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Nuclear Medicine and Drug Delivery

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Abstract

Nuclear Medicine is a molecular-imaging modality that diagnoses and treats diseases with very small amounts of radioactive materials, known as radiopharmaceuticals. Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect. The use of nuclear medicine and radiopharmaceuticals allows studying the *in vivo* behavior of developed drug-delivery systems, and pharmacoscintigraphy is, from the beginning, one of the most promising aspects of this medical specialty. In this chapter, we review the technologies, fundaments, rationales, and strategies more frequently used and present examples of their application in the development and evaluation of drug-delivery systems.

Keywords: nuclear medicine, radiopharmaceuticals, drug delivery, *in vivo* analysis

1. Introduction

Nuclear Medicine is a medical speciality that involves the application of small amounts of radioactive materials, known as radiopharmaceuticals, for the diagnosis and treatment of disease, without causing any physiological effect.

Drug-delivery strategies have been steadily being developed in order to obtain better therapeutic results, enhance adhesion to treatment, and mitigate side effects. The ever-increasing complexity of the systems, combined with the regulatory demands by the Medicines Authorities, made the *in vivo* analysis of those systems' behavior almost compulsory.

The unique characteristics of Nuclear Medicine and Radiopharmaceuticals make dynamic, noninvasive studies and therefore are frequently used in the evaluation and development of new drug-delivery systems. This chapter aims to review the different techniques available, their rationale and applications, using, whenever possible, examples from the literature as well as from the authors' own experience.

2. Molecular imaging and Nuclear Medicine

Molecular imaging is defined as the visualization, characterization, and measurement of physiological mechanisms at the molecular and cellular levels, in living systems. Apart from Nuclear Medicine, it includes several other techniques, such as magnetic resonance imaging and spectroscopy, certain ultrasound technologies, and others [1, 2].

One of the biggest advantages of molecular imaging is the ability to characterize specific disease processes in different individuals, using noninvasive assessment and quantification; i.e., providing information that is inaccessible with any other imaging techniques or that otherwise would require more invasive procedures such as biopsy or surgery. Also, it identifies disease in its earliest phases and determines the precise location of a tumor, frequently before symptoms occur or changes can be detected at the anatomical level. Identifying small differences between patients allows the tailoring of specific treatments for each individual [1–3].

Nuclear Medicine is a molecular-imaging modality that diagnoses and treats diseases using radioactive materials, known as radiopharmaceuticals. Radiopharmaceuticals, at diagnostic levels, have the ability to portray human physiology, biochemistry, or pathology without causing any physiological effect [1, 3].

For example, it can be used to identify the presence or absence of specific receptors or molecular changes, which are crucial for the selection of patients for certain targeted therapies [1].

This step for "personalized medicine" also allows a more precise identification of research subjects, leading to more exact and cost-effective clinical trials [3].

3. Detectors and imaging systems

Diagnostic imaging refers to the techniques and processes used to create anatomical and functional images and is one of the fields in Medicine with the greater recent development [1].

The first reference to structural imaging dates to 1895, when Wilhelm Conrad Röntgen identified electromagnetic radiation in a wavelength range now known as X-rays. Functional imaging started following the discovery of the scintillation scanner by Benedict Casen (using I-131 as a radiotracer for diagnostic imaging purpose), and developed as a diagnostic specialty in 1958, when Hal Anger introduced the gamma camera (based on the principle of scintillation

counting). Since then, Nuclear Medicine has considerably changed our view of looking at disease, by showing images of radiotracer distributions, providing functional images [1, 4].

A gamma camera is single-photon imaging equipment, also known as Anger camera or as scintillation camera. It contains a large radiation detector, consisting of a large thallium-activated sodium iodide crystal—the scintillator. A collimator, placed in front of the crystal, enables the γ-rays to be focused onto the detector. Coupled to the crystal are photomultiplier tubes, which detect the light pulses. The whole detection part of the equipment is shielded from undesirable radiation. An electronic system links the photomultiplier tubes to a computer and visual display unit [1, 5, 6, 7].

The basic principle of gamma cameras is that radionuclide concentrations in the body can be measured *in vivo*, by detecting the photons emitted during their radioactive decay. The first gamma cameras were only able to create two-dimensional (2D) representations. But in 1963, David Kuhl and Roy Edwards presented the first tomographic images using the Anger camera, by acquiring multiple planar images from different angles around the body and creating a three-dimensional representation. This technology, called single-photon emission computerized tomography (SPECT or SPET), is of special interest when studying complex three-dimensional anatomical structures [1, 6]. Besides static 2D and tomographic images, it is also possible to obtain dynamic, sequential images of the radiopharmaceutical's variation over time within a particular segment of the body [8].

Another indispensable nuclear-imaging method consists of positron emission tomography (PET). The distinction between SPECT and PET is based on the physical properties of the radioisotopes used for imaging. SPECT (single-photon imaging) relies on single γ-ray photon emitters. By contrast, PET uses positron emitters—radioisotopes that simultaneously emit two 511-keV photons, at approximately opposite directions. These photons are detected in the PET camera by a ring of detectors configured to detect coincidence. The registered events are then reconstructed into a three-dimensional image [5, 9].

Although PET offers some advantages over SPECT, such as improved resolution and increased quantitative capabilities, SPECT is often more practical because of its wider availability and lesser cost [3].

A typical nuclear-imaging procedure starts with the administration of the selected radiotracer, followed by image acquisition (through the detection of γ-rays, X-rays, or annihilation quanta in PET, using either a gamma camera or a PET scanner). The resulting image illustrates the tracer's location within the body [5, 10].

More recent developments in Nuclear Medicine include hybrid-imaging techniques. Hybrid imaging refers to the fusion of two (or more) imaging modalities, such as SPECT/CT, PET/CT, or PET/magnetic resonance (MR) devices. These modalities have the advantage of condensing molecular and anatomical information in a single examination, thus surpassing one major drawback of highly specific tracers: the lack of anatomical landmarks within the image [3, 4].

It should be noted that Nuclear Medicine can also operate without imagery. This can be achieved by the measurement of radioactivity in specified sites of accumulation or in biological samples following the administration of the radiopharmaceutical [1, 8].

4. Radiopharmaceuticals

The first radioactive tracer experiment was performed by George Charles de Hevesy in the 1920s. In the 1930s, Irene Curie and Frederic Joliot discovered artificial radioactivity. The discovery of the cyclotron by Ernest Lawrence opened the door for the production of radio-tracers of practically every element, thus enabling investigators to design radiotracers for the study of specific biochemical processes.

The European Pharmacopoeia describes "radiopharmaceutical" as any medical product which, when ready to use, contains one or more radionuclides included for a medicinal purpose [11].

Although the field of Nuclear Medicine evolved into a more sophisticated molecular-imaging technology, the term "radiopharmaceuticals" has extended to novel radiolabeled molecular-imaging probes [1, 4].

Most radiopharmaceuticals consist of a combination of a radioactive molecule—a radionuclide—and a biologically active molecule or a drug that acts as a carrier and determines localization and biodistribution. For a few radionuclides (such as radioiodine, gallium, or thallium), the radioactive atoms themselves act as the radiopharmaceuticals [3].

The radionuclide emits radiation that is detected externally using gamma cameras or PET cameras. Certain characteristics are desirable for clinically useful radiopharmaceuticals. Radionuclide decay should result in emissions of suitable energy (100–200 keV is ideal for gamma cameras) and in sufficient abundance for external detection. Particulate radiation (e.g., beta emissions) increases the patient radiation dose, and should be reserved for therapeutic use. Effective half-life should be only long enough for the intended application (usually a few hours). The radionuclide should be carrier-free—that is, not contaminated by other stable radionuclides or other radionuclides of the same element. Technetium-99m most closely fulfills these features for the gamma camera, and fluorine-18 for PET [2, 3].

Once a decision about a suitable nuclide has been made, an appropriate agent must be selected to carry the isotope. There are many different radiopharmaceuticals available to study the different parts of the body, which can be administered by injection, ingestion, or even inhalation. They are administered in sub-pharmacological doses (<100 μg) and "trace" a particular physiological or pathological process in the body, portraying the physiology, biochemistry, or pathology, without affecting it or without causing any other physiological effect [2, 3]. Thus, with the exception of some tracers in radio-immunoscintigraphy and radiotherapy, hypersensitivity reactions against tracers are very rare, as the administered quantities are below a threshold to trigger immune response. Even in known hypersensitivity to iodinated substances (i.e., hypersensitivity against contrast media in radiology), iodine tracers can be safely used for diagnosis and therapy [1].

Understanding the mechanism and rationale for the use of each agent is critical to understanding the normal and pathological findings demonstrated scintigraphically.

5. Nuclear Medicine: its applications

Taking advantage of the combination of individual characteristics of the patient and molecular specificities of the disease, Nuclear Medicine aims to integrate patient- and disease-specific information [4, 8].

Apart from its major diagnostic and therapeutic roles, Nuclear Medicine is important in establishing prognosis, assessing disease progression, identifying recurrence, selecting the most effective therapy, monitoring therapy, and adapting treatment plans in response to changes in cellular activity [1, 4, 8].

Additionally, Nuclear Medicine is an important tool in the development of new targeted drugs and in the design and implementation of improved patient-tailored therapies [1, 4, 8].

5.1. Diagnosis

Nuclear Medicine dedicates primarily to the diagnosis of medical conditions. Depending on the type of examination, radiopharmaceuticals are administered in the most suitable way, for example, intravenously or orally. Afterwards, external detectors capture the radiation emitted by those radiopharmaceuticals and images are formed, showing the radiopharmaceutical uptake distribution and, subsequently, the targeted sites.

5.2. Targeted therapy

Drugs are designed to treat diseases, correcting abnormal cellular or molecular processes [4]. In theory, any highly specific imaging tracer can be used for therapy if labeled with the suitable radionuclide.

The term theranostics refers to substances that have both diagnostic and therapeutic roles. One classic example is radioiodine, used to diagnose and treat some thyroid pathologies. Theranostics has played a vital role in radiation-based therapies, especially when using targeted radiopharmaceuticals [9, 12].

Therapeutic procedures in Nuclear Medicine use high-dose, nonpenetrating radiation emitting, targeted radiopharmaceuticals. Most therapies use beta-emitters (I-131, Y-90, and Lu-177), but Auger-, Alpha-, or conversion electron emitters are also good candidates [3, 8]. The targeting ligands can also be radiolabeled with suitable positron emitters such as F-18 and Ga-68, for PET monitoring and evaluation purposes [9].

Theranostics agents play a major role in the development of radiopharmaceuticals, validating its target profile and early-disease diagnostics. They help choose the more adequate candidates and therefore are frequently used by the pharmaceutical industry [9].

5.3. Drug and formulation development and drug-regulatory affairs

Nuclear Medicine studies on drug delivery have been accepted by regulatory authorities as supporting evidence in product registration dossiers such as Investigational New Drug Applications or New Drug Applications [13].

Nuclear Medicine stimulates and supports drug development in a noninvasive way. With the radiolabeling of drug molecules, it is possible to monitor distribution, release, and kinetics, through the observation of its *in vivo* distribution and allowing the visualization of their metabolism in both target and nontarget sites [1, 13]. These studies can be performed in both animals and humans.

In drug approval, most studies are performed with new chemical entities (NCEs), because information on their metabolic outcome is required. Studies of biopharmaceuticals metabolism using radiotracers are less frequent, because it can be difficult to substitute a radiotracer for a naturally occurring stable isotope [6].

Regulatory drug-testing programs that employ radiotracers are generally classified into two groups: explorative and standard studies. Standard studies are habitually done for the majority of NCEs, with varying characteristics, depending on the drug class and specific circumstances. Explorative studies, although very important (even mandatory sometimes), are not usually required. More than 80% of all drug-safety-testing assessment programs (by the US safety assessment process) used radiotracers [14].

6. Drug delivery and Nuclear Medicine

Drugs are usually administered as pharmaceutical dosage forms. In the development of these dosage forms, it is fundamental to ensure they will perform correctly. Before the submission to the regulatory authority for approval of a new medicine, detailed testing is required. To improve therapeutic effects and minimize toxicity, it is crucial to deliver the therapeutic drugs to the right target, in the desired time, and in the precise concentration—a "magic bullet" [7, 9].

The controlled and targeted delivery of therapeutic drugs improves their bioavailability (either by preventing premature degradation or by improving uptake), maintains their concentrations within the therapeutic window (by adjusting the release rate), and reduces side effects (by targeting disease site/cells). The ability to deliver therapeutic drugs to the target, in a minimally invasive approach, has advanced considerably with the growth of molecular-imaging techniques [9].

When molecular-imaging radiotracers are part of the drug-delivery system, they enable monitoring of its *in vivo* behaviour: pharmacokinetics, distribution, release at the target site, and excretion. Some of these evaluations (such as *in vivo* fate or delivery efficiency) are not possible with a nonimage-guided approach. Another issue with nonimaging techniques is that much testing (bioavailability, therapeutic efficacy, and dose response) must be done in separate experiments, which makes for a rather expensive and stressful process [9].

The use of Nuclear Medicine imaging in the study of a drug-delivery process dates back to the late 1970s and is well established in pharmaceutical development. Understanding drug action and providing key information about the drug-delivery process through a variety of routes, Nuclear Medicine can be used in the various stages of studies [6, 9, 13]. Without radiotracers, the comprehension of numerous biochemical processes would have been tremendously

difficult and, in some cases, maybe impossible. Its strength lies in the quantitative nature of the images. Only Nuclear Medicine techniques can determine the precise location of tablet disintegration in the gastrointestinal (GI) tract, the depth of penetration of a nebulized solution in the lungs, or for how long does the formulation stay in the cornea [6, 9, 13].

In image-guided drug delivery assessment, the image techniques are used for determining disease location, drug-targeting levels and localization, and release kinetics (before and during treatment). The type and stability of the labeling will depend upon whether the study is meant to examine release, deposition, retention/dispersion, or is being used to monitor the effects of physiological process [13, 15].

The majority of studies have evaluated gastrointestinal, pulmonary, and nasal drug delivery, but ophthalmic, buccal, rectal, vaginal, and parenteral routes have also been subject of research [6].

The required quantity of radiotracer in a drug formulation is very small and does not commit with the performance of the delivery system. Radiolabeling must reveal high *in vitro* and *in vivo* stability and can be performed in two different ways. The radiolabeled compound can be directly incorporated into the preparation, or a dosage form that contains a nonradioactive tracer can be neutron-activated. The latter is advantageous in extensive or complicated delivery systems, and also has the advantage of the dosage formulation being manufactured and produced under normal conditions [7, 9]. Still, Nuclear Medicine imaging of drug-delivery processes involves several challenges and is affected by numerous factors such as target expression, *in vivo* availability of the receptor, type of drug, enhanced permeability and retention effect, tracer protein dose, and timing of imaging [9].

Once administered, the radiolabeled compound will be monitored *in vivo* over a period of time (depending on its half-life), using appropriate image equipment: gamma-scintigraphy or PET. It is then crucial to choose the most suitable radioisotopes, with fitting half-lives to pair with the pharmacokinetics of their drug carriers, and the most adequate imaging system [6, 9, 13].

In the last decades, most studies used gamma-scintigraphy and Tc-99m-labeled radiopharmaceuticals containing chelating agents (such as diethylene-triamine-pentaacetic acid (DTPA)), colloids (such as sulfur colloid), diphosphonates (such as hydroxymethane diphosphonate (HDP)), cells and blood elements, and cellulose macromolecules [7, 13].

More recently, the use of PET is increasing, including in drug-delivery development studies. An important attribute of PET studies is that some of the radioactive atoms available include radioisotopes of carbon, nitrogen, and fluorine. This makes it possible to synthesize PET radiotracers with the same chemical structure as the unlabeled molecules, without altering their biological function [9, 13].

Unlike radiological imaging, Nuclear Medicine allows serial images to be obtained without submitting the subjects to higher radiation burdens, and radioactive concerns are neglected. Besides the reliability and reproducibility of Nuclear Medicine studies on the nature and characteristics of products, they may also be performed in the groups of patients intended to receive the dosage forms therapeutically, which is important since the presence of pathology can have significant impact on physiology [13].

It is well established that diseases alter physiological processes, and subsequently biodistribution of drug formulations. Thus, studies in humans are the most relevant and Nuclear Medicine imaging probably represents the only technique available that allows the quantification of drug release and pharmacokinetics in specific groups, namely patients with diseases [13]. This know-how has the potential for patient selection for targeted therapy and for the monitoring of therapeutic response after the drug is delivered [9].

Targeted therapy involves the integration of multidisciplinary fields such as cell and molecular biology, chemistry, physics, and so on. Significant advances in the field have been attributed to the progress in nanotechnology, with the development of nanosized, multifunctional drug-delivery platforms. For example, a single platform can be used to detect, treat, and monitor treatment response in tumors. These systems present several advantages, including minimal clearance by the immune system, prolonged circulating times, attachment to suitable vectors (peptides, proteins, antibodies, etc.) and targeting of specific receptors, and improved treatment effects by shielding entrapped drugs from degradation [9].

For example, stimulus-responsive polymeric nanomaterials can be synthesized to mimic the behavior of biological molecules, minimizing side effects and maximizing predictability. Another example, the liposomal carriers (the first and most extensive studied drug-delivery carriers), is used in the delivery of anticancer drugs, antineoplastic agents, antimicrobial compounds, immunomodulators, anti-inflammatory agents, cardiovascular drugs, and so on. Some other nanosized drug-delivery systems that have also been developed for molecular-imaging purposes are metallic nanoparticles, oxide nanoparticles, polymeric nanoparticles, and carbon nanostructures [9].

The major goal of molecular imaging is to maximize therapy effect in diseased tissues, and reduce systemic effects and toxicity as much as possible [9].

6.1. Gastrointestinal tract studies

Despite the vast diversity of new drug-delivery systems, oral administration is still preferred.

Most commonly, oral-dosage forms immediately release in the stomach, but the use of more sophisticated, modified release systems is increasing and requires new methods of evaluation. Furthermore, regulatory authorities require evaluation of the *in vivo* performance of new oral formulations.

Nuclear Medicine imaging is one of the most popular methods to investigate those GI release systems, because pharmacokinetic measurements are often unreliable. Its combination with pharmacokinetic studies provides accurate data about transit, absorption, and release performance of oral-dosage formulations [7].

Nuclear Medicine imaging provides information, from both control and patient groups, on swallowing dynamics of tablet and capsule formulations, disintegration of immediate release formulations, gastric emptying and gastroesophageal reflux, release of enteric-coated formulations, GI transit times, the effect of formulation size on GI delivery, visualization of targeted release or delivery to the colon, the effects of time of dosing on delivery, local permeability

within the colon, disintegration characteristics likely to influence drug absorption, and residence time of the material within the colon [7, 9].

GI nuclear studies often require both solid- and liquid-phase markers, there being two conventional approaches for the labeling of the oral-dosage forms. One method involves incorporating a nonabsorbable chelate of the radioactive isotope (e.g., DTPA-Tc-99m). The other incorporating a radiolabeled ion-exchange resin, which has the advantage of giving information about the *in vivo* position of the radiolabeled drug, because the resin remains within the device [7].
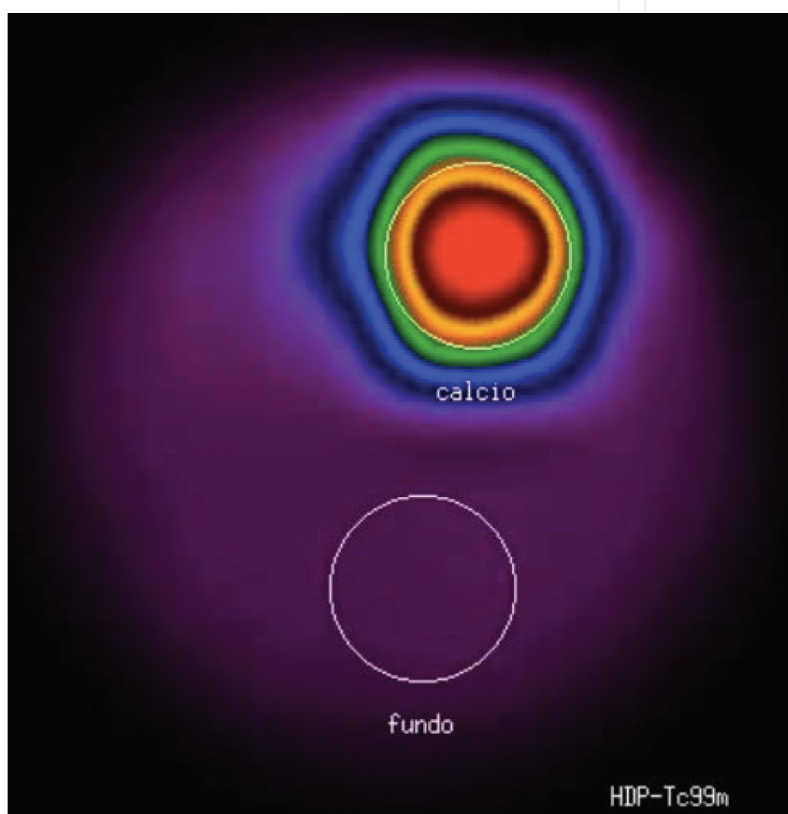

Figure 1. *In vitro* radiolabeling and evaluation of the drug-delivery system.

In two different studies aimed at evaluating the gastroretentive behavior of pharmaceutical dosage forms, Barata et al. used Tc-99m-HDP to label HMPC tablets supplemented with calcium phosphate. The radiolabeling process consisted in soaking the tablet in a Tc-99m-HDP and NaCl 0.9% solution, with activity counts of 400–600 millicuries. The addition of calcium to the systems did not affect drug release, but significantly increased the binding of the radiopharmaceutical to the dosage form. In fact, the dosage form remained integer and well radiolabeled for a period of over 4 h, which was sufficient to study the gastroretentive pattern of the produced tablets. This proved to be an easy and reproducible method of extemporaneously radiolabeling tablets produced outside Nuclear Medicine Department facilities, solving radiation-related transportation problems (see **Figure 1**).
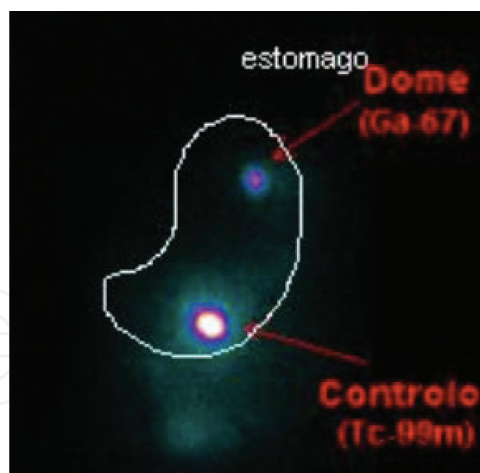
Figure 2. *In vivo* analysis of the drug-delivery system floating behavior.

For the floating-device study, a non-floating tablet was labeled with Tc-99m-HDP, while the floating pharmaceutical dosage form was labeled with Ga-68 (gallium-68), using the same soaking method. Despite not as effective as Tc-99m-HDP labeling, Ga-68 labeling was enough to allow a clear visualization of the system. The physical properties of the two radiopharma-ceuticals (different energy photons) enabled the simultaneous identifying of each system over time: initially, both in the stomach (floating in the upper part of the stomach or staying in the antrum), then, the effective gastroretention of the floating device for over 4 h (see **Figure 2**).

Figure 3. *In vivo* analysis of the drug-delivery system gastroretentive behavior.

In the other study, aiming to demonstrate the gastroretentive efficacy of high-density tablets, a similar process was used to radiolabel the produced tablets. Again, it was possible to see the *in vivo* positioning of the pharmaceutical dosage form and confirm that the high-density controlled release strategy is effective for delivering drugs with a narrow upper GI absorption window (see **Figure 3**).

These examples prove that incorporating gamma-emitting radionuclides into a delivery device or formulation provides an appropriate, simple method of observing the transit and residence

within the GI tract—of particular interest in determining the time and site of release of delayed release formulations.

6.2. Other system studies

Both SPECT and PET imaging play an increasing role in the development of new targeted drug-delivery systems [13].

Nuclear Medicine is being used to surpass the severe systemic toxicity of anticancer drugs, which are usually more effective in high doses. Additionally, numerous conventional therapeutic agents repeatedly fail to reach their target, rendering them ineffective. The ideal drug should be specific for the cancer cell and devoid of systemic effects. For these reasons, the ideal drug-delivery system is aimed, and Nuclear Medicine, with all its already-known advantages, plays an important role in this area [9, 16].

PET image-guided drug delivery allows for the treatment of a variety of diseases with minimal systemic involvement (sparing normal cells), while monitoring its efficacy.

In cancer-targeted treatment, chemotherapeutic drugs can be loaded onto multifunctional drug carriers (such as liposomes, micelles, and nanoparticles) and coupled with several targeting ligands (such as monoclonal antibodies, peptides, and antibody fragments). Carriers are multifunctional and may also carry PET radiopharmaceuticals for diagnostic purposes. These systems are important examples of theranostics. One example is the streptavidin/biotin interaction that is used for binding numerous carriers to targeting proteins and antibodies.

In another approach, therapeutic radionuclides are conjugated with targeting ligands (by means of bifunctional-linking strategies), without any image-enabling radionuclide. PET imaging for the diagnosis or monitoring of therapeutic response is carried out separately, by conjugation of the targeting ligands with suitable PET radioisotopes [9].

Investigation-wise, PET allows the *in vivo* quantification and drug distribution, determining its extraction fraction and washout from different organs/systems.

PET imaging allows the study of the first-pass liver elimination of a drug, a fundamental knowledge, since first-pass metabolism excludes oral delivery of several drug molecules and compounds.

PET studies are also useful in the understanding of the brain and of several neurological conditions, including anxiety and depression [13]. In Parkinson's and Alzheimer's diseases, the *in vivo* study of neuroreceptors binding is fundamental for the drug-design process (ex. enzyme/prodrug-based delivery approach with 18F for Parkinson's disease) [9, 13].

7. Conclusion

Nuclear Medicine is a very promising field and will surely increase its relevance on diagnostics and therapeutics in the near future. Also within the field of drug development and drug-

delivery systems research, it is expected to demonstrate an ever-increasing applicability and importance. The advent of new and more complex drugs, combined with more ingenious and technological delivery systems, will call for a more detailed and effective *in vivo* studies during the development and regulatory phases of the research and marketing authorization process. Radiopharmaceuticals and Nuclear Medicine will therefore be predictably ever more used with the purpose of obtaining better, safer, and more reliable drug-delivery systems.

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