

REVIEW ABOUT RADIOPHARMACEUTICALS: PREPARATION, RADIOACTIVITY, AND APPLICATIONS

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ABSTRACT

In the recent few decades, there was a growth in the field of radioactive medicinal agents called radiopharmaceuticals. Radiopharmaceuticals are consisting of radioactive materials called radioisotopes. Radiopharmaceuticals were recently used in both therapeutic and diagnostic purposes. More than 100 radioactive substances are used in nuclear medicine. According to the decay of radioactive substances, there are three types of radioactive decays, alpha particles, beta particles, and gamma radiations. Alpha particles consist of two protons and two neutrons with large mass and charge so it has no penetration power into the skin and has a destructive effect. Beta particles have less charge and less mass so, they can penetrate the tissue and have a less destructive effect than alpha particles and can be used in therapy. Gamma radiations have no mass or charge so they can penetrate the deep tissue of organs so used in diagnosis by imaging using a gamma camera. The radiopharmaceuticals were established in the diagnostic purpose and treatment of several diseases as thyroid gland cancer, hyperthyroidism, bone pain metastasis, kidney dysfunction, and myocardial and cerebral perfusion. The radioactive substance can also be used in the sterilization of thermo-labile substances as syringes, catheters, vitamins, hormones, and surgical dressing. The field of nuclear medicine has several advantages as localization of tumors, safe diagnosis, no accumulation of radiation, and high therapeutic efficacy. Nowadays, the branch of nuclear pharmacy is directed to introduce new radioactive pharmaceutical agents which will be important and effective in the treatment of cancer. The growth in the field of radiopharmaceuticals is important to help millions of patients suffering from tumors all over the world. The data of this review were collected by searching in Google Scholar and PubMed using the following keywords.

Keywords: Radiopharmaceuticals, Thyroid gland, Bone pain, Diagnosis, Therapeutic effect, Tumors, Myocardial and cerebral perfusion

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INTRODUCTION

Radiopharmaceuticals are radioactive substances used in the fields of diagnosis and therapy [1]. In 1978, the board of pharmaceutical specialties introduced the nuclear pharmacy as a specialty in pharmacy, which concerns the safe and effective application of radioactive agents [2].

There are more than 100 radioactive agents which used for therapeutic purpose as in localization of tumors, hyperthyroidism [3], toxic diffuse goiter [4], bone pain related to skeletal metastasis [5], cerebral perfusion [6]. Also, these radioactive drugs used in diagnosis as infection imaging and kidney dysfunction [7].

There are a wide variety of radiopharmaceuticals having different mechanisms of targeting and different forms and also different route of administration may be given in simple salt form or attached to more complex molecules [8]. There are different route of administration for radiopharmaceuticals, may be given orally parentally or installed into the eyes.

Most of the radiopharmaceuticals (about 95%) are used for diagnostic purpose while the remaining are used in therapy [9]. Radiopharmaceuticals are different than the traditional drugs in being there is no pharmacological effect [10].

The radiopharmaceuticals provide a non-invasive mechanism for targeting the therapeutic radiations with low side effects [11]. Also, in case of diagnosis, radioactive drugs represent non-invasive imaging agents which give information about the structure and function of diseased organs or tissue [12].

The aim of this review is to introduce valuable information about the safe and effective use of radiopharmaceuticals in the fields of diagnosis and therapy.

Radiopharmaceuticals

The radiopharmaceuticals are radioactive substances which disintegrate instantaneously by emitting radiations [13]. The

radioactive nuclides are like normal nuclides having the same number of protons with different numbers of neutrons. The emitted radiation may be in the form of alpha, beta, and gamma radiation [14]. The dose of radiopharmaceuticals is dispensed to the patient in the form of Curie, which equals to 3.7×10^{10} decomposition per second [15].

The radioactive substances are different in the half-life, which defined as the time needed to the disintegration of active substances to half the initial concentration [16]. As represented in table (1), an example of the most important radiopharmaceuticals and their half-life's.

Radiopharmaceuticals can be divided into four categories

• Radiopharmaceutical preparation

It is a preparation which contains radionuclide and ready to use by humans. The Presence of the radionuclide is very important, making the preparation useful in the diagnosis or therapy [28].

• Radionuclide generator

It is the system that allows separation of a daughter radionuclide (short half-life) from a parent radionuclide (long half-life) by elution or by other means to allow the use of later in the production of a radiopharmaceutical preparation [29].

• Radiopharmaceutical precursor

A radionuclide produced for the radiolabelling process with a resultant radiopharmaceutical preparation [30].

• Kit for radiopharmaceutical preparation

The kits intended for preparation of the radiopharmaceutical preparation are usually in the form of sterilized and validated vial containing the non-radionuclide components. The radionuclide is added to the vial just before use. After the addition of the appropriate radionuclide, additional steps may be needed as boiling, filtration, and buffering. The prepared radiopharmaceuticals must be used within 12 h after preparation [31].

Table 1: Different types of radionuclide and their halve life's

Radionuclide	Half-life	References
^{99m} Tc (Technetium-99m)	6.02 hour	[17]
¹³¹ I (Iodine-131)	8 d	[18]
¹⁸ F (Fluorine-18)	110 min	[19]
¹²³ I (Iodine-123)	13.27 h	[20]
⁶⁷ Ga (Gallium-67)	3.26 d	[21]
¹³³ Xe (Xenon-133)	5.24 d	[22]
²⁰¹ Tl (Thallium-201)	3.04 d	[23]
⁸⁹ Sr (Strontium-89)	50.53 d	[24]
¹²⁵ I (Iodine-125)	59.41 d	[25]
⁵⁷ Co (Cobalt-57)	271.79 d	[26]
¹⁵³ Sm (Samarium-153)	1.93 d	[27]

Radionuclide production

The radionuclides which intended for use in the radiopharmaceutical preparation can be prepared by one of the following methods.

• Nuclear fission

Nuclides with a high atomic number are characterized by being fissionable. The most common reaction is the fission of Uranium-235 by neutrons within the nuclear reactor. Another examples of radionuclides prepared by this method are Iodine-131 and Xenon-133. The radionuclides prepared by this method must be carefully controlled to avoid radiation impurities [32].

• Charged particle bombardment

In this method, the cyclotrons are used to produce the radionuclide by bombarding the non-radionuclide with charged particles [29].

• Neutron bombardment

In this method, the radionuclides are prepared in the nuclear reactor by bombarding the non-radionuclide by neutrons [33]. Didi *et al.* studied the feasibility of the production of iodine-131 using dioxide of tellurium-130 under neutron activation [34].

• Radionuclide generator systems

This method is used for preparing the radionuclides with short half-life by separating the daughter radionuclide (short half-life) from the parent one (long half-life) by physical or chemical means using radionuclide generator system [29].

Labeling and packaging of radiopharmaceuticals

The label on the package should have the following information [35]:

- The name of the product and also the name of the added radionuclide.
- The code of the product.
- The name of the manufacturing company.
- The batch number.
- For liquid preparations, the total volume in the vial, and the total concentration of radionuclide within the vial or the concentration per milliliter at the date and time of the manufacturing.
- For solid preparations (lyophilized powder), the total amount of radionuclide at the date and time of the manufacturing.
- For capsules, the total number of capsules in the package and also the amount of radionuclide in each capsule.
- All ingredients should be mentioned in the label.
- The route of administration and the expiration date.
- Specific storage conditions.

Packaging

The packing and labeling materials should be suitable for the condition of the product [36].

The package leaflets

Package leaflets of the kits or the product should include:

- The name and the use of the radioactive product.
- The name of all ingredients in the product.
- The name of the manufacturer of the kits and the address.
- The method of preparation of radiopharmaceutical from the kits and the Shelf-life of the prepared radiopharmaceutical.
- The route of administration, the pharmacological and toxicological effect of the prepared radiopharmaceutical and also the route of elimination from the body.
- The dose of radioactive substance from the prepared radiopharmaceutical.
- The Precautions which should be considered by the patient and the nuclear pharmacist during administration and the preparation of the product.
- The precautions which should be taken in consideration for the disposal of the container and its unused contents.
- The recommended dose of the prepared radiopharmaceuticals.

Storage of radiopharmaceuticals

The international standard guidelines for the storage of radioactive substances should be strictly applied [35]. The prepared radiopharmaceuticals should be stored in a well-closed container in a sufficiently shielded place to protect personnel from exposure to radiation.

Radioactivity

As shown in fig. (1), the different types of radioactive decays, which include alpha, beta, and gamma. The difference between the different types of radioactive decays is represented in table (2).

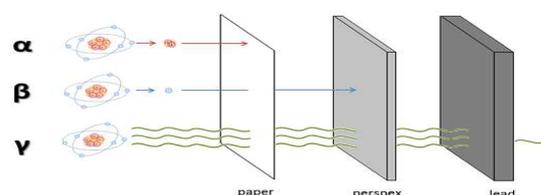


Fig. 1: Types of radioactivity: alpha, beta, and gamma decay [37]

➤ Alpha particle

Alpha particles as helium nucleus consisting of two protons and two neutrons, which means that when the radionuclide decay and emit alpha particle, its atomic number will be decreased by 2 and also the atomic mass decreased by 4. The alpha particles are heavy with high mass and slow so, they have low penetration power, which allows them to be stopped by a sheet of paper [38]. Due to the high mass of

the alpha particles, they can't penetrate the outer layer of the skin when the body exposed to it and not cause a hazard's effect. While when the alpha particle emitters are inhaled, ingested or injected, the alpha particles cause a serious hazard effect on the internal organs due to the high charge of the alpha particles.

➤ Beta particle

The beta particles resemble the electron in the mass and charge, which indicates that they have a very small mass in comparison to protons or neutrons. Beta particles may be of negative charge (negatron) or positive charge (positron). Due to the low mass of the beta particles, they have penetration power higher than the alpha particle which allows them to penetrate the sheet of paper but stopped by an aluminum sheet. Being charged, the beta particle has

a destructive effect on the organs but less than alpha particles so, they can be used in therapy especially for the destruction of the tumor tissue [39].

➤ Gamma radiation

The gamma radiations are emitted from the radioactive nuclide in the form of photons, not particles that means that they haven't a mass or charge. The radionuclides are decayed in the form of gamma radiations, the process not accompanied by any change in the atomic number or the atomic mass. Being radiation, the gamma rays have no mass so have high penetration power more the beta particles. Due to the absence of the charge, the gamma radiations have no destructive effect so, can be used for diagnosis. Technetium-99m is an example of a radionuclide which decayed in form of gamma radiation [39].

Table 2: Different types of radioactive decays of radiopharmaceuticals

Types of decay	Alpha (α)	Beta (β)	Gamma (γ)	Reference
Structure and origin	Like helium nucleus emitted from the radionuclide	Like electron emitted from the radionuclide	Like waves emitted from the radionuclide	[40]
Charge	α^{2+}	β^- or β^+ ,	Zero	[39]
Mass	4	$1/1836$	Zero	[39]
Ionization degree in the human body	Highly ionized so cause a destructive effect and can't be used in nuclear medicine	Less than alpha particle can't be used for diagnosis but used for therapy	No ionization so can be used in imaging	[40]
Suitability for nuclear imaging	Not suitable	Not suitable	Highly suitable	[39]

The nuclear medicine

Radiopharmaceuticals are pharmaceutical preparations that contain radioactive substances and radiolabel substances to be used either in diagnosis or therapy.

The Society of Nuclear Medicine, state that 20 million nuclear medicine procedures are carried out in the United States every year.

These procedures are done using the prepared radiopharmaceuticals and the imaging equipment for the diagnosis of a different disease or in treatment targets [41].

Advantages and disadvantages of nuclear medicine

Advantages of nuclear medicine

As shown in fig. (2), nuclear medicine has several advantages

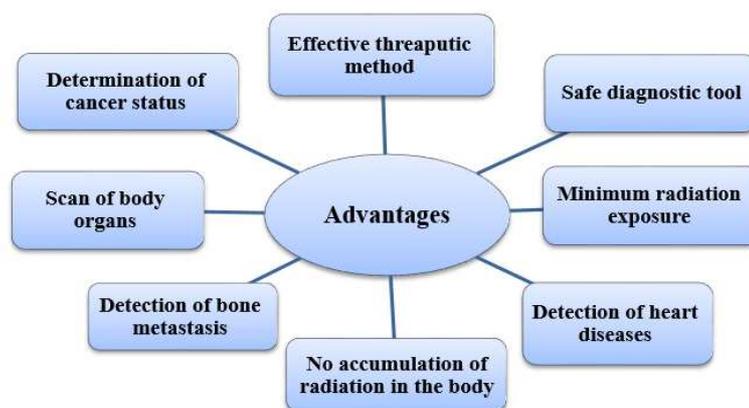


Fig. 2: The advantages of nuclear medicine

• Providing information about the function and anatomy of the body

The tests of nuclear medicine give complete information about the functions and anatomy of body organs. It represents a useful tool for the physician to determine the case of the patient and the best treatment. From the scan of the body, it is easy to decide on the tumor is malignant or benign, the physician can determine if surgery is required or not, and it is easily discovering the presence of disease before the appearance of the symptoms [42].

• Determination of the cancer status

Nuclear medicine is a useful tool for determining the status of the tumor. The physician can know if the tumor is metastasized or returned after size reduction [43].

• Nuclear medicine is important in bone metastasis

The bone pain source and the presence of bone cancer can be detected by nuclear medicine. Also, for an elderly patient, nuclear medicine serves as a tool for detecting the hidden features which resulted from osteoporosis [44, 45].

• Nuclear medicine is important in heart disease (cardiology)

Nuclear medicine is used by the cardiologist to recognize the causes of certain symptoms like the breath shortage and chest pain. Also, the nuclear medicine used for diagnosis of coronary artery disease caused by high cholesterol level, which causes the block of the blood and oxygen supply to the heart [46].

- **Nuclear medicine minimizes the amount of radiation**

The tissue and organ damage for patients can be done due to too much exposure to the radiation. While in the use of nuclear medicine, the amount of radiation is minimized to be as the usual x-ray [29].

- **Nuclear medicine helps in accurate, painless, and safe diagnosis of several diseases**

Nuclear medicine represents as accurate, non-invasive, safe, effective tool to manage the complex diagnosis as in case of patients suffering from many concurrent diseases. It gives a clear image and important information that can't be given with other diagnostic tests. It is important in the diagnosis of thyroid disease, bone pain, and blood imbalance [29].

- **Nuclear medicine is important in therapy**

Some of the radioactive agents have therapeutic efficacy so they can be used by the physician in the treatment plan. They are used for the treatment of cases that can't be controlled by conventional drugs as in case of bone pain. Nuclear medicine also is useful in the case of thyroid cancer and hyperthyroidism [47].

- **The radioactivity of radiopharmaceutical agents passes through the patient's body**

After administration of the accurate dose of the radiopharmaceuticals, the gamma rays are emitted to give the therapeutic effect and the excess is passed through the body via stool and urine, so no accumulation of radiation inside the body due to radioactive decay [48].

The disadvantages of nuclear medicine

Nuclear medicine has several disadvantages as shown by a fig. (3)

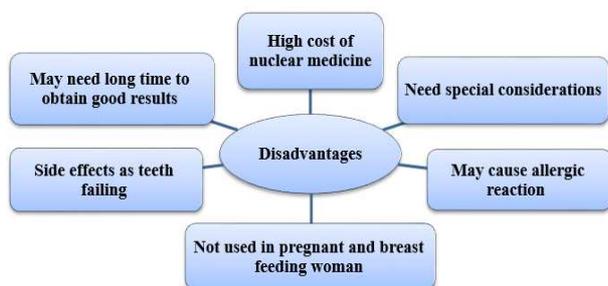


Fig. 3: The disadvantages of nuclear medicine

- **Nuclear medicine is not recommended for the pregnant and breastfeeding woman**

The unborn babies have great sensitivity to the radiation of radiopharmaceutical drugs than children and adults [49].

- **Nuclear medicine may cause an allergic reaction in some cases**

The allergic reaction accompanied to nuclear medicine is rare. It may occur for 1 every 400000 cases. The patient should speak with the physician about his history before stating nuclear medication, especially if the patient suffered from any medication allergy or have anaphylaxis shock in the past. The most popular side effects of radiotherapy are headache, dizziness, low blood pressure, and abnormal heart rate [50].

- **Specific consideration should be followed before starting the nuclear medicine in some cases**

A special construction should be followed by the patient before starting a nuclear medicine such as in the case of thyroid, heart, and gastrointestinal tract scan. In the thyroid scan, the patient should

stop any medication for about 2-4 w before the nuclear medicine. In the case of heart examination, the patient should fast for at least 4 h before nuclear medicine. In the case of the gastrointestinal system, the patient should undergo certain required premedication tests and be fasted for about 4 h before starting the nuclear medication [51].

- **The high cost of nuclear medication**

Most of the patients can't tolerate the therapy cost, so these patients resort to cover the cost of treatment by medical insurance or to be taking a grant from the government. The high cost of nuclear medicine is due to the medical instruments used in this purpose [52].

- **Side effects related to nuclear medicine**

The exposure of the patient to the nuclear medication may lead to the teeth failing, dental braces and distortion around the mouth area [53].

- **Nuclear medicine may consume a long time**

When the patient receives a radiopharmaceutical agent, the imaging may be done after about 30-60 min, several hours, or several days to obtain good results. The time varies according to the decay time of the radiopharmaceutical agent to emit the radiations [54].

Application of radiopharmaceuticals

Radiopharmaceuticals have several applications as shown by a fig. (4).

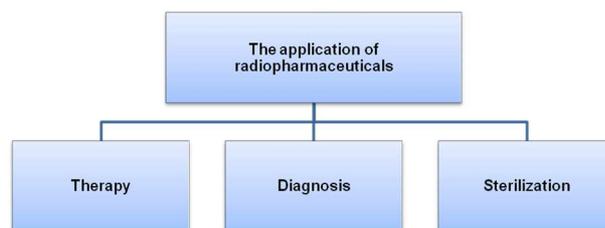


Fig. 4: The applications of radiopharmaceuticals

A-The therapeutic application of radiopharmaceuticals

The radiopharmaceutical preparations intended for therapeutic purposes are designed to deliver the radiolabeled molecules to specific diseased sites inside the body to allow the emission of charged beta particles in the target site to give therapeutic responses as in the case of tumors. As represented in table (3), some radiopharmaceuticals with their therapeutic applications.

The ideal properties of therapeutic radiopharmaceuticals are [9]:

- High uptake at a specific site
- Less activity in the blood
- No retention in any other tissue or organ
- Excretion through the renal pathway

The therapeutic radiopharmaceuticals are used in different fields as in cardiology for myocardial perfusion, oncology for tumors, and neurology for cerebral perfusion.

Application of radiopharmaceuticals in the treatment of hyperthyroidism and thyroid cancer

Hyperthyroidism is the elevated production of thyroid hormone from the thyroid gland, which resulted in a clinical case called thyrotoxicosis [55].

Oral administration of Iodine-131 has been a frequently accepted route for the treatment of malignant and benign thyroid disorder and hyperthyroidism [56].

Iodine-131 is a radioisotope with a half-life of 8 d. It decays in the form of gamma rays and beta particles [57]. The therapeutic effect

of Iodine-131 depends on the ability of iodine to concentrate in the thyroid gland [58].

The radiolabeled Iodine-131 can be administered as first-line treatment if the hyperthyroidism returns or not controlled after treatment with an anti-thyroid drug or after thyroid surgery [59].

The radiolabeled Iodine-131 is selectively accumulated in the tissue of thyroid gland and decays by emission of alpha particle, which destroys the tumor tissue in case of thyroid cancer.

Radiolabeled Iodine-131 may be administered in oral dosage form (liquid or capsules) or parentally (intravenous injection) for patients having difficulty in swallowing or vomiting.

Application of radiopharmaceuticals in the treatment of bone metastasis

Bone metastasis is the most common type of pain in cancer patients. It reduces patient quality of life and linked with many complications, such as hypercalcemia, bone fractures, spinal cord compression [5]. Treatment is mainly palliative by using analgesic drugs, anti-inflammatory drugs, radiotherapy and surgery [60].

Various radionuclides are used to provide analgesic treatment of bone metastases, including samarium-153 (Sm-153), phosphorus-32 (P-32) and strontium-89 (Sr-89) [10].

Samarium-153 is a radionuclide with 1.9 d half-life which can be used for diagnosis and treatment of bone metastasis due to the emission of both beta particle and gamma radiation [10]. Samarium-153 has the ability to target the bone tumor, it goes to the source of cancer bone pain and emits the beta particles resulting in pain relief. In the majority of patients, pain relief occurs within the first week of therapy.

Phosphorus-32 used to suppress hyper proliferative cells. It emits beta particles with a physical half-life is 14.3 d. It decays in the form of beta particles with a maximum energy of 1.71 MeV allow it to be useful in case of bone metastasis [61].

Strontium-89 chloride is administered intravenously, it decays and emits beta particles. The physical half-life of Strontium-89 is 51 d. It has the ability to accumulate metastatic bone lesions in higher concentrations than in healthy normal bone. After intravenous injection, the Strontium-89 acts as calcium it selectively cleared from the blood and localized in the bone minerals [62].

Table 3: The therapeutic application of radionuclides

Radionuclide	The therapeutic use	Reference
Iodine-131, Yttrium-90	Used for treatment of non-Hodgkins lymphoma	[63, 64]
Americum-241, Californium-252	Used for treatment of cancers and tumors	[65, 66]
Cobalt-60, Gold-194		
Holmium-66	Used for treatment of liver cancers	[10]
Iodine-131	Used as antineoplastic, and for Grave' disease (hyperthyroidism and differentiated thyroid cancer.	[67]
Rhenium-186	Used for relief the pain associated with bone metastasis	[68]
Yttrium-90	Used as cancer brachytherapy	[69]
Samarium-153, Strontium-89	Palliative treatment of bone metastasis	[70-72]
Phosphorus-32		
Erbium-169, Yttrium-90	Relief of arthritis pain	[73]
Samarium-153	Pain relief in bone cancer, prostate and breast cancer	[70]
Strontium-89	Reduces pain in prostate and bone cancer	[74]

B-The diagnostic application of radiopharmaceuticals

The bodies' organs differ in their function. Throughout the study, the physicians identified the chemical substances which can be uptaken and absorbed by each organ. For example, the thyroid gland selectively uptake Iodine, the brain uptake the glucose, and the bones uptake the calcium. This idea is used in the case of radiopharmaceuticals, where the radioisotope when entering the body is selectively uptaken by certain organs. The ideal diagnostic radionuclide is that with short half-life and decay by emission of gamma radiation. Technetium-99 m is considered the ideal diagnostic radionuclide as it has a short half-life (6 h), decay by emission of gamma radiation only, and efficiently detected by gamma camera [75].

As represented in table (4), diagnostic radiopharmaceuticals can be used to detect different diseases and image different organs.

Curtis *et al.* used radioactive fluorine-18 for early diagnosis of Alzheimer's disease [76]. Vente *et al.* used radioactive Holmium-166 to detect and diagnose liver cancer [77]. Maxon *et al.* used Radioiodene-131 in the diagnosis of metastatic thyroid cancer [78]. Mandel, *et al.* used iodine-123 in the scanning of thyroid remnants in patients with differentiated thyroid cancer [79]. El-motaleb *et al.* prepared radioiodoproporanol using iodine-125 for lung perfusion scan [80]. Visakh *et al.* estimated the amount of radiation that entered the thyroid region during a computed tomography (CT) brain scan [81].

Table 4: The diagnostic application of radionuclides

Radionuclide	The diagnostic use	Reference
Technetium-99 m	Used in diagnosing of cardiac amyloidosis	[82]
Chromium-51	Used in diagnosis of pernicious anemia	[83]
Fluorine-18	Used in positron emission tomography to assess alternations in glucose metabolism in brain and cancer	[76]
Holmium-166	Used in the diagnosis of liver cancer	[77]
Iodine-125	Used in diagnosis and evaluation of the glomerular filtration rate of kidneys	[84]
Gallium-67	Used in tumors imaging	[85]
Potassium-42	Used in determination of exchangeable potassium in coronary blood flow	[86]
Rubidium-86	Used in determination of myocardial blood flow	[87]
Iodine-131	Used in studying the function of the thyroid gland	[88]
Selenium-75	Used to study the production of digestive enzymes	[89]
Sodium-24	Used to study sodium exchange	[90]
Xenon-133	Used to study the pulmonary ventilation	[91]
Thallium-201	Used to diagnose coronary artery disease, death of heart muscle, and the location of lymphoma (low grade)	[92]
Strontium-92	Used in imaging of neuroendocrine tumors	[10]

C-Application of radioactive substances in sterilization

The thermo-labile substances are sterilized by radiation. The radioisotopes are used for this purpose. The thermo-sensitive substances include hormones, vitamins, antibiotics, surgical dressings, and disposable syringes. Cobalt-60 is an example of radioisotopes that decay by gamma radiation and used for sterilization of the thermo-labile substances [93].

CONCLUSION

The authors concluded that there are a lot of radioactive substances that have a great effect on diagnosis and therapy. Nowadays, the branch of nuclear pharmacy is directed to introduce new radioactive pharmaceutical agents which will be important and effective in the treatment of cancer. The growth in the field of radiopharmaceuticals is important to help millions of patients suffering from tumors all over the world.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to this work

CONFLICT OF INTERESTS

The authors disclose that no conflicting interests associated with the manuscript exist.

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