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Radio Pet Therapy of Healthy Wistar Rats with $^{64}CuCl_2$ Labeled to $^{64}Cu(AcAc)_2$ Supported in Functionalized TiO_2 Nanoparticles

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Abstract

In recent years Copper-64 in the chemical form of copper chloride ($[^{64}Cu]CuCl_2$) has been identified as a potential agent for PET imaging and radionuclide therapy. The aim of this research was to determine the biodistribution and the labeling of radio nanoparticle with $^{64}CuCl_2$, the nanoparticles $Cu(acac)_2$/**F**-TiO_2 were mixed with $^{64}CuCl_2$ (20-37 MBq), then the final solution was used to injected healthy Wistar rats to probe the absorption of nanoparticle inside tissue trough of the groups OH that are formed during the functionalization of the $Cu(acac)_2$/**F**-TiO_2. The "*in vivo*" evaluation after realize the images study in micro PET equipment, uptake of the radio-nanoparticle was observed in the digestive system in the healthy Wistar rats.

Keywords

PET Therapy, Nanoparticles, Functionalized Titania (**F**-Tio_2), Titanium Acetylacetonate [**Cu (AcAc)$_2$**], $Cu(Acac)_2$/**F**-Tio_2, PET Lesion Detection, Imaging

1. Introduction

Assumed its half-life and decay scheme, ^{64}Cu (T1/2 = 12.7 h, 17.4% β+, 39% β–, 43.6% EC) has the potential to serve a dual role in the development of molecular agents for PET imaging and radioimmunotherapy drugs in oncology [1]. In this

study, small irradiations were performed, demonstrating the feasibility of ^{64}Cu production by this method [2] [3]. ^{64}Cu of a high specific activity in the form of copper chloride ($CuCl_2$) was produced at the Radiopharmacy Cyclotron Unit of the Faculty of Medicine, UNAM by the ^{64}Ni(p,n)^{64}Cu reaction with 11 MeV protons as previously reported [1]. After radiochemical purification, the copper fraction was evaporated to dryness, and the metal was recovered with a physiological saline solution for injection [3]. The use of ^{64}Cu has dramatically increased in the past decade and its production has now been reported by academic sources in the United States, Europe, and Japan [4] [5] [6] [7].

Developing countries have been performing Emission Tomography (PET) scans, first animals and then with patients. Nearest PET of Mexico, it was at Los Angeles California University (UCLA). In Mexico the application of diagnostic technique began in an academic environment at UNAM in 2002. The institution few years later, began to research on animals, as well as provides studies to localize cancer at public [8].

The first reported system for small animal imagining was developed by Pichler *et al.* [8] [9] and used the combination of lutetium oxyorthosilicate (LSO) and Avalanche Photon Diodes (APDs) which was the state of the art technology at this time. The system had an outer diameter of 120 mm and was placed inside the gradient of a 7-T magnetic resonance (MR) imagine scanner, while the radiofrequency coil had an outer diameter of 60 mm and was fitted inside the PET ring. Each detector had 19 × 19 mm^2 crystal block and each block consisted of a 12 × 12 array of 1.5 × 1.5 × 4.5 mm^3 LSO crystals, each crystal block was placed on a monolithic 3 × 3 APD. The system showed very good performance with no interference from the magnetic field and reported energy resolution of ~15%. All crystal pixels were clearly resolved, and success simultaneous mouse imagine was performed [9] [10] [11].

A series of new hexadentate and pentadentate chelators were designed and synthetized as chelators ^{64}Cu. The new chelators contain different types of donor groups and are expected to form neutral complexes with copper (II). This was aimed to detect and treat at the same time the cancer. Ewen Bodio *et al.* [12]. propose different compounds tetradentates, where the ligands are joint easily to ^{64}Cu [13].

The aim of this research was to evaluate the radiolabeling and biodistribution of a new nanocompound ^{64}Cu-(acac)$_2$/**F**-TiO_2 [14]. The radioactive material was administered in three male Wistar rats to visualize biodistribution of this new nanoradio compound in the organs. This compound will be tested after biodistribution, in rats with specific tumors of cancer.

Across the world, it was tried chelating ^{64}Cu-$CuCl_2$ with molecules containing "*d*" metals of the periodic table through covalent bonds. In addition, porphyrin compounds, among others.

2. Methodology

Copper production was carried out in a cyclotron (Siemens Eclipse HP) via the

reaction ^{64}Ni (*p, n*) ^{64}Cu 11 MeV proton using ^{64}Ni and electrodeposited on a gold disc as a white solid. Three male Wistar rats (195 ± 18 g) were used to visualize the *in vivo* whole-body (WB) distribution of the radionuclide by micro-PET imaging with a Focus 120 instrument (Concorde Microsystems). A series of microPET images were acquired with the rats under gaseous anesthesia ((2 - 3)% isoflurane) 30 min after injections (p.i.) of 20 - 37 MBq of ^{64}CuCl2. The procedure for labeled nanoparticles was performed using 20 μg of the nanocatalysts, which were dissolved in absolute ethanol placing them under constant stirring during 10 minutes at 600 rpm. Then the $^{64}CuCl_2$ (20 - 37 MBq) was added to the final solution, at pH ~3. Finally, it were placed in incubation at 85˚C and 450 rpm, during 30 minutes. After the incubation 200 μL of saline solution (17%) was added at pH~5. Healthy rats were intravenously injected with the radio-nanoparticle solution. The studied rats were treated under protocol of The Universidad Nacional Autónoma Metropolitana accepted by COFEPRIS (Mexican FDA)

3. Results

The results obtained in this research shown the caption of the radionanoparticle this radionanoparticle linked to $^{64}CuCl_2$ trough of the groups OH (**Figure 1**), that are formed during the functionalization of the Cu(acac)$_2$/**F**-TiO_2. Previous works have reported that the marked radionanoparticles have been used linked to chelate agent (^{68}Ga, ^{64}Cu and ^{89}Zr) [15]. Then the Cu(acac)$_2$/**F**-TiO_2 acts at the same way behavior as chelate agent mixed with $^{64}CuCl_2$.

The Cu(acac)$_2$/**F**-TiO_2, acetylacetonate in the copper may have different arrangements. The ligand acetylacetonate in nanomaterial may take different structures, depending where is bonding (**Figure 2**).

The aqueous-solution coordination chemistry of copper is limited to three oxidation states (I, II, III). Due to the lability of most Cu(I) complexes, they typically lack sufficient kinetic stability for radiopharmaceutical applications, while

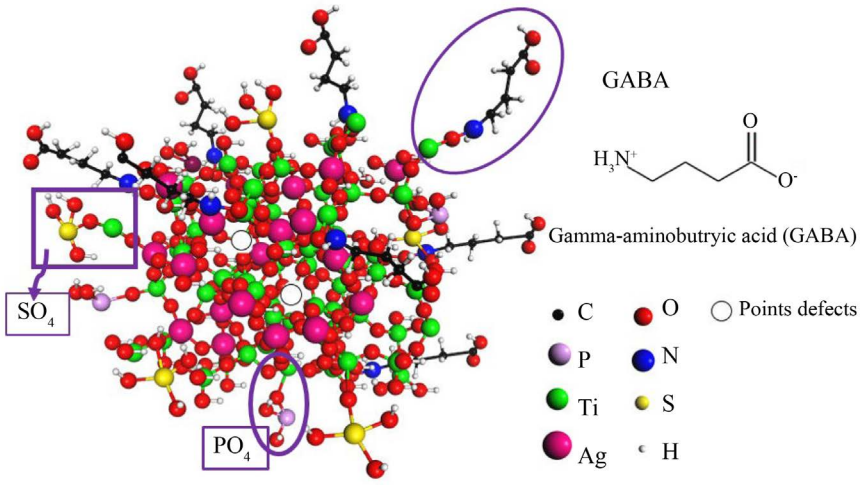

Figure 1. Functionalized nanoparticles.

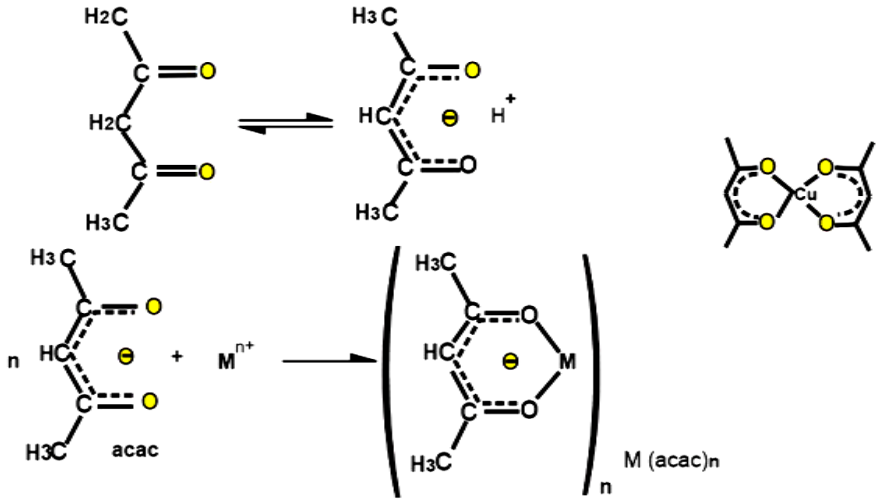

Figure 2. Copper acetylacetonate with different arrangements.

Cu(III) is very rare and difficult to attain without the use of strong *p*-donating ligands. Therefore, it is easy to incorporate copper acetylacetonate in a matrix of Titania sol-gel.

4. Discussion

One of the main tests in developing radiopharmaceuticals labeled with ^{64}Cu is their *in vivo* stability important for averting transchelation of copper with the many copper chelating proteins present in the blood.

The most important of this research is: a) verify if the $^{64}CuCl_2$ linked to the new nanoparticle proposed having incorporated copper; b) Achieved the goal a), healthy rats are injected with the radioactive solution, it is important verify if exist any signal.

The "*in vivo*" evaluation after realize the images study in micro PET equipment, uptake of the radio-nanoparticle was observed in the digestive system in the healthy Wistar rats, as shows the **Figure 3**.

The nanoparticle $Cu(acac)_2$/**F**-TiO_2 is functionalized with SO_4^{2-}, PO_4^{3-} and GABA (aminobutyric acid), the final result is a nanomaterial OH saturated [12] [14] [15]; it is the ligand which $^{64}CuCl_2$ is labeled.

In previous studies, have been proved that elimination of radionuclide is trough liver and intestines with little accumulation in the kidneys [11] [16] [17].

5. Conclusions

In this research healthy Wistar rats were used as a control, for the biodistribution study of 30 min [5]. An uptake of the radio-nanoparticle is observed in the digestive system. Nevertheless, the nanoparticle linked to $^{64}CuCl_2$ is useful for purposes.

Now, it is well known that this system is useful for detecting damaged zones while treating those areas. In the references given in the discussion part clearly, it illustrates how the nanomaterial of just 10 nm cross-cell barriers.

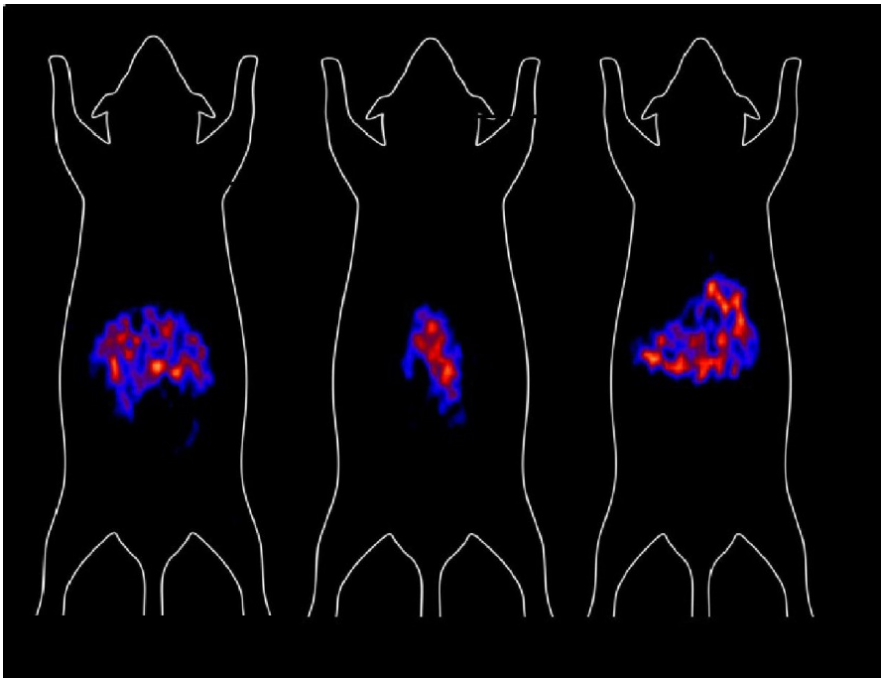

Figure 3. Representative whole body maximum intensity projections of micro PET images showing the biodistribution of $^{64}Cu(AcAc)_2$.

Therefore the radioactive properties of 64Cu (T1/2 = 12.7 h, 17.4% β+, 39% β–, 43.6% EC) make them ideal candidates for use in theragnostic applications.

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