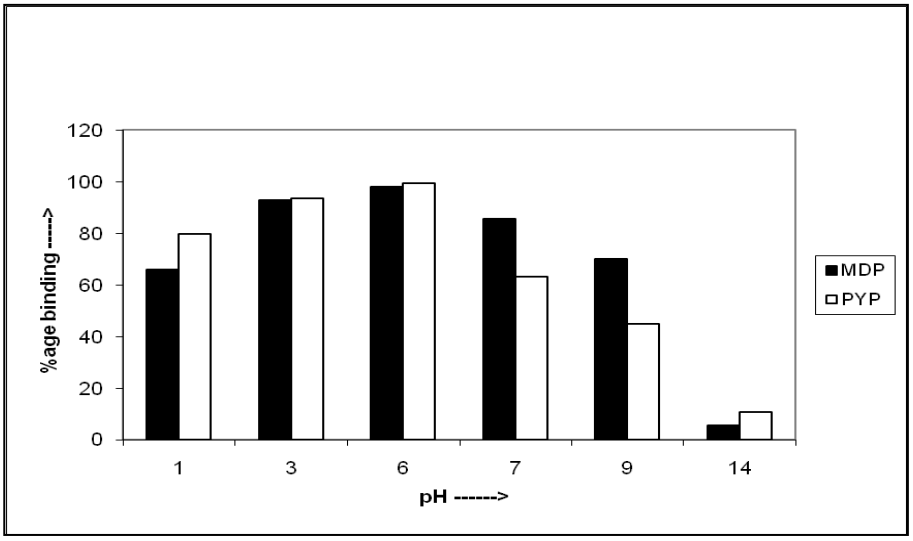


Figure 5. Percent binding versus pH of MDP and PYP in the final mixture.

The data on stability experiment of technetium labelled MDP is given in Table 4 and displayed in Figure 6. The compound was fairly stable for upto 4 hours.

Pyrogenicity of the products

No pyrogenic reactions were observed after injection of the labeled compound into the rabbit. The rectal temperatures remained stable for upto 5 hours.

Data on biological distribution of the labeled compound in rabbit is given in Table 5 and displayed in Fig. 7.

Scan results.

The radionuclide scans obtained with a rabbit is shown in Fig. 8. The bone scans obtained on a normal person and a patient with cancer of the prostate is shown in Fig. 9.

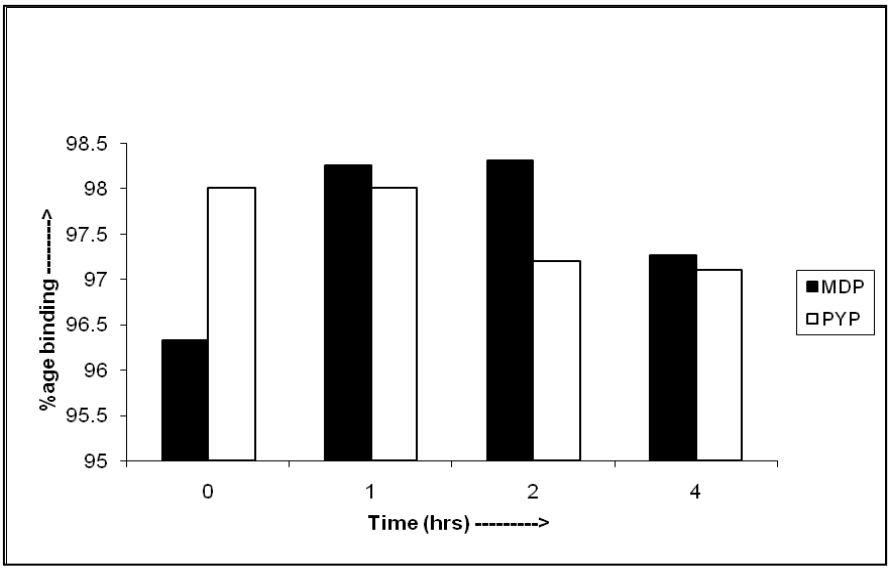


Figure 6. Percent binding versus time showing stability results of ^{99m}Tc-MDP and ^{99m}Tc - PYP in the final mixture

Table 3. Radiochemical binding at various concentrations of pH .

pH	MDP % bound activity	PYP % bound activity
1	65.8	79.5
3	92.6	93.4
6	98	99.3
7	85.6	63.2
9	69.9	44.8
14	5.5	10.6

Table 4. Radiochemical binding at different time intervals.

Time (hr)	MDP % bound activity	PYP % bound activity
1	96.33	98
2	98.25	98
3	98.31	97.2
4	97.26	97.1

Labeling of pyrophosphate with ^{99m} Tc.

Chromatographic data on optimization of concentration of $SnCl_2$, concentration of PYP and optimization of pH is given in tables 1, 2, 3 and displayed in figures-3, 4 & 5 respectively The optimum concentration of $SnCl_2$ was observed was 1-2 .

Table 5. Comparison between biological distribution of ^{99m}Tc - MDP and ^{99m}Tc –PYP.

No.	Organ or tissue	^{99m}Tc –MDP %activity/gm.	^{99m}Tc –PYP %activity /gm.
1	Bone	23.8	10.60
2	Bladder	24.3	30.99
3	Kidney	5.5	32.08
4	Liver	7.9	1.31
5	Lung	1.28	1.24
6	Heart	3.16	7.07
7	Stomach	1.30	0.07
8	Small intestine	0.87	1.20
9	Large intestine	0.37	1.13
10	Blood	2.2	3.42
11	Skin	4.2	3.29
12	Other tissues plus losses through urine	25.12	7.6
Thyroid, muscle, spleen etc.			

mg/ml whereas the observed optimum concentration of PYP was about 10 mg/ml. The observed pH value was around 6.

The data on stability experiment of technetium labelled PYP is given in Table 4 and displayed in

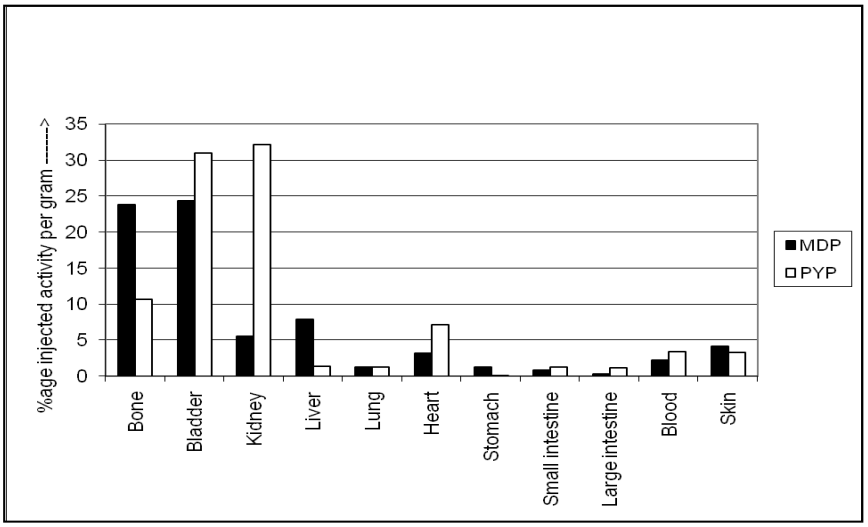


Figure 7. Comparison of biological distribution of ^{99m}Tc-MDP and ^{99m}Tc-PYP (expressed as % age of injected dose per gram).

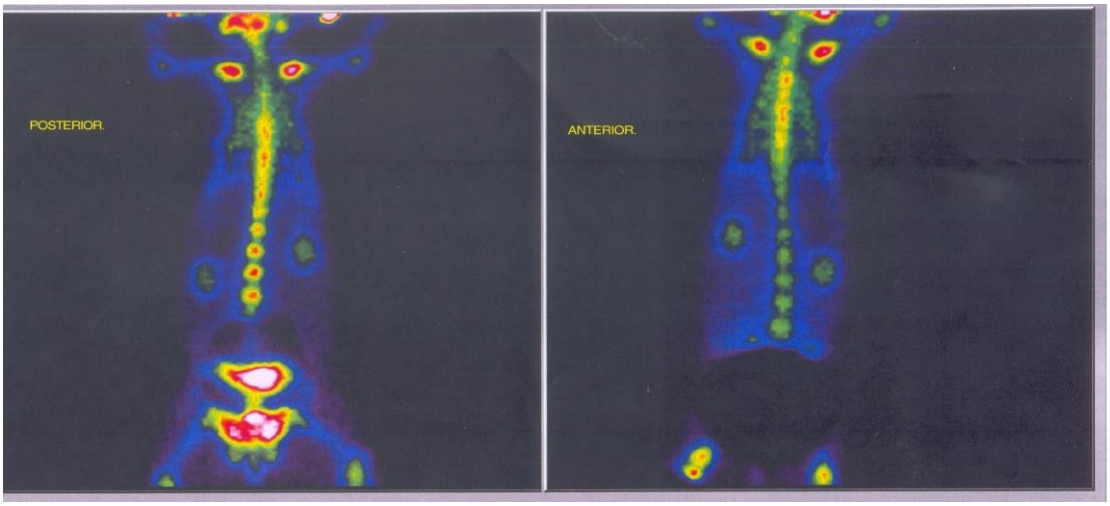


Figure 8. The radionuclide scans obtained on a rabbit using ^{99m} Tc-MDP.

figure 6. The labeled compound was fairly stable for upto 4 hours. Here again no pyrogenic reactions were observed after injection of the labelled compound into the rabbit. The rectal temperatures remained stable for upto 5 hours.

Data on biological distribution of the labelled compound in rabbit is given in Table 5 and displayed in Fig. 7. The radionuclide scan obtained with a rabbit is shown in Fig. 10. Bone scan of a normal person and a patient with metastatic lesion in lumber region is shown in Fig. 11.

4. Discussion

^{99m}Tc-labeled pyrophosphate and methylene diphosphonate (MDP) are most commonly used compounds for bone imaging [6].

Bone scintigraphy or bone imaging with technetium-99m–labeled diphosphonates is one of the most frequently performed radionuclide procedures. The technique has excellent sensitivity for many pathologic conditions like bone trauma, and osteomyelitis. Radionuclide bone imaging will likely remain a popular and important imaging modality for years to come [7]. These compounds bind to the surface of bone by a process called chemisorption. Chemisorption or chemical adsorption results from chemical bond formation (strong interaction between the adsorbent and the adsorbate) in a monolayer on the surface. (IUPAC, Compendium of terminology 2nd Ed. 1997). The exact mechanism is not known although many mechanisms have been proposed [8-10]. In the radiopharmaceutical laboratories of our country

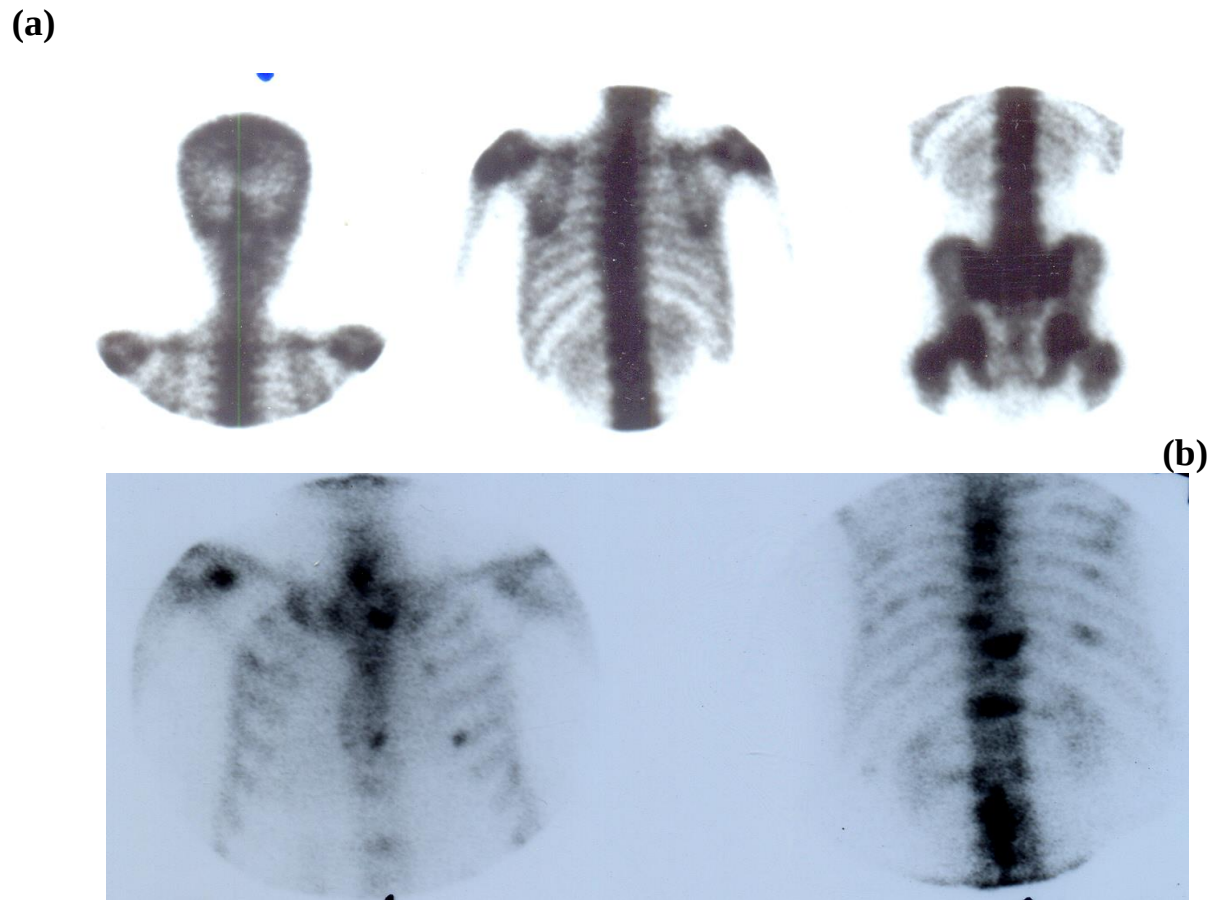
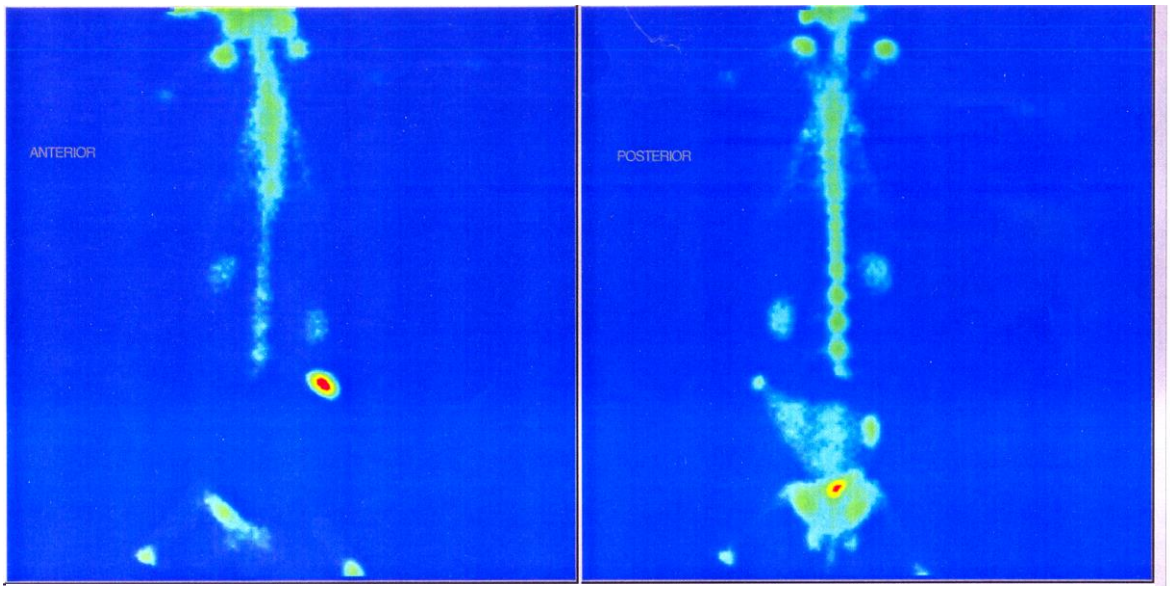


Figure 9. Bone scans obtained with ^{99m}Tc-MDP (a) Normal person (b) Patient with metastasis in bone (Ca-prostate). The scan shows multi-focal areas of increased radiotracer uptake in the skeleton.

ready-made commercial kits or homemade reagents are used for bone scanning. However qualitative and safety evaluations are always needed especially when local preparations are involved. Our experimental findings on optimization experiments show that optimum amounts of $SnCl_2$ in ^{99m}Tc- $SnCl_2$-MDP & ^{99m}Tc-$SnCl_2$–PYP mixtures were almost the same. (Table 1). The optimum concentrations of MDP and PYP were however slightly different (5-7.5 mg for MDP and ~10mg for PYP). The maximum radiochemical binding observed in these preparation was also similar in these preparations (>99% and >98% respectively. The optimum value for pH was also the same.

Chromatographic data obtained in stability experiment (Table 4) shows that more than 97% activity in ^{99m}Tc -MDP preparation remained tagged to MDP for more than 4 hours. The stability of ^{99m} Tc-PYP is also similar till 2 hours after preparation with slight decrease afterwards.

When these agents were injected to rabbits they gave no pyrogenic effects indicating the complete safety of these preparations. The comparison of biodistribution of these agents shows that^{99m}Tc-PYP has relatively poor bone affinity (10.60%) relative to ^{99m}Tc-MDP. The target to non-target ratio is, therefore, low in ^{99m}Tc-PYP. This indicates that the plasma clearance of ^{99m}Tc-PYP is slow relative to ^{99m}Tc-MDP and there is little efficacy of ^{99m}Tc-PYP compound in bone imaging. However the agent can be used as blood pool agent as recommended by others [11]. The results confirm the observations made by Charito Love et al. (2003) [7] that Tc-99m MDP had superior bone uptake than other phosphates. The image quality with ^{99m}Tc-MDP was better than ^{99m}TcPYP (see Figures 8 and 10) in case of rabbit. Similar results were obtained when we tried these preparations on normal persons & patients (Figures 8-10).



(a). Anterior view **(b). Posterior view**

Figure 10. The radionuclide bone scan of rabbit obtained with ^{99m}Tc-PYP.

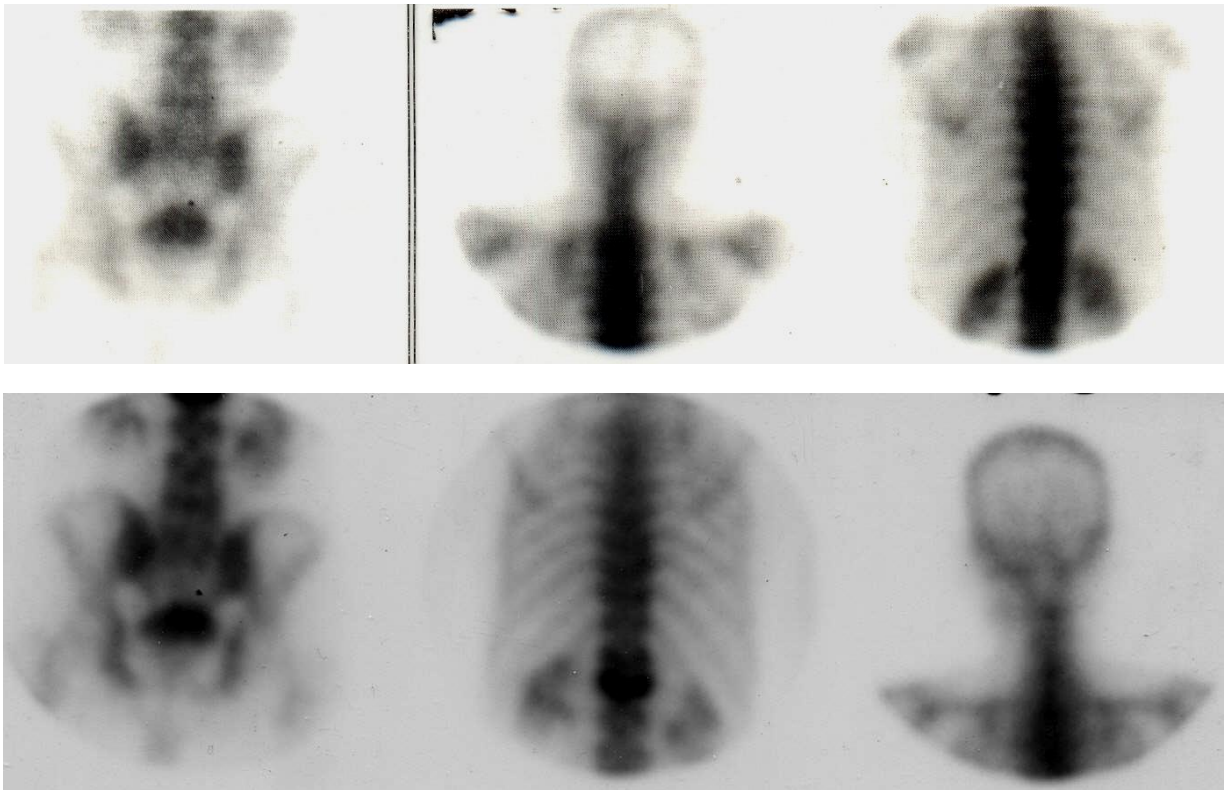


Figure 11. Bone scans obtained with ^{99m}Tc-PYP (a). Normal person (b). Patient with increased radionuclide uptake in lumber region. The scan shows multi-focal areas of increased radiotracer uptake in the skeleton.

We, therefore, conclude that the locally developed techniques for preparation of ^{99m}Tc-MDP and ^{99m}Tc-PYP are simple, safe and low cost. The data on biodistribution in these bone agents suggests relatively good target to non-target contrast with ^{99m}Tc-MDP. The image quality with

patient scans is also superior with ^{99m}Tc-MDP. This confirms that the home made ^{99m}Tc-MDP is superior in quality than ^{99m}Tc-PYP. This is in agreement with the previous findings.

5. References

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