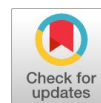




Technetium-99m Methylene Diphosphonate (^{99m}Tc -MDP): A Comprehensive Review of Its Chemistry, Clinical Utility, and Emerging Applications

Kifyat Tasnim*, Mst. Soheli Akhter Nifa, Koma Afrin Rintu



Abstract: Methylene diphosphonate (^{99m}Tc -MDP) is a bone-imaging radiopharmaceutical widely used in nuclear medicine for decades. This review provides a detailed introduction to ^{99m}Tc -MDP bone imaging, including preparation, chemical properties, radiolabeling techniques, quality control, clinical applications, and recent developments. This article emphasises MDP kit preparation, the basic principles of radiopharmaceutical labelling, and the importance of technetium-99m as a diagnostic radionuclide. Over the years, researchers have also emphasised radiolabeling efficiency, radiochemical purity, and the stability of radiopharmaceutical preparations to ensure safe, effective use. This review highlights the clinical role of ^{99m}Tc -MDP in detecting and evaluating different skeletal lesions (i.e., fractures, bone metastases, metabolic bone diseases). It also describes the current state of bone imaging and the enduring role of ^{99m}Tc -MDP as a diagnostic tool. The discussion also covers new applications, technological advances, radiation exposure, and patient safety. It also discusses future perspectives in nuclear pharmacy, including the development of new radiopharmaceuticals and improved imaging strategies. This review compiles available data and provides insights for nuclear medicine professionals, radiologists, and researchers on current applications, technical aspects, and prospects for ^{99m}Tc -MDP in imaging skeletal phenomena.

Keywords: MDP, Radiopharmaceuticals, Radiolabeling, Metastases.

Nomenclature:

^{99m}Tc : Technetium-99m

^{99}Mo : Molybdenum-99

MDP: Methylene Diphosphonate

^{99m}Tc -MDP: Technetium-99m Methylene Diphosphonate

RCP: Radiochemical Purity

PET: Positron Emission Tomography

SPECT: Single-Photon Emission Computed Tomography

MAG3: Mercaptoacetyltriglycine

DTPA: Diethylenetriaminepentaacetic acid

GFR: Glomerular Filtration Rate

RBCs: Red Blood Cells

CUDs: Cold Unit Doses

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*Correspondence Author(s)

Kifyat Tasnim*, Department of Pharmacy, Stamford University, Dhaka, Bangladesh. Email ID: kifyatlin@gmail.com, kifyat@stamforduniversity.edu.bd, ORCID ID: [0009-0009-6554-5021](https://orcid.org/0009-0009-6554-5021).

Mst. Soheli Akhter Nifa, Department of Pharmacy, Stamford University, Dhaka, Bangladesh. Email ID: sohelinifa07@gmail.com, ORCID ID: [0007-0907-6916](https://orcid.org/0007-0907-6916).

Koma Afrin Rintu, Department of Pharmacy, State University of Bangladesh, Dhaka, Bangladesh. Email ID: afrinrintu361@gmail.com, ORCID ID: [0000-0003-3089-110X](https://orcid.org/0000-0003-3089-110X).

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I. INTRODUCTION

Targeted radionuclide therapies are mainly a multidisciplinary field where radionuclides can be expected to work in harmony and cooperation with specialists of various disciplines [1]. Radiologists are constantly studying the clinical and biological effects of ionizing radiation, particularly cellular and molecular mechanisms underlying radiation responses [2]. Progression in nuclear medicine has largely been propelled through the wide accessibility and clinical flexibility of radiopharmaceuticals containing ^{99m}Tc (approximately 80% of this single isotope is used for several diagnostic procedures; furthermore, close to 25 million (high) necessities are done by both visualisation examinations using either the ^{99m}Tc -labeled counterparts); but also, at a rate on the request of around roughly–15% yearly) [3]. ^{99m}Tc is the most widely used radionuclide in diagnostic imaging [4], a noninvasive method used to diagnose disease, evaluate disease state, and monitor treatment outcomes [5]. Radiopharmaceuticals are an advanced class of compounds widely used in nuclear pharmacy that contain a bound radionuclide [6]. Radiopharmaceuticals are compounds intended for diagnostic and therapeutic use that may not alter physiological processes; they consist of two major components: the pharmaceutical part and the radioactive tracer molecule [7].

The pharmaceutical component primarily acts as a carrier, delivering radioactive tracers to various organs and tissues [8]. In the pharmaceutical industry, MDP is used as a stabilising agent in formulations of metal-ion-carrying drugs, such as iron or calcium [9]. MDP is also an excellent bone imaging agent [10]. MDP can bind to calcium salts in bones because it clears quickly from the blood [11]. ^{99m}Tc -MDP is a radiopharmaceutical; like other radiopharmaceuticals, it consists of two parts: a radioactive tracer element (radionuclide, ^{99m}Tc) and a pharmaceutical compound (MDP) that acts as a carrier. Both the cold MDP kit and the dry (lyophilised) MDP kit can be labelled with an adequate volume of ^{99m}Tc [12], which is generally eluted from a $^{99}\text{Mo}/^{99m}\text{Tc}$ generator. After radiolabeling, radiochemical purity determination is another step before exploring the MDP study area. A high RCP value is a positive sign for bone imaging because it indicates the amount of TcO_2 [13]. Several studies report that ^{99m}Tc -MDP has a broad range of clinical applications; this article focuses on its therapeutic and diagnostic uses.



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II. MATERIALS AND METHOD

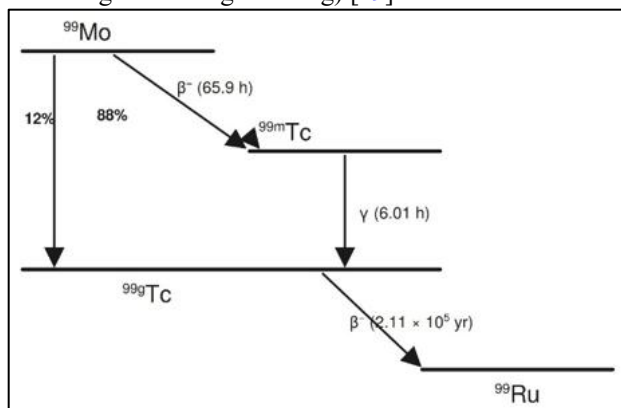
In this literature review of the current clinical applications of radiopharmaceuticals, we employed a systematic approach. We searched databases such as PubMed, Web of Science, and Google Scholar using terms including MDP, ^{99m}Tc , and $^{99m}\text{Tc-MDP}$. After removing duplicates, we reviewed 100 unique articles and manually searched the reference lists of relevant reviews, resulting in 50 included articles. We systematically extracted data, including author(s), publication year, and key findings. The included studies raised no ethical concerns or conflicts of interest.

A. ^{99m}Tc as a Radionuclide

^{99m}Tc has a major advantage because it can form a variety of complexes with specific desired characteristics; moreover, it offers versatile chemistry [14]. Hundreds of ^{99m}Tc complexes are useful for diagnostic procedures, and over thirty are used in clinical studies [15]. Despite the increase in Positron Emission Tomography (PET) procedures, technetium-99m (^{99m}Tc ; $t_{1/2}=6$ h, $E_{\gamma}=140$ keV) remains a fundamental agent in nuclear medicine imaging.

Technetium is a transition metal with the electron configuration $[\text{Kr}] 4d^5 5s^2$. This configuration allows it to complex with a range of ligands and adopt oxidation states from +1 to +7 [16].

Technetium forms σ (sigma) and π (pi) bonds. Sigma may refer to either a pair of unpaired electrons or a pair donated by a ligand [17]. The stability of these technetium complexes depends on the coordinating atoms and their orientation. Pertechnetate, in the +7 oxidation state, is remarkably stable in aqueous solutions [18]. Free pertechnetate can contaminate some technetium-labelled preparations (mainly after long-term storage following labelling) [19].



[Fig.1: Graphical Depiction of the Mo-99 Decay Chain (this Flowchart is Drawn by Canva Illustration)]

Technetium-99 is produced as a byproduct of nuclear fission during nuclear reactor operation and in explosive devices, and it occurs in the waste from these processes [20]. One of its metastable states, technetium- ^{99m} , has extensive applications in diagnostic nuclear medicine. Technetium- ^{99m} has a physical half-life of ~ 6 hours, making the radiation available for diagnostic imaging without lengthy continued exposure. It decays into technetium- ^{99} , which has a much longer half-life [21].

The elution of ^{99m}Tc from the generator is, in fact, a pertechnetate anion. Heptavalent technetium must be reduced to a lower oxidation state to become chemically reactive for labelling; additionally, ^{99m}Tc pharmaceuticals are predominantly complexes of ^{99m}Tc in different oxidation states (I to V) [22].

Commercial cold kits are available with lyophilised components ready for ^{99m}Tc -pertechnetate labelling, which greatly simplifies the preparation of ^{99m}Tc pharmaceuticals [23].

B. Diagnostic usage of ^{99m}Tc

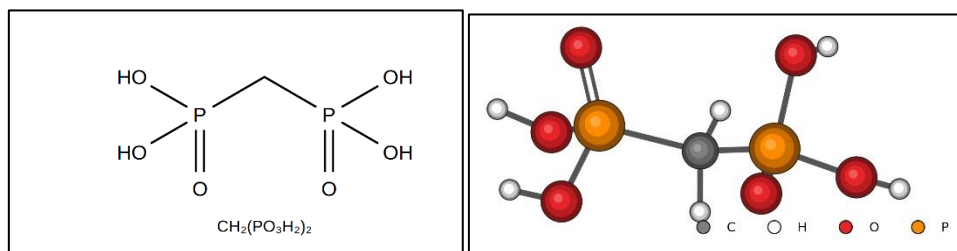
Today, nuclear medicine and advanced science use the radioactive isotope ^{99m}Tc (technetium- ^{99m}) for diagnostic purposes. Its distinctive properties make it an ideal choice for a range of diagnostic imaging techniques. Here is the list of recent applications of ^{99m}Tc

- Nuclear Imaging:** In single-photon emission computed tomography (SPECT) imaging, ^{99m}Tc is frequently employed and can be used to evaluate the state of various bodily systems as well as the organs in terms of their functionality. Imaging of the heart (myocardial perfusion imaging), the bones (bone scans), the lungs (ventilation/perfusion scans), and the liver and spleen (hepatobiliary scans) are examples of nuclear imaging [24].
- Thyroid Imaging:** Assessment of the thyroid glands' anatomy and function; ^{99m}Tc -pertechnetate is utilised and absorbed by the thyroid and also aids in determining the presence of thyroid nodules, hyperthyroidism, and hypothyroidism [25].
- Renal Imaging:** ^{99m}Tc -mercaptoacetyl triglycine (MAG3) and ^{99m}Tc -diethylenetriamine penta-acetic acid (DTPA) are used to evaluate the structure and function of the kidneys. These agents help assess renal blood flow, glomerular filtration rate (GFR), and urinary tract obstruction [26].
- Gastrointestinal Imaging:** ^{99m}Tc -labelled compounds such as sulfur colloid and labelled red blood cells (RBCs) are used for imaging the gastrointestinal system. They can help evaluate gastrointestinal bleeding, detect sites of infection or inflammation, and assess liver function [27].

III. OVERVIEW OF METHYLENE DIPHOSPHONIC ACID

Methylene diphosphonic acid (MDP) is commonly used as a sequestering agent [28]. In the pharmaceutical industry, MDP is used as a stabilising agent in formulations of metal-containing drugs, such as iron or calcium. It can help prevent degradation and improve efficacy and shelf life [29]. Researchers have also investigated MDP for potential therapeutic applications [30]. For example, Research has demonstrated its anti-inflammatory and antioxidant properties, and it may have potential as a treatment for conditions such as osteoporosis and cancer and cancer [31].





[Fig.2: 2D and 3D Conformation of MDP (Structure was Drawn Using ChemDraw)]

Because of the two phosphonic acid groups, MDP is acidic. At higher pH levels, these acid groups can donate protons (H^+) to aqueous solutions, forming MDP anions ($CH_2(PO_3H)^{-2}$). In many chemical conditions, pH-dependent ionisation affects MDP's solubility and reactivity [32].

IV. DIAGNOSTIC USAGE OF MDP

Methylene diphosphonic acid (MDP) is mainly known for its diagnostic usage in nuclear medicine imaging. It is commonly used as a radiopharmaceutical agent in bone scintigraphy, specifically as technetium-99m (^{99m}Tc)-labelled MDP. Here are some details about the diagnostic usage of MDP:

- A. Bone Scintigraphy:** MDP is used to assess various bone conditions and diseases through a diagnostic imaging technique known as bone scintigraphy or bone scan. A small amount of ^{99m}Tc -labelled MDP is injected intravenously. The radiopharmaceutical is then distributed throughout the skeletal system, mainly targeting areas of active bone metabolism [33]
- B. Detection of Bone Abnormalities:** Once inside the body, the ^{99m}Tc -labelled MDP emits gamma radiation, which is detected by a gamma camera. Abnormalities, such as bone tumours, metastases, infections, and fractures, can appear as "hot spots" on scintigraphy images. Conversely, areas with decreased bone activity may display as "cold spots" [34]
- C. Assessment of Bone Metabolism:** Bone scintigraphy provides valuable insights about bone metabolism and blood flow. It can help diagnose conditions like osteomyelitis (bone infection), osteoporosis, stress fractures, and bone tumours. It also assesses treatment response and monitors disease progression [3].

V. INTRODUCING ^{99m}Tc -MDP AS A RADIOPHARMACEUTICAL

Designing a radiopharmaceutical involves crucial decisions, such as choosing a suitable vector molecule and an appropriate radionuclide, while considering the nature and location of the molecular target, the intended use, and the time limitations imposed by the relatively short half-life of radionuclides [35]. Well-designed in vitro and in vivo experiments permit nonclinical validation of the radiotracer. In particular, the rediscovery of technetium- ^{99m} remains important in nuclear medicine because of its ideal nuclear properties and the ease of preparing radiopharmaceuticals without costly infrastructure or complex procedures [16].

A. Radiolabelling and Radiochemical Purity

The instant method of radiolabeling is the most common technique [36]. To prepare the ^{99m}Tc -MDP

radiopharmaceutical, MDP should be labelled with an adequate volume of ^{99m}Tc [37]. Determining radiochemical purity is essential because adulterants may arise from incomplete labelling and breakdown of radiolabeled formulations over time due to incompatibilities or other unwanted occurrences. Radiochemical purity, or RCP, can be determined by thin-layer chromatography, paper chromatography, high-performance liquid chromatography, etc. [38]

B. Research Arena of ^{99m}Tc -MDP

Numerous studies show that Technetium- ^{99m} (^{99m}Tc) meets the criteria for diagnostic nuclear medicine imaging, making it a high-impact, widely used radionuclide in medicine.

- i. **Diagnostic Imaging:** The ^{99m}Tc -MDP radiopharmaceutical is widely used as a bone imaging agent that plays a vital role in the diagnostic arena [39].
- ii. **Detection of Bone Metastases:** Statistical analysis of quantitative data showed that the lesion-to-normal bone ratio was significantly higher when using MDP with ^{99m}Tc [40]
- iii. **Study of the Effect of Whole-Blood Vibration:** This investigation indicates that vibration in whole blood (in Wistar rats) could produce metabolic alterations with an influence on the uptake of the radiopharmaceutical ^{99m}Tc -MDP in bone, stomach, bowel, prostate, kidney and bladder [41].
- iv. **Detection of Alveolar Bone Loss:** After a single injection of ^{99m}Tc -methylene diphosphonate, it shows significant radiopharmaceutical uptake that detects active alveolar bone destruction in human periodontal disease [44]
- v. **Miscellaneous:**
 - **Incidence of Intestinal ^{99m}Tc -MDP Uptake:** ^{99m}Tc -MDP uptake can be observed in the intestines during bone scan due to Chilaiditi's syndrome as well as delayed imaging [42].
 - **Observation of Unwanted Uptake of ^{99m}Tc -MDP:** ^{99m}Tc -MDP is accumulated by soft tissues, which occurs occasionally due to some clinical conditions in patients [43].
 - **Abnormal Skull Uptake of ^{99m}Tc -MDP:** Unusual uptake of ^{99m}Tc -MDP by the skull can be found in numerous neoplastic and non-neoplastic diseases [44].

VI. CONCLUSION

The main purpose of this review is to help us understand different aspects



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of research on the diagnostic and therapeutic phases of ^{99m}Tc-MDP. This matters because researchers have used different approaches to study this radiopharmaceutical. Most of the research found focused on bone cancer, metastases, cardiac infarction, and bone scintigraphy with ^{99m}Tc-labelled kits. More research and testing are needed to understand better why this particular radiopharmaceutical is preferred; formal production can also be established.

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DECLARATION STATEMENT

Some of the cited references are older and are noted explicitly as [6], [20], [21], [29], [36] and [40]. However, these works remain significant for the current study, as they are pioneering in their fields.

After aggregating input from all authors, I must verify the accuracy of the following information as the article's author.

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- **Author's Contributions:** The authorship of this article is contributed equally to all participating individuals.

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AUTHOR’S DETAILS



Kifyat Tasnim completed my academic journey at Jashore University of Science and Technology and began my teaching career as a Lecturer of Pharmacy at Stamford University Bangladesh in January 2025. I teach Pharmacy courses, including Inorganic Pharmacy, Medicinal Chemistry, Pharmaceutical Marketing, and Cosmetology, as well as related laboratory courses. My research experience includes work in radiopharmaceuticals at the Atomic Energy Research Establishment, where I explored innovative radiopharmaceuticals to advance nuclear medicine and healthcare; this work was published in the *Bangladesh Journal of Nuclear Medicine*. Recently, I presented one of my projects at ICPS 2026. Beyond academics, I actively organise and participate in meaningful extracurricular activities. I have contributed to initiatives such as medical health camps, academic seminars, and workshops that bridge the gap between theory and practice.



Mst. Soheli Akhter Nifa, M.Pharm, is a Lecturer in the Department of Pharmacy at Stamford University Bangladesh, Dhaka. I earned my Bachelor of Pharmacy (Professional) and Master of Pharmacy from Pabna University of Science and Technology, where I ranked second in my batch in both programs. My research focuses on medicinal mushrooms and natural products, including phytochemical characterisation, in vitro and in vivo pharmacological evaluation, and in silico analysis. My work on the methanolic extract of *Ganoderma lucidum* was published in the *Journal of Ethnopharmacology* (2026) and presented at international conferences, including ICRAST 2025, EFAST 2026, and ICPS 2026. I have received the Dean's Award, the NST Fellowship from the Ministry of Education, and university merit scholarships. I am keen to pursue doctoral training in pharmaceutical sciences, focusing on bioactive compounds from natural products.



Koma Afrin Rintu, B.Pharm (Professional), M.Pharm, and a Lecturer in the Department of Pharmacy at State University of Bangladesh. I completed my B. Pharm (Professional) and M.Pharm in Pharmaceutical Chemistry at the University of Dhaka. I completed my B. Pharm (Professional) and M.Pharm in Pharmaceutical Chemistry at the University of Dhaka. I completed my B. Pharm (Professional) and M.Pharm in Pharmaceutical Chemistry at the University of Dhaka. I completed my B. Pharm (Professional) and M.Pharm in Pharmaceutical Chemistry at the University of Dhaka. I completed my B. Pharm (Professional) and M.Pharm in Pharmaceutical Chemistry at the University of Dhaka. With approximately 1.5 years of teaching experience, my research interests include phytochemistry, pharmaceutical technology, and drug delivery systems. I am passionate about pharmacy education and pharmaceutical research.

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